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Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis

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Fingolimod;
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Satisfaction;
Fatigue;
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Abstract
Background: The Evaluate Patient OutComes (ClinicalTrials.gov Identifier: NCT01216072) study was conducted in North America to assess patient- and physician-reported treatment satisfaction in patients with relapsing multiple sclerosis (MS) who received oral fingolimod for 6 months after switching from an injectable disease-modifying therapy (iDMT), without an intervening washout.
Methods: In this open-label, multicenter study, patients were randomized 3:1 to once-daily fingolimod 0.5 mg or iDMT. The primary study objective was to evaluate differences in satisfaction measured using the Treatment Satisfaction Questionnaire for Medication v1.4.

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Results: Of 1053 patients randomized, 790 patients received fingolimod and 263 patients received iDMT. Treatment satisfaction improved significantly in patients who switched to fingolimod compared with those who continued iDMT. Patients also reported significant improvements in health-related quality of life, reduced depression, and reduced fatigue severity after a switch to fingolimod. No difference between the treatment groups was detected on the Patient Reported Indices for MS Activities scale. The safety profile of fingolimod was consistent with that reported in the pivotal phase 3 studies. The most commonly reported adverse events were more prevalent in patients who switched to fingolimod than in those who continued iDMT (headache: 12% vs 3%; fatigue: 12% vs 6%). No significant relationship between lymphocyte counts and infection rates was observed and there was no evidence of additive immune-system effects, which might be expected when switching to a different class of immunomodulatory therapy with no intervening washout.
Conclusion: Patients who switched from iDMT to fingolimod had significant improvements in most self-reported outcomes compared with those who continued iDMT.

1. Introduction

Multiple sclerosis (MS) is a debilitating neurological disease affecting over 2.5 million people worldwide (Sospedra and Martin, 2005). In relapsing-remitting MS (RRMS), neurological deterioration typically progresses over time, leading to accumulation of disability (Sospedra and Martin, 2005, Weinshenker et al., 1989) and reduced quality of life (QOL) (Janardhan and Bakshi, 2002).

Disease-modifying therapies (DMTs) are used in patients with RRMS to reduce the frequency of clinical relapses and delay the progression of physical disability. Traditional injectable DMTs (iDMT), such as interferon beta (IFNβ) and glatiramer acetate (GA), have been the mainstay of first-line RRMS treatment for the past two decades. However, the efficacy of these agents may be limited in some patients (La Mantia et al., 2010, Nikfar et al., 2010, Oliver et al., 2011, Qizilbash et al., 2012, Rice et al., 2001). In addition, the need for long-term self-administration of injections imposes a burden on patients because of tolerability issues and injection-site-related side effects (Brandes et al., 2009, Treadaway et al., 2009b).

Fingolimod is a once-daily oral DMT (Brinkmann et al., 2010). It was the first oral immunotherapy to gain US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the treatment of relapsing forms of MS. By modulating sphingosine 1-phosphate receptors (S1PRs) on T-lymphocytes, fingolimod selectively and reversibly retains naïve and central memory T-lymphocytes within lymph nodes, and thereby prevents them from circulating to other tissues, including the central nervous system (Francis et al., 2010, Hofmann et al., 2006). However, C-C chemokine receptor 7 (CCR7)-negative effector memory T-lymphocytes, which are less dependent on S1PRs to circulate through lymph nodes, are largely unaffected by fingolimod, and can therefore continue to fulfill their role in peripheral immune surveillance (Brinkmann, 2010).

The efficacy of fingolimod has been demonstrated in three large, randomized, controlled clinical trials of patients with RRMS (Calabresi et al., 2014, Cohen Ja et al., 2010b, Kappos et al., 2010). In the TRANSFORMS study, at the approved dose of 0.5 mg daily, fingolimod significantly reduced annualized relapse rates by 52% relative to intramuscular (IM) IFNβ-1a over 1 year (ARR: 0.16 vs 0.33, respectively; $p<0.001$) (Cohen Ja et al., 2010b). More patients treated with fingolimod than with IFNβ-1a IM were free from gadolinium-enhancing lesions (90% vs 81%, respectively; $p<0.001$) or had no new or enlarging T2 lesions (55% vs 46%, respectively; $p=0.01$). Also, at 12 months the mean percentage reduction in brain volume from baseline was significantly lower with fingolimod than with IFNβ-1a IM ($p<0.001$) (Cohen Ja et al., 2010b). Fingolimod has a well-characterized tolerability and safety profile (Cohen Ja et al., 2010b, Kappos et al., 2010), and its known adverse effects (including bradycardia, macular edema, and elevated levels of liver enzymes) are generally identifiable and manageable with appropriate monitoring.

Patients switch MS therapies for a variety of reasons, including tolerability issues and inadequate disease control. The phase 4 Evaluate Patient OutComes (EPOC; ClinicalTrials.gov Identifier: NCT01216072) study was conducted to assess patient-reported outcomes in individuals switching from an iDMT to oral fingolimod therapy, compared with remaining on or switching to another iDMT. The study also examined the safety and tolerability of fingolimod therapy after a switch from iDMT without a washout.

2. Patients and methods

2.1. Study design

The EPOC study (ClinicalTrials.gov Identifier: NCT01216072) was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2013), the Harmonised Tripartite Guidelines for Good Clinical Practice with applicable local regulations (ICH, 1996), and the ethical principles of the Declaration of Helsinki (WMA, 2014). Before conducting the study, the Institutional Review Board at each participating medical center provided ethical approval of the study protocol as well as the case report forms, patient information, and informed consent forms. Written informed consent was obtained from each patient, or their legal representative, before enrollment.

The EPOC study was a 6-month, randomized, open-label, multicenter trial with an optional 3-month extension (Cascione et al., 2013). Patients were randomized using an interactive voice response system (IVRS) to either the once-daily

fingolimod (FTY720; Gilenya™, Novartis Pharma AG, Basel, Switzerland) 0.5 mg arm or the iDMT arm, in a 3:1 ratio. A patient randomization list was produced by the IVRS using a validated system that automated the random assignment of patient numbers to the different treatment arms. If the patient failed to be randomized for any reason, the assigned number was not reused by another patient. Fingolimod capsules (0.5 mg) were supplied, packaged, and labeled in accordance with the US Code of Federal Regulations governing the handling of investigational treatments. The capsules were dispensed by the study physician and supplied by Novartis Drug Supply Management.

Patients randomized to the iDMT group could choose to either remain on the same therapy or, following a consultation with a physician, switch immediately to another approved iDMT. Injectable DMT was defined as therapy with either: IFNβ-1b (Extavia® or Betaseron®) 0.25 mg injected subcutaneously (SC) every other day; IFNβ-1a (Avonex®) 30 μg injected IM once a week; IFNβ-1a (Rebif®) 22 μg or 44 μg injected SC three times a week; or GA (Copaxone®) 20 mg injected SC once daily.

For the core study, visits occurred at screening, baseline, and weeks 1, 4, 12, and 24. Patients were considered to have completed the trial if they attended all study visits and completed all assessments. After the core study, an optional 3-month extension study was conducted to enable patients in the iDMT arm, who had completed all core study visits, to switch to treatment with oral fingolimod. Additional study visits then occurred during the extension study at weeks 28 and 36 for these patients.

2.2. Patients

Patients were enrolled from 152 centers in the USA and 6 centers in Canada between August 2010 and August 2012. All patients had been treated with an iDMT for at least 6 months before screening and entered the study without an intervening washout period. In addition, patients were required to meet all of the following criteria: adults under 65 years of age with relapsing MS in accordance with the 2005 McDonald criteria (Polman et al., 2005), an Expanded Disability Status Scale (EDSS) score of 0-5.5 (Kurtzke, 1983), and treatment-naïve to fingolimod.

Key exclusion criteria were consistent with those described in the phase 3 fingolimod clinical trials (Cohen Ja et al., 2010b, Kappos et al., 2010) and were as follows: history of chronic disease of the immune system (except MS), history of active malignancy (except localized basal/squamous cell carcinoma of the skin), uncontrolled diabetes mellitus (glycosylated hemoglobin >7%), macular edema present at screening, active systemic bacterial, viral, or fungal infection(s), pregnancy, and certain cardiovascular, pulmonary, and hepatic conditions.

2.3. Study assessments

2.3.1. Treatment Satisfaction Questionnaire for Medication (TSQM) v1.4

The primary study objective was to evaluate changes in treatment satisfaction between baseline and month 6, as measured by the Global Satisfaction subscale score on the TSQM v1.4 (Atkinson et al., 2004). Higher scores on the TSQM indicate greater satisfaction. Secondary objectives were to evaluate changes from baseline to month 6 in Effectiveness, Side Effects, and Convenience, also using the TSQM v1.4. The subscale was considered invalid if more than one item was missing from it.

2.3.2. Evaluation of other patient-reported outcomes

Secondary objectives of the EPOC study included evaluation of changes in fatigue, depression, activities of daily living, and health-related QOL between baseline and month 6.

The Fatigue Severity Scale (FSS) was used to assess the severity of fatigue and its effects on daily living (Valko et al., 2008). The Beck Depression Inventory II (BDI-II) was used to evaluate changes in patient-reported depression during the trial (Arnau et al., 2001). The Patient Reported Indices for Multiple Sclerosis (PRIMUS) Activities scale was used to evaluate changes in activities of daily living (Doward et al., 2009). For all of these instruments, the result was specified as 'missing' if more than 20% of the total number of scores was absent.

The 36-item Short-Form Health Survey v2 (SF-36 v2) was used to evaluate health-related QOL (Jenkinson et al., 1999). In addition, two summary scale scores (the Physical Component Summary and the Mental Component Summary) can be calculated. If more than half of the questions for any of the eight domains were not answered, the patient score for that domain was stated to be "missing". If the patient was missing any of the eight scale scores, the Physical and Mental Component Summaries were also stated to be "missing".

2.3.3. Clinical global impression of improvement (CGI-I)

A further secondary study objective was to examine whether physicians' views of their patients' condition changed during the study using the seven-point CGI-I scale (Berk et al., 2008), in which 1=very much improved since the initiation of treatment, 2=much improved, 3=minimally improved, 4=no change from baseline, 5=minimally worse, 6=much worse, and 7=very much worse.

2.3.4. Safety

Safety and tolerability (secondary study objectives) were assessed via reporting of adverse events (AEs) and through physical examinations (ophthalmologist examinations, and evaluations of vital signs, chest x-rays, and electrocardiograms), laboratory evaluations (measurement of hematology parameters, chemistry, urinalysis, serology, and lymphocyte counts), and MS relapse activity. A relapse was defined as the appearance of a new or worsening recurrent neurological abnormality, separated by at least 30 days from the onset of a preceding clinical demyelinating event as confirmed by neurological examination and accompanied by an increase in EDSS score.

All patients who initiated treatment with fingolimod were required to be observed following the administration of the first dose for signs and symptoms of bradycardia, in accordance with the current prescribing information for fingolimod (US prescribing information, 2014).

2.4. Statistical analysis

The primary outcome measure was the TSQM Global Satisfaction subscale. A sample size of approximately

1000 patients (750 patients in the fingolimod treatment group, 250 patients in the iDMT treatment group) was predicted to have 90% power to detect a difference between treatment groups in the change from baseline in this subscale score, assuming an effect size of 0.25 at a significance level of $p<0.05$.

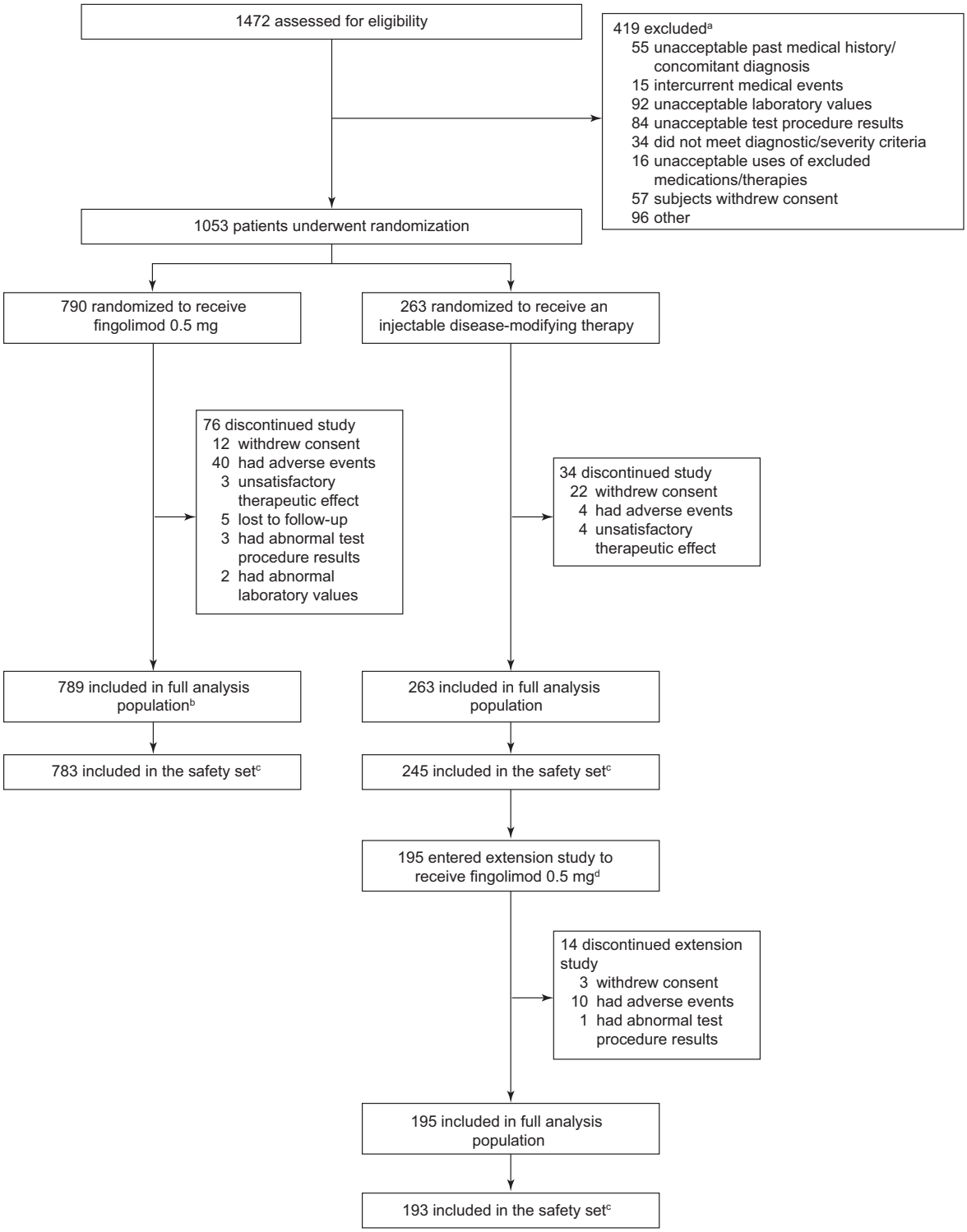


Fig. 1 Study patient flow diagram.

[a] Some patients were excluded for more than one reason.

[b] One patient in the fingomod 0.5 mg group was randomized in error, never received treatment and was not included in the full analysis set.

[c] The safety set comprised all patients who had received at least one dose of study drug.

[d] Only patients in the injectable disease-modifying therapy arm who completed all core study visits were allowed to enter the optional extension study.

Table 1 Overview of demographic and baseline characteristics, treatment history, patient disposition, and reason for switching injectable disease-modifying therapy.

	Fingolimod 0.5 mg (*n*=790)	Injectable DMT (*n*=263)
Patient demographics (all randomized patients)		
Age, years	46.0 (9.82)	45.1 (9.82)
Men/women, *n* (%)	189/601 (23.9/76.1)	55/208 (20.9/79.1)
Race, *n* (%)		
Caucasian	642 (81.3)	211 (80.2)
Black	113 (14.3)	43 (16.3)
Native American	4 (0.5)	1 (0.4)
Asian	3 (0.4)	0
Other	28 (3.5)	8 (3.0)
Disease characteristics		
Duration of MS symptoms, years	12.1 (8.38)	11.7 (8.44)
Number of relapses within last year	0.8 (1.20)	0.8 (1.32)
Number of relapses within last 2 years	1.4 (2.04)	1.4 (1.93)
EDSS score[a]	2.4 (1.32)	2.4 (1.32)
Previous MS treatment (all randomized patients)		
Injectable DMT at screening, *n* (%)		
Glatiramer acetate	263 (33.3)	92 (35.0)
IFNβ-1a IM	205 (25.9)	60 (22.8)
IFNβ-1a SC	196 (24.8)	65 (24.7)
IFNβ-1b	125 (15.8)	46 (17.5)
Natalizumab[b]	1 (0.1)	0
Corticosteroid used in the 6 months before screening, *n* (%)	155 (19.6)	55 (20.9)
Number of corticosteroid courses used in the 6 months before screening[c]	1.7 (2.31)	1.9 (3.23)
Primary reason for switching injectable DMT, *n* (%) (all randomized patients)		
Dissatisfaction with mode of administration	489 (61.9)	160 (60.8)
Tolerability issues	111 (14.1)	35 (13.3)
Lack of efficacy	95 (12.0)	42 (16.0)
Patient request	71 (9.0)	17 (6.5)
Other	20 (2.5)	7 (2.7)
Compliance	3 (0.4)	2 (0.8)
Concerns regarding safety with current product	1 (0.1)	0
Patient disposition (core study, all randomized patients)		
Completed study, *n* (%)	714 (90.4)	229 (87.1)
Discontinued study, *n* (%)	76 (9.6)	34 (12.9)
Subject withdrew consent, *n* (%)	12 (1.5)	22 (8.4)
Discontinued owing to AE(s), *n* (%)	40 (5.1)	4 (1.5)
Unsatisfactory therapeutic effect, *n* (%)	3 (0.4)	4 (1.5)
Lost to follow-up, *n* (%)	5 (0.6)	0
Abnormal test procedure result, *n* (%)	3 (0.4)	0
Abnormal laboratory value, *n* (%)	2 (0.3)	0

AE, adverse event; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; IM, intramuscular; MS, multiple sclerosis; SC, subcutaneous.
All values are mean (standard deviation) unless otherwise stated.
[a]EDSS scores range from 0–10, with higher scores indicating greater disability.
[b]This enrolled patient was ineligible for inclusion according to study protocol.
[c]The mean number of corticosteroid courses was calculated only for the patients who took corticosteroids.

Analyses of primary and secondary outcomes were performed using the full analysis set, which comprised all randomized patients to whom study medication was assigned, following the intent-to-treat principle. Missing data were imputed using the last-observation-carried-forward (LOCF) method. Between-group differences for all patient-reported variables were calculated using analysis of covariance (ANCOVA) models that included baseline score and treatment as explanatory variables. Physician-reported CGI-I scores were assessed using analysis of variance (ANOVA). For all variables, the least-squares (LS) mean, LS mean difference of the treatment groups, and 95% confidence interval (CI) for the difference between the two treatment groups were reported. Supportive analyses were performed using a Wilcoxon rank sum test.

Safety data were summarized descriptively using data from the safety set, which comprised all patients who had received at least one dose of study drug. Safety data were summarized separately for patients who received fingolimod during the core phase and the extension. In line with the known safety and tolerability profile of fingolimod (Cohen Ja et al., 2010b, Kappos et al., 2010), AEs of specific interest in the study included infections, macular edema, and cardiac events. The last post-baseline lymphocyte count assessment was used to analyze infection incidence by lymphocyte count category.

3. Results

3.1. Patient disposition and baseline characteristics

Of 1053 patients randomized to treatment, 790 patients were randomized to fingolimod 0.5 mg and 263 patients were randomized to an iDMT (Fig. 1). The mean time from the last dose of previous iDMT to the start of study drug administration was 2.68 days (median, 2 days). In total, 90.4% of patients (*n*=714/790) in the fingolimod arm and 87.1% of patients (*n*=229/263) in the iDMT arm completed the core study (Table 1). Following the core study, 74.1% of patients (*n*=195/263) from the iDMT arm took part in the

fingolimod extension study, with 92.8% (n=181/195) of those completing it. Baseline demographic and disease characteristics were similar between the two study arms (Table 1).

At randomization, proportionately more patients were receiving GA than any other iDMT (Table 1). Baseline reasons for wishing to switch from previous DMT included: dissatisfaction with mode of administration (61.9% and 60.8% of patients in the fingolimod and iDMT arms, respectively); tolerability issues (14.1% and 13.3%); and lack of efficacy, as determined by the physician (12.0% and 16.0%). A total of 9.9% of patients (n=26/263) in the iDMT group switched to a different iDMT at baseline. Of these, 7 patients discontinued during the core study and were not eligible for the extension. Of the patients who were eligible to enter the extension study, 14 patients opted to do so, and 5 patients did not. No reason was obtained for those who chose not to enter the extension study.

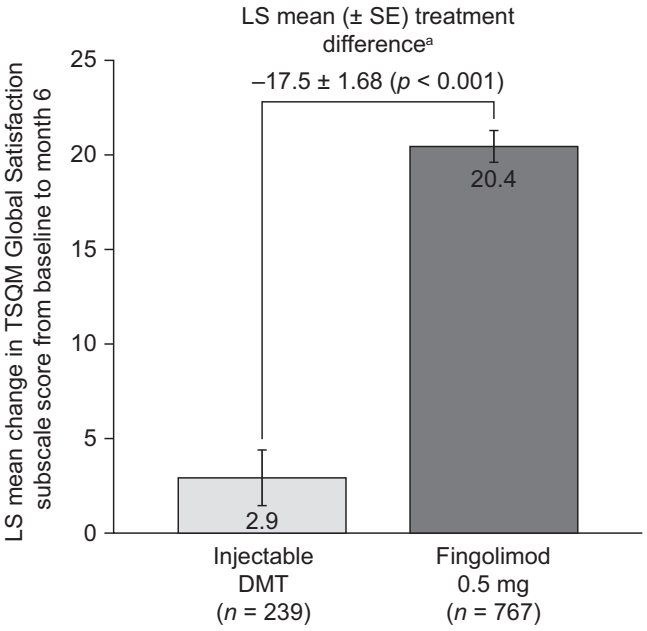


Fig. 2 Changes from baseline to month 6 in the Global Satisfaction subscale score of the Treatment Satisfaction Questionnaire for Medication (TSQM). A higher score indicates greater satisfaction. ANCOVA, analysis of covariance; DMT, disease-modifying therapy; LS, least-squares; SE, standard error.
[a] Between-group difference tested by an ANCOVA model that included baseline score and treatment as explanatory variables.

3.2. Patient-reported outcomes

3.2.1. Treatment Satisfaction Questionnaire for Medication

Patient satisfaction, as measured by changes in the TSQM Global Satisfaction subscale score from baseline to month 6, improved to a significantly greater extent with fingolimod than with iDMT (Fig. 2). The LS mean (±standard error [SE]) treatment difference from baseline to month 6 was −17.5±1.68 (p<0.001).

Improvements in the TSQM subscale scores for Effectiveness, Side Effects, and Convenience at 6 months were also significantly greater with fingolimod than with iDMT (p<0.001 for each subscale score) (Fig. 3). The LS mean treatment differences (±SE) were −12.5±1.66, −18.5±1.62, and −37.6±1.00 in favor of fingolimod versus iDMT for the Effectiveness, Side Effects, and Convenience subscales, respectively.

3.2.2. Fatigue, depression, and activities of daily living

There was pronounced improvement in both fatigue severity and depression in patients who received fingolimod at month 6 compared with those who received iDMT (Fig. 4). In terms of fatigue, the LS mean FSS score decreased in the

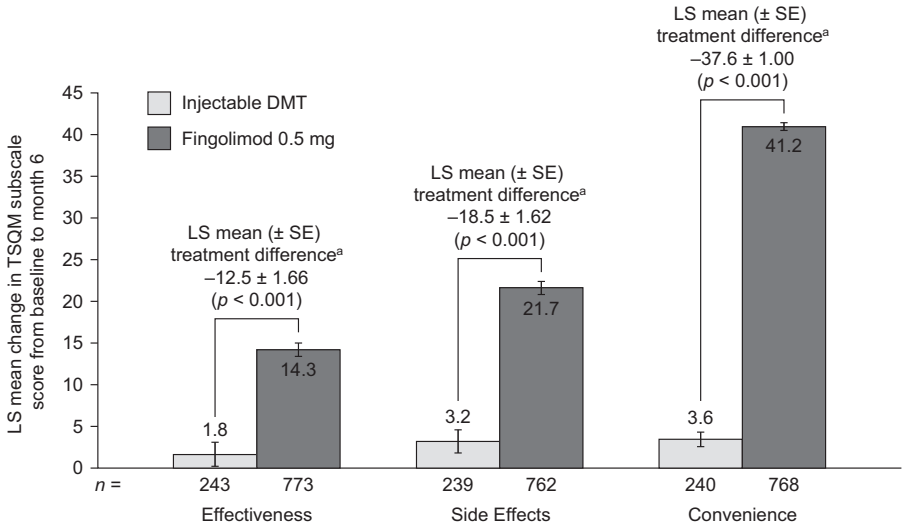
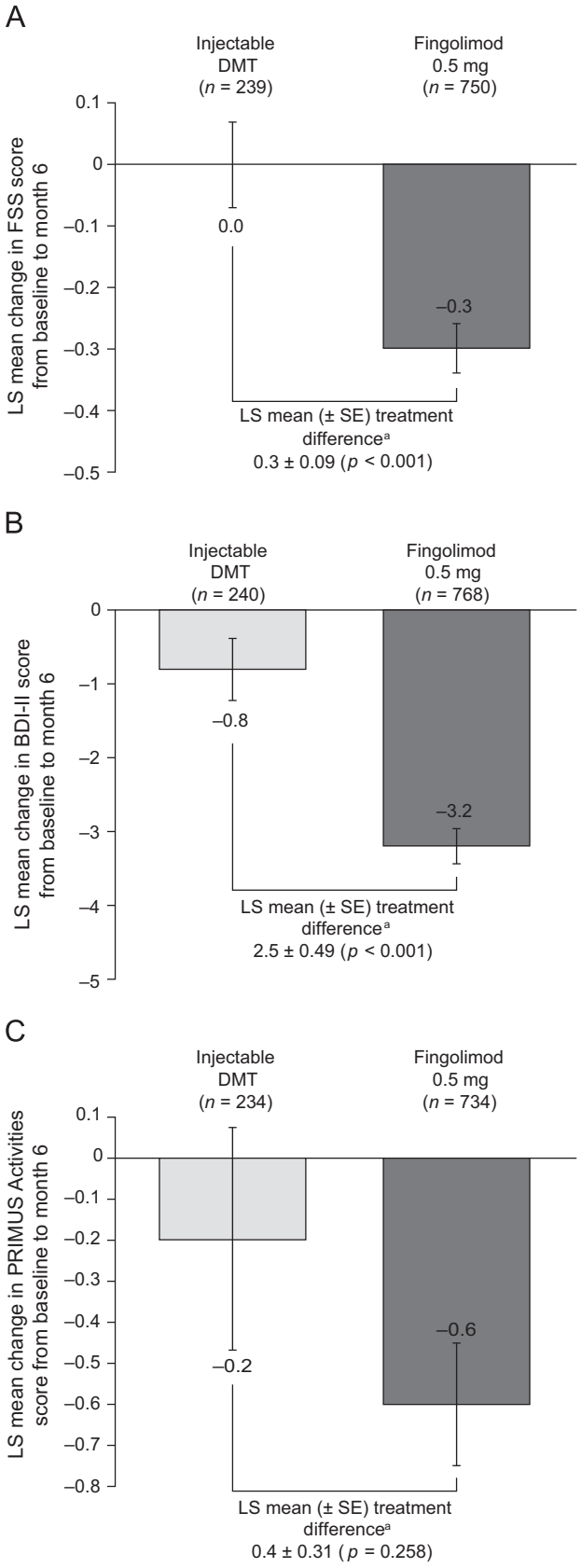


Fig. 3 Changes from baseline to month 6 in the Effectiveness, Side Effects, and Convenience subscale scores of the Treatment Satisfaction Questionnaire for Medication (TSQM). Higher scores indicate greater satisfaction. ANCOVA, analysis of covariance; DMT, disease-modifying therapy; LS, least-squares; SE, standard error.
[a] Between-group difference tested by an ANCOVA model that included baseline score and treatment as explanatory variables.

fingolimod group by 0.3 between baseline and month 6, while remaining unchanged in the iDMT group (difference between treatment arms ± SE: 0.3 ± 0.09; $p < 0.001$).



Regarding depression, the LS mean BDI-II score changed by −3.2 in the fingolimod group versus −0.8 in the iDMT group (difference ± SE: 2.5 ± 0.49; $p < 0.001$). Fingolimod-treated patients demonstrated numerically higher scores of perceived activity limitations (measured by the PRIMUS Activities scale), as compared with those obtained for the iDMT group, albeit not reaching statistical significance (Fig. 4).

3.2.3. Health-related quality of life

QOL scores for all domains of the SF-36 v2 increased at month 6 relative to baseline in the fingolimod group (Fig. 5). The LS mean difference was significant after 6 months of treatment in favor of fingolimod versus iDMT for the SF-36 v2 domains of Physical Health ($p = 0.008$), Bodily Pain ($p < 0.001$), Vitality ($p = 0.002$), Social Functioning ($p = 0.023$), Role Limitation due to Emotional Problems ($p = 0.023$), and General Mental Health ($p = 0.010$); the same was found for the Physical Component Summary ($p = 0.011$), and the Mental Component Summary ($p = 0.011$). The scores for Physical Functioning and General Health Perceptions were increased at 6 months relative to baseline versus iDMTs but these increases did not reach statistical significance.

3.3. Physician-reported outcomes

After 6 months, CGI-I scores were significantly lower for fingolimod than for iDMT, reflecting a greater perceived improvement. The mean CGI-I scores were 3.2 in the fingolimod group and 3.9 in the iDMT group ($p < 0.0001$). These scores translated to a range from minimum improvement (3) to no change (4) (Fig. 6).

3.4. Safety and tolerability

During the core study, the overall incidence of AEs was 78.8% in the fingolimod group and 62.0% in the iDMT group (Table 2). The two most frequently reported AEs observed in the fingolimod group were headache and fatigue (12.4% and 11.5%, respectively). These AEs were reported in 3.3% and 5.7% of patients in the iDMT group, respectively. Serious AEs occurred in 31 patients (4.0%) in the fingolimod group and 5 patients (2.0%) in the iDMT group. MS relapse was the most prevalent serious AE (0.6% for fingolimod versus 0.8% for iDMT) followed by lymphopenia (0.3% versus 0%), non-cardiac chest pain (0.3% versus 0%), and migraine (0.3% versus 0%). In total, 45 patients (4.4%) discontinued treatment owing to AEs, with 41 of these patients receiving fingolimod (5.2%; Table 2). The most frequent AEs leading to treatment discontinuation within the fingolimod group were macular edema and fatigue (each reported in four patients,

Fig. 4 Changes from baseline to month 6 in the (A) Fatigue Severity Score (FSS; a lower score indicates less fatigue severity), (B) Beck Depression Inventory-II (BDI-II) score (a lower score indicates less severe depression), and (C) PRIMUS Activities score (a lower score indicates less activity limitation). ANCOVA, analysis of covariance; DMT, disease-modifying therapy; LS, least-squares; PRIMUS, Patient-Reported Indices for Multiple Sclerosis; SE, standard error.
[a] Between-group difference tested by an ANCOVA model that included baseline score and treatment as explanatory variables.

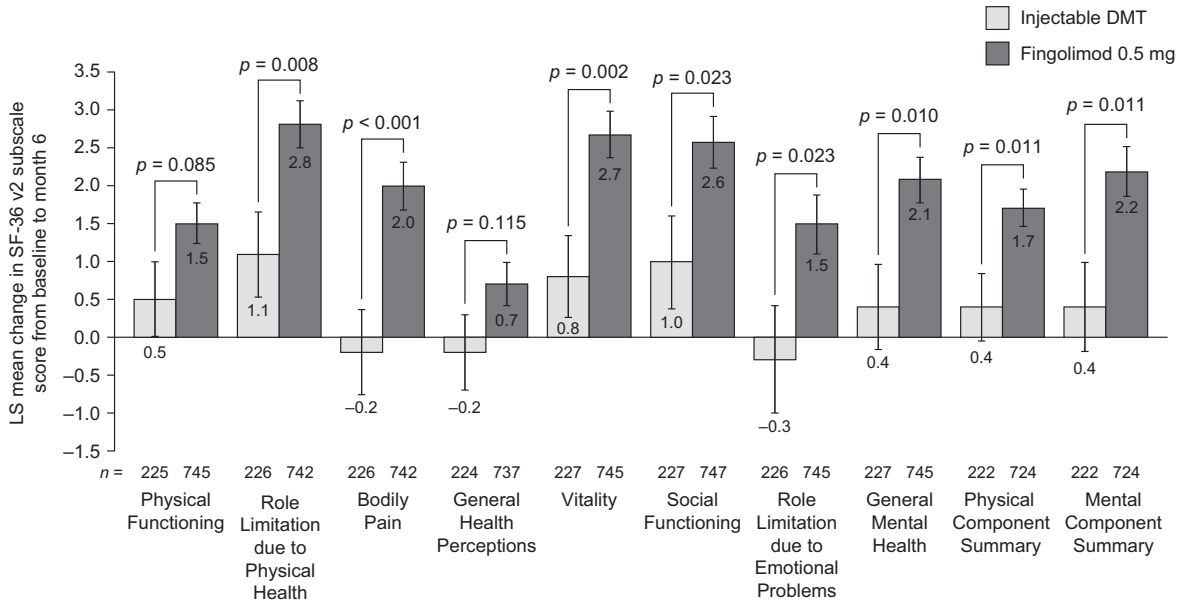


Fig. 5 Changes from baseline to month 6 in the 36-item Short-Form Health Survey v2 (SF-36 v2; higher scores indicate a better health-related quality of life). ANCOVA, analysis of covariance; DMT, disease-modifying therapy; LS, least-squares.
[a] Between-group difference tested by an ANCOVA model that included baseline score and treatment as explanatory variables.

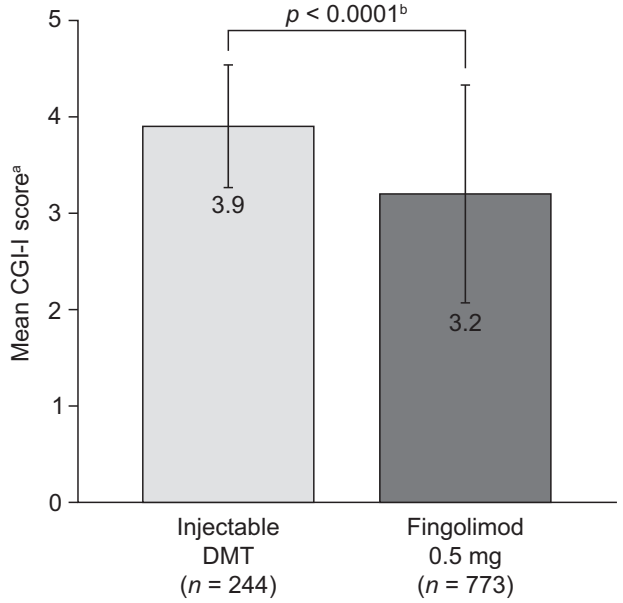


Fig. 6 Changes from baseline to month 6 in the Clinical Global Impression of Improvement (CGI-I) score. A lower score indicates better improvement. DMT, disease-modifying therapy; SD, standard deviation.
[a] CGI-I score: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; and 7=very much worse.
[b] *p* value was from a two-sample *t*-test comparing the two treatment groups.

0.5%). Further details are provided in Supplementary Safety Results.

In the extension study, 123 patients (63.7%) experienced AEs, most commonly infections/infestations and nervous

Table 2 Most common adverse events (AEs) and serious AEs.

Patients, *n* (%)	Fingolimod 0.5 mg (*n*=783)	Injectable DMT (*n*=245)
Deaths	0	0
AEs leading to study drug discontinuation	41[a] (5.2)	4 (1.6)
Any serious AEs (>1 case in any group)	31 (4.0)	5 (2.0)
MS relapse	5 (0.6)	2 (0.8)
Lymphopenia	2 (0.3)	0
Non-cardiac chest pain	2 (0.3)	0
Migraine	2 (0.3)	0
Any AE (>5% in any group)	617 (78.8)	152 (62.0)
Headache	97 (12.4)	8 (3.3)
Fatigue	90 (11.5)	14 (5.7)
Upper respiratory tract infection	51 (6.5)	9 (3.7)
Dizziness	50 (6.4)	7 (2.9)
Nausea	48 (6.1)	5 (2.0)
Nasopharyngitis	43 (5.5)	13 (5.3)
Hypertension	43 (5.5)	4 (1.6)
Diarrhea	41 (5.2)	4 (1.6)
Urinary tract infection	40 (5.1)	10 (4.1)

DMT, disease-modifying therapy; MS, multiple sclerosis.
[a]Includes one patient who experienced an AE at the end of the study. This AE was incorrectly recorded as leading to study drug discontinuation.

Table 3 Adverse events of interest from the core study and extension study.

Core study		
Patients, *n* (%)	**Fingolimod 0.5 mg (*n*=783)**	**Injectable DMT (*n*=245)**
Any infection and infestation AE	**236 (30.1)**	**68 (27.8)**
Infection and infestation AEs (reported in ≥2% of patients in any group)		
Upper respiratory tract infection	51 (6.5)	9 (3.7)
Nasopharyngitis	43 (5.5)	13 (5.3)
Urinary tract infection	40 (5.1)	10 (4.1)
Sinusitis	26 (3.3)	12 (4.9)
Bronchitis	12 (1.5)	5 (2.0)
Cardiac disorder AEs	**34 (4.3)**	**2 (0.8)**
Cardiac disorder AEs (>1 case reported in any group)		
Bradycardia	17 (2.2)	0
Palpitations	12 (1.5)	1 (0.4)
Cardiac flutter	2 (0.3)	0
Macular edema		
Left eye	1 (0.1)	0
Right eye	3 (0.4)	0
Bilateral	3 (0.4)	0

Extension study	
Patients, *n* (%)	**Fingolimod 0.5 mg (*n*=193)**
Any infection and infestation AE (reported in ≥2% of patients)	**38 (19.7)**
Upper respiratory tract infection	9 (4.7)
Nasopharyngitis	7 (3.6)
Urinary tract infection	6 (3.1)
Sinusitis	3 (1.6)
Bronchitis	3 (1.6)
Cardiac disorder AEs	**6 (3.1)**
Bradycardia	3 (1.6)
Palpitations	1 (0.5)
First-degree AV block[a]	1 (0.5)
Second-degree AV block[a,b]	1 (0.5)
Tachycardia	1 (0.5)
Macular edema	
Left eye	0 (0.0)
Right eye	2 (1.0)
Bilateral	1 (0.5)

AE, adverse event; AV, atrioventricular; DMT, disease-modifying therapy.
[a]The same patient had both first-degree and second-degree AV block.
[b]Mobitz type I.

system disorders (both 19.7%). The two most common reported AEs in the extension group were headache (10.4%) and nausea (6.2%). Seven patients (3.6%) experienced serious AEs during the extension study. No individual serious AE occurred in more than one patient.

No deaths occurred during the study. One patient who had been in the fingolimod group died suddenly following a fall after study completion. The death was determined to be unrelated to study treatment. It is not known whether this patient had continued taking fingolimod after the core study ended.

In the core study, infections were reported in 236 patients (30.1%) in the fingolimod-treated group and 68 patients (27.8%) in the iDMT group (Table 3). Infections were suspected to be treatment-related in 54 patients (6.9%) in the fingolimod group and 7 patients (2.9%) in the iDMT group.

At month 6, no statistically significant differences were found between the peripheral lymphocyte counts, or lymphocyte subset counts or ratios, in fingolimod-treated patients who experienced an infection compared with those who did not experience an infection (Table 4). Similar rates of infection were seen in those with both the lowest and highest peripheral lymphocyte counts (Fig. 7). Supplementary Safety Results provide further lymphocyte counts details.

Table 4 Summary of lymphocyte counts and ratios by occurrence or non-occurrence of infection in fingolimod-treated patients during the EPOC core study.[a]

	Patients without infection (*n*)	Patients with an infection (*n*)	*p* value
Any infection			
Mean total lymphocyte count (cells/μL)	430 (528)	440 (230)	0.78
Mean CD4+ lymphocyte count (cells/μL)	78.1 (295)	72.3 (125)	0.75
Mean CD8+ lymphocyte count (cells/μL)	121.4 (295)	136.9 (125)	0.26
Mean CD4/CD8 ratio	0.7 (295)	0.64 (125)	0.59
Respiratory tract infection			
Mean total lymphocyte count (cells/μL)	440 (615)	430 (143)	0.74
Mean CD4+ lymphocyte count (cells/μL)	74.4 (341)	84.9 (79)	0.62
Mean CD8+ lymphocyte count (cells/μL)	123.5 (341)	137.0 (79)	0.40
Mean CD4/CD8 ratio	0.67 (341)	0.7 (79)	0.79
Urinary tract infection			
Mean total lymphocyte count (cells/μL)	440 (714)	400 (44)	0.50
Mean CD4+ lymphocyte count (cells/μL)	79.2 (397)	26.1 (23)	0.15
Mean CD8+ lymphocyte count (cells/μL)	127.4 (397)	103.2 (23)	0.38
Mean CD4/CD8 ratio	0.70 (397)	0.38 (23)	0.10

EPOC, Evaluate Patient OutComes.

[a]Summaries are presented for any infection, and for respiratory tract and urinary tract infections, which were the most commonly occurring infections in fingolimod-treated patients during the EPOC study. No statistical or numerical relationship was identified for herpes, fungal, gastroenteritis, viral, eye, skin, or other infections (data not shown).

4. Discussion

This is the first randomized clinical trial to prospectively investigate patient-reported satisfaction in patients with RRMS switching from an iDMT to fingolimod therapy. Our results demonstrate that patients with RRMS achieve greater satisfaction when switched to fingolimod 0.5 mg from an iDMT compared with those who stayed on, or switched to another iDMT. According to the validated instruments used, improvements in convenience, fatigue, depression, and health-related QOL were significantly greater in patients who switched to oral fingolimod compared with those who continued on an iDMT. Patients receiving fingolimod also reported greater satisfaction with side effects and treatment effectiveness compared with those receiving iDMT, suggesting that fingolimod use was associated with greater tolerability and efficacy. However, this study was not powered to detect differences in side effects and treatment effectiveness.

Findings were similar to the 12-month, phase 3, double-blind, double-dummy, randomized, TRANSFORMS study, which found significant improvements in the PRIMUS Activities score (which reflects changes in activities of daily living) in fingolimod versus IFNβ-1a IM groups ($p<0.05$) (Cohen et al., 2010a). In EPOC, however, improvements in PRIMUS Activities score in the fingolimod versus iDMT groups did not reach statistical significance. It is possible that the 6-month EPOC study was of insufficient duration to detect differences between the groups in this parameter; additionally, patients who have been on DMT for over 10 years and without relapse during the study period might not report significant changes in activities of daily living.

Nevertheless, our findings are consistent with those of studies in other diseases, such as thromboembolism prophylaxis, iron chelation, and oncology, which have also found greater levels of patient satisfaction and improved QOL associated with oral versus injectable therapies (Jensen et al., 2008, Lima and del Giglio, 2005, Osborne et al., 2007, Peidro-Garces et al., 2013, Twelves et al., 2006). In addition, the improvements observed in the CGI-I score, which is a reflection of a physician's overall impression of the patient's improvement during the trial, significantly favored fingolimod over iDMT. Whilst the CGI-I score was in the range of only minimal improvement to no change in both the fingolimod and the iDMT groups, it is worth noting that the effect was measured early in the course of fingolimod treatment in this cohort of patients with long-standing MS.

The overall safety profile of fingolimod was generally consistent with that observed in previous clinical studies (Cohen Ja et al., 2010b, Kappos et al., 2010). Notably, the absence of a washout period between cessation of the iDMT and initiation of fingolimod did not appear to be associated with deleterious additive immune system effects. This may be explained by the selective action of fingolimod on circulating naïve and central memory T cells, allowing effector memory T cells to provide immune surveillance (Buzzard et al., 2012). However, unlike the TRANSFORMS study, where AEs were reported in similar proportions across fingolimod and IFNβ-1a IM groups (Cohen Ja et al., 2010b), in EPOC there was a higher overall incidence of AEs in the fingolimod group. This may be partly due to the study design because it might be anticipated that study-reported AEs would occur more often following a change of therapy, where patients are more likely to report new symptoms as AEs. For example, fatigue AEs were reported in a significantly higher proportion of patients who switched to fingolimod, which is discrepant with findings of patient-reported evaluation of fatigue (as measured by the FSS) that significantly favored fingolimod over iDMT. Another plausible

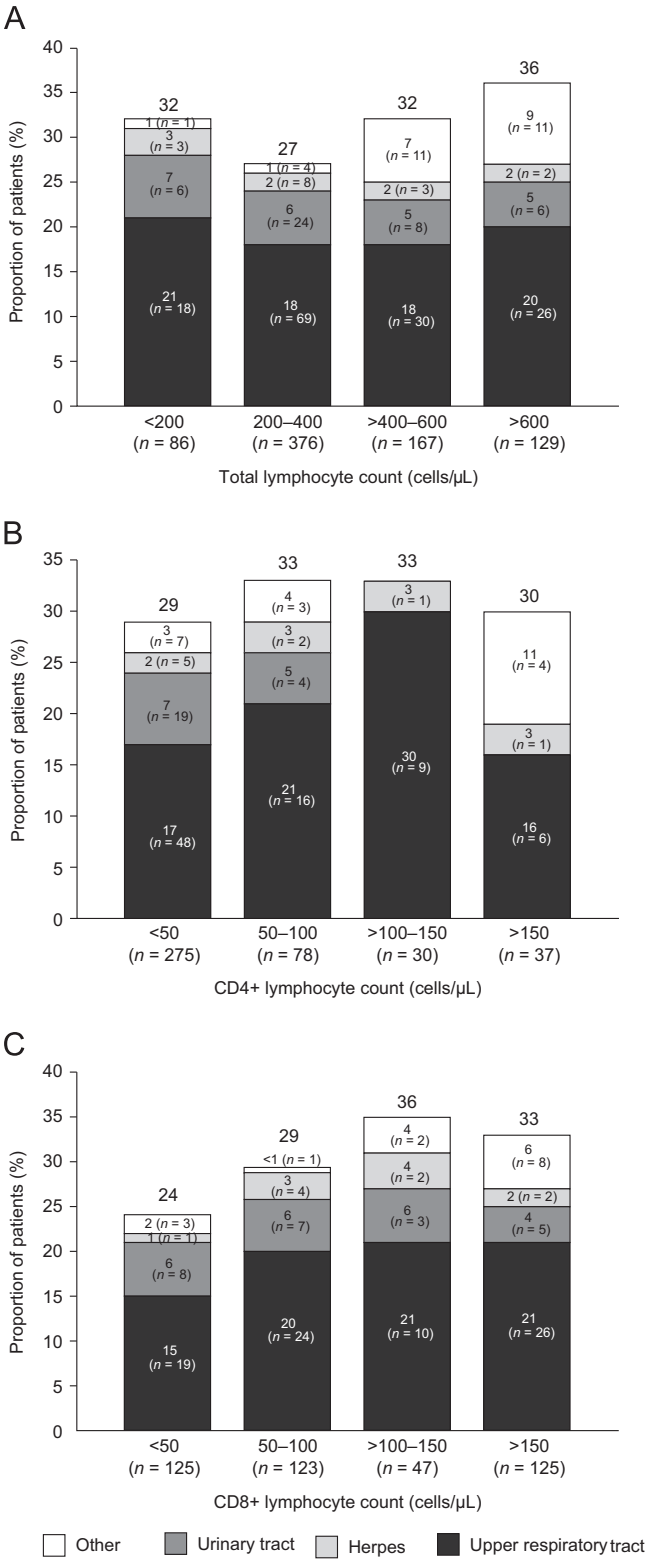


Fig. 7 Infection incidence by (A) total lymphocyte count category, (B) CD4+ lymphocyte count, and (C) CD8+ lymphocyte count in the fingolimod group. Data are for the fingolimod 0.5 mg group only. In patients with <200, 200-400, >400-600, and >600 lymphocytes/μL, the overall infection rates by total lymphocyte count were 33%, 28%, 31%, and 35%, respectively. Infection rates by CD4+ count were 29%, 32%, 33%, and 30%, respectively. Infection rates by CD8+ count were 25%, 29%, 36%, and 33%, respectively.

explanation may be that the FSS measures the effects of fatigue on daily living, as opposed to just presence or absence of fatigue.

Despite the increased incidence of reported AEs among patients switching to oral fingolimod, the TSQM results indicated that patients were significantly more satisfied with side effects associated with fingolimod than with those of iDMTs. This suggests that AEs with fingolimod are generally well tolerated. This is an important observation as poor tolerability has been identified as a common source of treatment non-adherence among patients with MS (Treadaway et al., 2009a), and non-adherence is associated with an increased risk of relapse (Tan et al., 2011). Furthermore, there are several reasons why patients, with physician support, switch DMTs, including lack of efficacy (La Mantia, 2010, Nikfar, 2010, Oliver, 2011, Qizilbash, 2012, Rice, 2001), convenience (avoiding both the need for frequent self-administered injections over the long term and needle aversion), and tolerability (avoiding injection-site-related side effects) (Brandes, 2009, Treadaway, 2009b). For example, in a survey that looked at adherence to iDMTs in patients with MS, 32% of individuals gave injection-related reasons (tired of taking shots, pain at injection site, and injection anxiety) for not adhering to their treatment schedule (Bayas, 2013). In line with these findings, a retrospective observational claims database study found that patients on fingolimod were more adherent and stayed on their treatment longer than those on an iDMT (Agashivala and Kim, 2012).

As with any open-label study, EPOC study results should be interpreted with caution. In particular it should be noted that patients desired a change in therapy. This limitation is minimized, to some extent, by the inclusion of the control iDMT arm for objective comparison, in which approximately 10% of patients switched to another iDMT. The efficacy benefits of fingolimod over both placebo or IFNβ-1a IM have been established previously in double-blind clinical studies (Cohen Ja et al., 2010b, Kappos et al., 2010), and the open-label study design employed in the EPOC study is useful in assessing the patient-reported outcomes that might be expected in real-world clinical practice.

5. Conclusion

The findings from the open-label, phase 4 EPOC study demonstrate that, in those patients desiring a change in therapy from iDMT, patient satisfaction is superior in those who changed to fingolimod compared with in those who continued on an iDMT. The ongoing, non-interventional PANGAEA and PEARL studies (Ziemssen et al., 2013) aim to evaluate patient satisfaction of fingolimod versus IFNβ and GA over a longer period of time.

Conflict of interest

Edward Fox has received consultancy fees, honoraria, travel, and research support from Acorda Therapeutics, Bayer, Biogen Idec, Eli Lilly, EMD Serono, Genzyme, GlaxoSmithKline, Novartis, Ono, Opexa Therapeutics, Roche, Sanofi, and Teva Neuroscience.

Keith Edwards has received financial compensation from Biogen Idec, Novartis Pharmaceuticals Corporation, and Genzyme for serving on their scientific advisory boards, as well as from Acorda, Biogen Idec, EMD Serono, Genzyme, and Novartis Pharmaceuticals Corporation for serving as a speaker. He has received financial support for research activities from Acorda, Actelion, Biogen Idec, Eli Lilly, EMD Serono, Genzyme, Janssen, Novartis Pharmaceuticals Corporation, and Sanofi.

J. Gordon Burch has no relationships or financial issues that are related to the trial.

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Edward Kim is an employee of Novartis Pharmaceuticals Corporation.

Linda Pestreich was an employee of Novartis Pharmaceuticals Corporation at the time of manuscript preparation.

Kevin McCague is an employee of Novartis Pharmaceuticals Corporation.

Luigi Barbato is an employee of Novartis Pharmaceuticals Corporation.

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Appendix A. Supplementary material

Supplementary data associated with this paper can be found in the online version at http://dx.doi.org/10.1016/j.msard.2014.06.005.

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