

Effectiveness of delayed-release dimethyl fumarate on patient-reported outcomes and clinical measures in patients with relapsing–remitting multiple sclerosis in a real-world clinical setting: PROTEC

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Abstract

Background: Patient-reported outcomes (PRO) and clinical outcomes give a broad assessment of relapsing–remitting multiple sclerosis (RRMS) disease.

Objective: The aim is to evaluate the effectiveness of delayed-release dimethyl fumarate (DMF) on disease activity and PROs in patients with RRMS in the clinic.

Methods: PROTEC, a phase 4, open-label, 12-month observational study, assessed annualized relapse rate (ARR), proportion of patients relapsed, and changes in PROs. Newly diagnosed and early MS (≤ 3.5 EDSS and ≤ 1 relapse in the prior year) patient subgroups were evaluated.

Results: Unadjusted ARR at 12 months post-DMF versus 12 months before DMF initiation was 75% lower (0.161 vs. 0.643, $p < 0.0001$) overall ($n = 1105$) and 84%, 77%, and 71% lower in newly diagnosed, ≤ 3.5 EDSS, and ≤ 1 relapse subgroups, respectively. Overall, 88% of patients were relapse-free 12 months after DMF initiation (84%, newly diagnosed; 88%, ≤ 3.5 EDSS; 88%, ≤ 1 relapse). PRO measures for fatigue, treatment satisfaction, daily living, and work improved significantly over 12 months of DMF versus baseline.

Conclusion: At 12 months after versus 12 months before DMF initiation, ARR was significantly lower, the majority of patients were relapse-free, and multiple PRO measures showed improvement (overall and for subgroups), suggesting that DMF is effective based on clinical outcomes and from a patient perspective.

Clinical trial: A Study Evaluating the Effectiveness of Tecfidera (Dimethyl Fumarate) on Multiple Sclerosis (MS) Disease Activity and Patient-Reported Outcomes (PROTEC), NCT01930708, <https://clinicaltrials.gov/ct2/show/NCT01930708>.

Keywords: Dimethyl fumarate, multiple sclerosis, relapsing–remitting, patient-reported outcome measures, quality of life, treatment outcomes, activities of daily living

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Introduction

The debilitating character of multiple sclerosis (MS) makes the assessment of quality of life (QoL) and patient-reported outcomes (PROs) very important to the patient, their families, and healthcare providers. PROs are valuable tools for assessing disease states

and the effects of treatments from the patients' perspective, allowing direct feedback on their well-being and the impact of treatment on their health. PROs can provide a broader overall assessment of MS disease state and progression than clinical and

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neurological outcome measures such as annualized relapse rate (ARR).^{1,2}

Delayed-release dimethyl fumarate (DMF) is approved as an oral treatment for relapsing and relapsing–remitting MS (RRMS).^{3–5} As of 30 June 2019, >415,000 patients have been treated with DMF, representing >780,000 patient-years of exposure; ~6335 patients (14,065 patient-years) were from clinical trials (Biogen data on file). DMF demonstrated sustained efficacy on clinical and neuroradiological measures, and a favorable benefit-risk profile, in patients with RRMS in two phase 3 studies, DEFINE (NCT00420212) and CONFIRM (NCT00451451), and a phase 4 long-term extension study ENDORSE (NCT00835770).^{6–8} PROs were significantly improved with DMF treatment versus placebo between integrated analysis of DEFINE and CONFIRM, measured by EuroQol 5-Dimensions visual analogue scale (EQ-5D VAS) and 36-Item Short Form Health Survey,⁹ not measured in a clinical setting. Patients with RRMS receiving DMF experienced increased work productivity and health-related QoL (HRQoL), measured by the EuroQol-5D (EQ-5D), versus patients receiving beta interferons or glatiramer acetate.¹⁰

Patients with RRMS have better long-term outcomes when treated early with therapy controlling disease activity.¹¹ In post hoc analyses, efficacy in patients with early MS, including newly diagnosed patients, was consistent with the overall study populations.^{8,12}

This analysis presents the primary outcome results from PROTEC (NCT01930708), a 12-month observational study that evaluated DMF's effectiveness on disease activity and PROs in patients with RRMS in a real-world clinical setting. An exploratory endpoint subgroup analysis evaluated DMF's effectiveness in newly diagnosed and other patients with early MS in PROTEC.

Materials and methods

Study design

PROTEC was a phase 4, open-label, single-arm, observational, multicenter study conducted in Europe and Canada from October 2013 to March 2016. Patients received the approved dosage of DMF orally, 120 mg twice daily during the first week and 240 mg twice daily thereafter. Relapses, Expanded Disability Status Scale (EDSS), and adverse events (AEs) were evaluated at scheduled and unscheduled visits. PROs were assessed at

clinic visits scheduled at Baseline, 3, 6, and 12 months after DMF treatment initiation. The EDSS scores¹³ ranged from 0.0 (normal) to 10.0 (death due to MS). Patients were assessed for relapses over the 12 months prior to DMF initiation.

Patients

Patient eligibility criteria included: age ≥ 18 years, diagnosis of RRMS, and no prior treatment with DMF or second-line MS therapies (e.g. natalizumab, fingolimod, alemtuzumab). Exclusion criteria included pregnancy or risk of pregnancy (unless approved by Investigator), currently receiving other RRMS therapies (e.g. interferon- β , glatiramer acetate, or teriflunomide), hypersensitivity to DMF active component, or current enrollment in other clinical trials, other than Pregnancy Exposure Registry or other non-conflicting studies. Patients discontinued DMF if their lymphocyte counts were $< 0.5 \times 10^9/l$ for 24 weeks.

Primary and secondary endpoints

The primary endpoint reported ARR 12 months after DMF treatment in patients with RRMS. The secondary endpoints evaluated mean changes in PRO scores from Baseline over 12 months; proportion of patients with confirmed 24-week EDSS progression at 12 months after enrollment; ARR over 12 months before enrollment and at 12 months after enrollment; proportion of patients relapsed at 12 months after enrollment; proportion of patients with relapses associated with intravenous steroid use; and proportion of patients who report taking the prescribed DMF dose, overall percent adherence, and reasons for not taking full dose over a 12-month period. Additional outcomes included association between health care resource utilization and disease activity with PROs over a 12-month period, and association between patient-reported adherence and PROs over a 12-month period.

Patient-reported outcomes

For assessment of DMF impact on PROs, patients completed the following instruments (language translated). The PRIMUS-Activity Limitations questionnaire was not completed in Portugal due to lack of available local translation. The Multiple Sclerosis Impact Scale (MSIS-29) measures the physical (20 items) and psychological (nine items) impact of MS on the patient's previous 2-week day-to-day life.^{14,15} The Modified Fatigue Impact Scale 5-Item (MFIS-5) consisted of five items describing how fatigue affected a person.¹⁶ Treatment Satisfaction Questionnaire for Medication 14-item (TSQM-14) measures the patient's level of satisfaction/dissatisfaction with

medication (14 items);¹⁷ only patients with previous treatment were assessed for TSQM-14. EuroQol5D 5 level version (EQ-5D-5L) included two components: the EQ-5D, a descriptive system of the patient's health state profile in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and the EQ-5D VAS, a quantitative measure in which patients described their health on that day on a scale from 0 to 100.¹⁸ For each patient, EQ-5D scores were derived based on value sets for England.¹⁸ Patient-reported Indices for Multiple Sclerosis activity limitations (PRIMUS-Activity Limitations) assessed the patient's ability to perform various activities of daily living during the previous week without the use of aids (e.g. cane, walker, or wheelchair) or assistance (15 items).^{19,20} Work Productivity and Activity Impairment Multiple Sclerosis Version (WPAI-MS) assessed employment status and, during the previous 7 days, hours worked (if employed), hours of missed work due to MS or other reasons, effect on productivity due to MS while working, and activity impairment attributable to health problems (six items);²¹ WPAI-MS scores are only reported for patients who were employed at the time of PRO administration. Beck Depression Inventory-Fast Screen (BDI-Fast Screen) evaluated depression in patients with medical illness during the prior 2 weeks (seven items).²²

Early MS subgroups

Three early MS subgroups were pre-specified in the statistical analysis plan as an exploratory endpoint: (a) Newly diagnosed: diagnosed with MS ≤ 1 year before study entry, naive to approved MS therapies; (b) EDSS:²³ baseline EDSS score ≤ 3.5 ; and (c) Relapse: ≤ 1 relapse in the prior year.

Statistical analysis

An MS relapse was defined as new or recurrent neurological symptoms not associated with fever or infection, lasting ≥ 24 hours, accompanied by new objective neurological findings upon examination by the Investigator, followed by 30 days of stability or improvement (new or recurrent neurological symptoms that occurred < 30 days following the onset of a protocol-defined relapse were considered part of the same relapse). ARR was calculated as the total number of relapses in a period divided by the total patient-years of exposure in that period. The primary analyses for ARR, proportion of relapse, and PROs were conducted in the primary analysis population, comprising all eligible subjects, who provided signed informed consent, enrolled, and took ≥ 1 dose of DMF. Ninety-five percent confidence intervals (CIs) of unadjusted ARR and rate ratio were

estimated based on robust standard errors derived from an unadjusted Poisson regression model using the generalized estimating equation method. The proportion of patients relapsed from Baseline to 12 months was estimated using the Kaplan–Meier method based on time-to-first-relapse survival distribution. If patients did not experience a relapse prior to DMF discontinuation, they were censored on the last date known to be in the study. Mean and median change in PROs from Baseline to 12 months was assessed using a Wilcoxon signed-rank test; only patients with no missing data were included in the tabulation. The frequency of patients with non-missing data at each time point was presented. In general, if there was $< 15\%$ of missing data at any time point, data for that specific endpoint were imputed and the primary analyses were based on patients with non-missing data. If there was $> 15\%$ missing data at any time point, analysis was based on a mixed-effects model.

The estimated proportion of patients with 24-week confirmed disability progression was based on the Kaplan–Meier product limit method, up to 52 weeks. Confirmed EDSS disability progression was defined as ≥ 1.0 point increase in EDSS from a baseline EDSS ≥ 1.0 , or ≥ 1.5 point increase from a baseline EDSS of 0, or ≥ 0.5 point increase from a baseline EDSS ≥ 6 and confirmed at 6 months (154 days) after initial progression. Progression could start at a scheduled assessment or relapse assessment during the treatment period but could be confirmed during either the treatment and/or follow-up 24-week period. EDSS assessments during relapse assessments were not used for confirmation. Patients were censored at the earliest of the last EDSS assessment date during the treatment period or the last dose of DMF if they did not have progression.

Analysis methods for the subgroups are consistent with the primary analysis. For the association between change from baseline of the PROs and resource utilization (visit with neurologist: Yes/No) and treatment adherence ($\geq 80\%$ vs. $< 80\%$), mixed-model repeated measures method was adjusted for baseline PRO values, baseline EDSS (≤ 3.5 vs. > 3.5), visit and visit by the factor of interest interaction term in the model. All analyses were performed using SAS[®] v9.2 or higher (SAS Institute, Cary, NC, USA).

Standard protocol approvals, registrations, and patient consents

The study was approved by central and local ethics committees and conducted in accordance with

International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Results

Patients

A total of 1105 (1114 enrolled) patients were included in the primary analysis population (Figure 1). Most baseline characteristics were similar to the phase 3 pivotal studies;^{6,7} however, there were notable differences for PROTEC (Table 1) versus the combined DEFINE/CONFIRM populations²⁴ for relapses in the year before study enrollment (0.6 vs. 1.3) and percentage of patients with any prior MS medication (77% vs. 48%). Median (min, max) duration of DMF treatment was 12.0 (0.03, 16.3) months; the majority of patients (941/1106, 85%) remained on DMF treatment for >9 months. Mean (SD) overall adherence (weeks with full prescribed dose taken divided by the total 0 weeks during follow-up) was 80 (21%); 16% of patients did not take the full prescribed dose during the study due to side effects.

ARR

Unadjusted ARR at 12 months after DMF treatment initiation was 75% lower than for 12 months before DMF initiation (0.161 vs. 0.643, $p < 0.0001$; Figure 2); and 88% of patients were relapse-free 12 months after DMF initiation versus 48% at 12 months before DMF initiation. A total of 710 relapses were experienced in 579 patients in the 12 months prior to initiating DMF, versus 155 relapses in 135 patients in the 12 months after treatment with DMF. Based on Kaplan–Meier estimates, 88% of patients were relapse-free 12 months after DMF

initiation. At 1 year following DMF initiation, 21 (1.9%) patients had 24-week confirmed disease progression prevalence; the cumulative incidence estimated proportion was 2.2% by Kaplan–Meier analysis. Among patients who experienced a relapse requiring IV steroid therapy, 97 (9%) experienced one, 11 (1%) experienced two, and one (< 0.1%) experienced three relapses. Median (min, max) EDSS scores showed minor improvements from Baseline, 2.0 (0.0, 7.0), to Month 12, 1.5 (0.0, 7.0), $p = 0.0136$.

PROs

A total of 84% of patients treated with DMF completed the 12-month follow-up period. Overall, patients generally demonstrated improvement across several PRO measures compared with baseline (Table 2). For MSIS-29, measuring the physical and psychological impact of MS of the patient’s day-to-day life, there was significant improvement in mean (SD) scores between Baseline and Month 12 for physical: 22.8 (21.5) versus 18.3 (19.8), and psychological: 34.8 (23.7) versus 25.6 (22.2), $p < 0.0001$ for both comparisons. For MFIS-5, assessing the effects of fatigue on physical, cognitive, and psychosocial functioning, there was significant improvement in mean (SD) scores between Baseline and Month 12, 8.2 (5.0) versus 6.2 (5.1), $p < 0.0001$. Similarly, mean (SD) scores between Baseline and Month 12 scores in several WPAI measures improved, measuring impairment in work and activities due to MS: overall work impairment in the past 7 days, 23.7 (27.1) versus 19.1 (24.7), $p = 0.0081$; activity impairment in the past 7 days, 28.5 (27.8) versus 22.8 (26.0), $p < 0.0001$.

Other PRO measures showed small but significant functional differences in scores. TSQM-14 scores (patient satisfaction with their current medication)

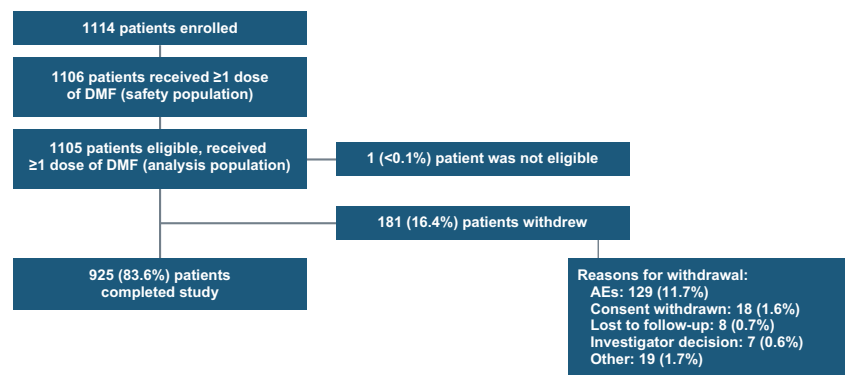


Figure 1. Patient disposition for the PROTEC study is shown. AE: adverse events, DMF: delayed-release DMF.

Table 1. Patient baseline characteristics.

Characteristic	Total N = 1105	Newly diagnosed n = 184	EDSS \leq 3.5 n = 978	Relapse \leq 1 n = 993
Mean (SD) age, y	38.8 \pm 10.0	35 (10)	38 (10)	39 (10)
Age category, y, n (%)				
18–19	17 (2)	6 (3)	16 (2)	14 (1)
20–29	202 (18)	63 (34)	199 (20)	164 (17)
30–39	367 (33)	60 (33)	338 (35)	329 (33)
40–49	363 (33)	39 (21)	311 (32)	338 (34)
50–59	124 (11)	13 (7)	93 (10)	118 (12)
\geq 60	32 (3)	3 (2)	21 (2)	30 (3)
Female, n (%)	805 (72)	116 (63)	704 (72)	718 (72)
Relapses in year before study enrolment, mean (SD)	0.6 (0.7)	1.1 (0.7)	0.6 (0.7)	0.5 (0.5)
Time since most recent pre-study relapse, mean (SD), y ^a	4.7 (3.3)	4.1 (3.0)	4.8 (3.3)	5.1 (3.4)
Time since diagnosis of MS, mean (SD), y	6.6 (6.1)	0.4 (0.5)	6.0 (5.5)	6.9 (6.1)
EDSS score, median (range)	2.0 (0, 7.0)	1.6 (0, 6.5)	1.6 (0, 3.5)	2.0 (0.7)
Patients with any prior MS disease-modifying therapy n (%) ^{b,c}	828 (75)	2 (1)	722 (74)	763 (77)
Interferon beta-1a	499 (45)	0 (0)	442 (46)	460 (45)
Glatiramer acetate	318 (28)	0 (0)	276 (29)	293 (29)
Interferon beta-1b	175 (16)	0 (0)	139 (15)	157 (15)
Median (min, max) time since last MS disease- modifying therapy discontinuation, mo	0.57 (0.03, 363.2)			
Reason for prior MS treatment discontinuation, n (%) ^d				
Tolerability	556 (50)	0 (0)	495 (52)	519 (51)
Efficacy reasons	335 (30)	0 (0)	266 (28)	291 (29)
Safety	58 (5)	1 (50)	50 (5)	53 (5)
Other	167 (15)	1 (50)	145 (15)	156 (15)

Total are patients in the primary analysis population.

EDSS: Expanded Disability Status Scale; values represent mean (SD) unless stated otherwise.

Race was not reported in 1001 patients due to confidentiality reasons implemented during the study.

^aBased on data from 583 patients.

^bOnly MS therapies taken before the first dose date of DMF initiation were included; patients may have received >1 therapy for MS.

^cMedications previously taken by >10% of patients are shown. Other medications taken by >1% of patients include azathioprine, interferon beta, interferon, and teriflunomide.

^dIf patients have >1 discontinuation reason for same MS therapy, only the last reason was used.

improved significantly between Baseline and Month 12 for the global score and its components: TSQM-14 global score, 51.4 (22.5) versus 73.6 (21.0); effectiveness, 54.3 (21.7) versus 70.1 (24.7); side effects, 60.1 (30.6) versus 85.4 (19.4); convenience, 52.4 (21.2) versus 85.5 (17.2), $p < 0.0001$ for all comparisons. There were significant improvements from Baseline to Month 12 for EQ-5D, 0.8 (0.2) versus 0.9 (0.2); EQ-5D VAS, 74.1 (18.7) versus 79 (17.5); and BDI-FAST, assessing depressive symptoms, 2.8 (3.2) versus 1.9 (3.0), $p < 0.0001$ for all comparisons.

PRIMUS-Activity Limitations scores remained stable between Baseline and Month 12, mean (SD)

3.1 (4.6) at Baseline versus 2.6 (4.3) at Month 12, suggesting no significant change in patients' ability to perform various activities of daily living without aids or assistance. There was no evidence of change in PRO scores between Baseline and Month 12 for patients who visited a neurologist and those who did not. Similarly, there was no evidence of a change in PRO scores between Baseline and Month 12 patients with < 80% adherence versus \geq 80% adherence.

Early MS and other subgroups: Relapses and PRO

The effectiveness of DMF in newly diagnosed patients and different levels of disability was analyzed by dividing the population into subgroups. Among the patients who received \geq 1

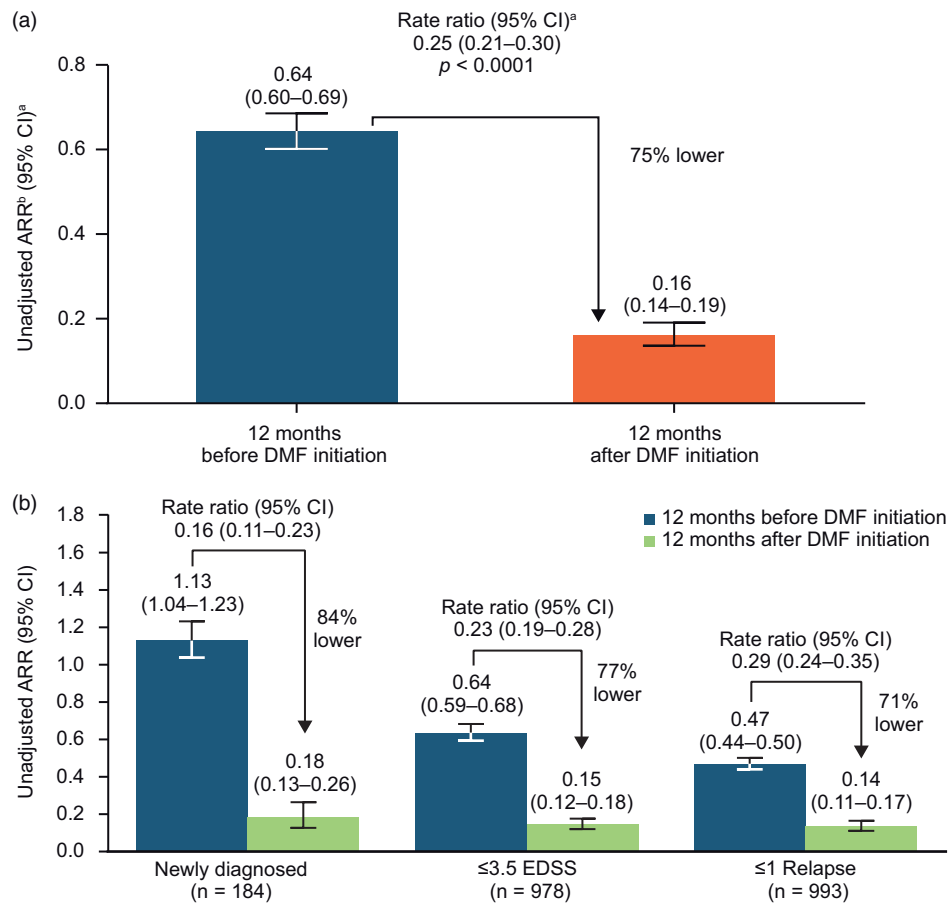


Figure 2. ARR at 12 months before and after DMF initiation for (A) all patients and (B) early MS subgroups.

^aBased on empirical (robust) SE from a generalized estimating equation using an unadjusted Poisson regression model.
^bARR was calculated as the total number of relapses that occurred during that period of time for all patients, divided by the total number of patient-years followed in that period.

Subgroups are defined as: EDSS = baseline EDSS score ≤ 3.5 ; Relapse = ≤ 1 relapse in the prior year.
DMF: delayed-release DMF.

dose of DMF, 184 were newly diagnosed, 978 in the EDSS ≤ 3.5 subgroup, and 993 in the ≤ 1 relapse subgroup. Similar to the overall population, ARR at 12 months after DMF initiation was 84% lower than ARR estimated for the 12 months before DMF initiation in newly diagnosed patients, 77% in the EDSS ≤ 3.5 subgroup, and 71% in the ≤ 1 relapse subgroups, $p < 0.0001$ for all subgroup (Figure 2(b)). Based on Kaplan–Meier estimates, the percentages of patients relapse-free 12 months after DMF initiation were 84.2% for newly diagnosed patients, 87.7% in the EDSS ≤ 3.5 subgroup, and 88.4% in the ≤ 1 relapse subgroup.

Significant improvements in scores from baseline to 12 months were observed across all early MS

subgroups for MSIS-29, MFIS-5, EQ-5D, and EQ-5D VAS (Table 3).

Safety

Overall, 914 (83%) patients experienced an AE; serious AEs occurred in 41 (4%) patients (Table 4). One death occurred due to an accident, deemed unrelated to DMF treatment. A total of 126 (11%) patients discontinued DMF treatment due to AEs. The most common treatment-related AEs leading to DMF discontinuation ($\geq 1\%$ of patients) were abdominal pain (2%), diarrhea (1%), and vomiting (2%).

No cases of progressive multifocal leukoencephalopathy were reported. Mean absolute lymphocyte counts at 12 months ($1.26 \times 10^9/l$) remained above

Table 2. Mean change in PROs from baseline to 12 months.

Measure	Description	Component	Mean (SD) change from baseline to Month 12			p-value
			Improved	Stable	Worsened	
MSIS-29 ^a	20 items assess physical impact of MS in terms of mobility and self-care	Physical impact <i>n</i> = 868	+			<0.0001
			-3.0 (14.1)			
	9 items assess psychological impact of MS	Psychological impact <i>n</i> = 860	+			<0.0001
			-8.0 (18.6)			
MFIS-5 ^b	5 items assess how fatigue impacts patients' lives	<i>n</i> = 867	+			<0.0001
			-1.7 (3.8)			
TSQM-14 ^c	14 items assess patient treatment satisfaction	Effectiveness <i>n</i> = 492	+			<0.0001
			14.4 (29.5)			
		Side effects <i>n</i> = 500	+			<0.0001
			25.4 (31.4)			
		Convenience <i>n</i> = 505	+			<0.0001
			33.4 (25.7)			
		Global score <i>n</i> = 511	+			<0.0001
			21.8 (26.9)			
EQ-5D-5L ^d	5 items assess mobility, self-care, usual activities, pain and discomfort, anxiety and depression	EQ-5D <i>n</i> = 792	+			<0.0001
			0.02 (0.1)			
		EQ-5D VAS <i>n</i> = 803	+			<0.0001
			3.7 (15.9)			
PRIMUS activity limitations ^e	15 items assess activities of daily living	<i>n</i> = 545		±		0.2134
				-0.14 (3.2)		
WPAI-MS ^f	6 items assess the number of work hours missed, impact on productivity, and daily activities during past 7 days	Work impairment ^f <i>n</i> = 327	+			0.008
			-2.2 (19.5)			
		Activity impairment <i>n</i> = 851	+			<0.0001
			-4.2 (22.3)			
BDI-Fast Screen ^g	7 items assess depression during the past 2 weeks	<i>n</i> = 854	+			<0.0001
			-0.8 (2.5)			
EDSS ^h	Assesses disease progression	<i>n</i> = 940		±		0.0136
				-0.05 (0.65)		

BDI-Fast Screen: Beck Depression Inventory-Fast Screen; EDSS: Expanded Disability Status Scale; EQ-5D-5L: EuroQol-5D 5-level version; MFIS-5: Modified Fatigue Impact Scale 5-item version; MSIS-29, Multiple Sclerosis Impact Scale; PRIMUS: Patient-Reported Indices for Multiple Sclerosis; PRO: patient-reported outcome; TSQM-14: Treatment Satisfaction Questionnaire for Medication; WPAI-MS: Work Productivity and Activity Impairment for Multiple Sclerosis.

Mean change in PROs from baseline to 12 months was assessed using a Wilcoxon signed-rank test.

^aLower score indicates better outcome; range, 0–100 (scores were transformed).

^bLower score indicates improved functioning; range, 0–20.

^cHigher score indicates greater satisfaction; range, 0–100; only patients with previous treatment were assessed.

^dHigher score indicates better health; range, 0–100.

^eHigher score indicates better outcome; range, 0–30.

^fHigher score indicates higher impairment and lower productivity; scores are only reported for patients who were employed at the time of PRO administration.

^gLower score indicates less severe depressive symptoms; range, 0–21.

^hLower score indicates less severe disability symptoms; range, 0–10.

Table 3. Change in PROs from baseline to 12 months in early MS subgroups.

Measure	Description	Component	Newly diagnosed (n = 184)	EDSS ≤3.5 (n = 978)	Relapse ≤1 (n = 993)
MSIS-29 ^a	20 items assess physical impact of MS in terms of mobility and self-care	Physical impact	+ −3.1 (14.8)	+ −2.7 (13.4)	+ −3.2 (14.2)
	9 items assess psychological impact of MS	Psychological impact	+ −9.1 (16.9)	+ −8.0 (18.2)	+ −8.1 (18.5)
MFIS-5 ^b	5 items assess how fatigue impacts patients' lives		+ −1.6 (3.5)	+ −1.7 (3.7)	+ −1.7 (3.8)
EQ-5D VAS ^c	5 items assess mobility, self-care, usual activities, pain and discomfort, anxiety and depression		+ 4.1 (13.7)	+ 3.6 (15.1)	+ 3.7 (15.9)

EDSS: Expanded Disability Status Scale; EQ-5D VAS: EQ-5D visual analogue scale; MFIS-5: Modified Fatigue Impact Scale 5-item version; MSIS-29: Multiple Sclerosis Impact Scale; PRO: patient-reported outcome.
+ = Statistically significant improvement; ± = no statistically significant change; − = statistically significant worsening.
^aLower score indicates better outcome; range, 0–100 (scores were transformed).
^bLower score indicates improved functioning; range, 0–20.
^cHigher score indicates better health; range, 0–100.

Table 4. Summary of adverse events.

AE, n (%)	Total n = 1106
Any AE	914 (83)
Most common AEs in ≥10% patients	
Flushing	477 (43)
Diarrhea	172 (16)
Abdominal pain upper	120 (11)
Abdominal pain	115 (10)
Any SAE	41 (4)
Most frequently occurring SAEs in ≥2 patients	
Fall	4 (<1)
Lymphopenia	3 (<1)
Breast cancer	2 (<1)
MS relapse	2 (<1)

AE: adverse event; SAE: serious adverse event.

the lower limit of normal ($0.91 \times 10^9/l$) (Table 5), consistent with trial data.^{6,7} Of the 400 patients with ≥2 post-baseline lymphocyte assessments, 44 (11%) had moderate, persistent lymphopenia (≥2 consecutive lymphocyte levels of $<0.8 \times 10^9/l$ 180 days apart), and four (1%) had severe, persistent lymphopenia (two consecutive lymphocyte levels of $<0.5 \times 10^9/l$ 180 days apart).

Discussion

The results reported are consistent with DMF effectiveness data from other real-world phase 4 studies (RESPOND; NCT01903291),²⁵ supporting the findings from phase 3 studies of DMF.^{6,7} Unadjusted ARR at 12 months after DMF treatment initiation was significantly lower compared with 12 months before DMF initiation. The majority of patients were relapse-free 12 months after DMF initiation. Safety and tolerability were consistent with the known safety profile of DMF.^{3,4,6,7,24} Lymphocyte counts were similar to those reported in pivotal clinical trials and clinical practice.^{6,7,26–28} Statistically significant improvements from baseline to 12 months were observed for the majority of PROs, indicating that DMF is an effective MS treatment from a patient perspective as well as based on classical clinical outcomes.

Clinical significance of PROs scores

In patients with MS and other chronic diseases, a widely used threshold for discrimination of meaningful change in HRQoL is 1/2 SD change in PRO score over 1 year.²⁹ In a population of patients with RRMS, a ≥7.50 point worsening was determined to be a practical threshold for identifying a clinically significant change in the physical impact of MS using the MSIS-29 physical score.³⁰ The threshold

Table 5. Lower lymphocyte counts.

	Total
Mean (SD) lymphocyte counts, $\times 10^9/l$	1.26 (0.55)
Baseline, $n = 1038$	1.93 (0.61)
Month 12, $n = 897$	1.26 (0.55)
0.8 – <0.91 (LLN), n/N (%) ^a	69/831 (8)
0.5 – <0.8, n/N (%) ^a	133/831 (16)
<0.5, n/N (%) ^a	17/831 (2)
Patients with ≥ 2 post-baseline lymphocyte assessments, n	400
Moderate, persistent lymphopenia ^b , n	44
Severe, persistent lymphopenia ^c , n	4

ALC: absolute lymphocyte count; LLN: lower limit of normal.
^aFor patients with at least 1 baseline assessment >LLN.
^bALC of at least 2 consecutive lymphocyte levels of $<0.8 \times 10^9/L$ 180 days apart.
^cALC of at least 2 consecutive lymphocyte levels of $<0.5 \times 10^9/L$ 180 days apart.

for worsening was defined as < -0.074 points for EQ-5D³¹ and < -5.5 points for EQ-5D VAS,³² although these thresholds were not calculated in patients with MS. In this analysis, the mean change was -3.0 for MSIS-29 physical score, 0.02 for EQ-5D, and 3.7 for EQ-5D VAS: statistically significant, although they may not be meaningful clinical changes based on criteria described in previous studies. By the 1/2 SD rule, MFIS-5 (mean -1.7 ; SD 3.8), TSQM-14 side effects, TSQM-14 convenience, and TSQM-14 global score reached clinically significant change.

Early MS treatment has been associated with a reduction in disease progression.^{33,34} When considering the optimal treatment for reducing disease progression risk in patients with early MS, relapses, MRI lesions, disability progression, and brain volume loss are four key measures of disease activity.³⁵ For treatment-naïve patients, IFN- β , glatiramer acetate, teriflunomide, and DMF, followed by fingolimod, natalizumab, and alemtuzumab, have been suggested in patients with breakthrough disease activity.³⁵ ARR and PRO results for the newly diagnosed subgroup and the subgroups with EDSS ≤ 3.5 or relapse ≤ 1 in the prior year were similar to the overall group, indicating DMF is effective in a broad range of patients.

The results and interpretations are subject to several limitations common to real-world studies, including the observational nature of the study, short duration of follow-up time on DMF, and lack of active comparators. Potential bias arises due to regression to the mean because the majority of patients enrolled had previous experience with disease-modifying

therapies (DMTs) for MS. Therefore, familiarity to compliance with treatment and dosage requirements impact the generalizability of results for treatment-naïve or less adherent patients. Due to the real-world nature of the study, eligibility criteria did not restrict participation to patients with ≥ 1 relapse over the 12-month period prior to study entry, as in DEFINE and CONFIRM, rendering it possible that patients in this study had a less severe progression of MS at enrollment. Therefore, these patients may have exhibited lower risk possibly resulting in lower incidence of relapse over the study period, regardless of treatment. The study design may impede researchers dictating when PRO assessments are completed relative to relapses. PRO assessments obtained shortly after relapse have a greater risk of being affected by the relapse compared with PROs obtained with no recent relapse, although comparisons of PRO outcomes in patients with or without relapses during the study found either a marginal difference or no difference in the change from Baseline to Month 12. Missing data from patient-reported measures is a limitation of real-world studies; however, mitigating the risk of missing data impacting study results, the proportion of missing data was described and accounted for throughout the statistical analyses. Unfortunately, the influence of patients “not missing at random” may introduce bias in both the estimate and variance for which the sensitivity analysis cannot account. To minimize potential bias due to methods of data collection, case report forms were carefully designed, with clear instructions and training provided to site staff; furthermore, mitigations were carried out if data entry concerns were identified. Finally, the 11.7% of patients who discontinued due to AEs

may introduce possible confounding or bias in the QoL measures, given the symptomatic nature of some AEs and their impact of QoL outcomes.

Comparing treatment-satisfaction scores between previously discontinued drugs with treatment-satisfaction scores in drugs not discontinued for ≥ 12 months could be biased in favor of DMF purely because of patient selection. Sensitivity analyses were performed for primary and secondary endpoints using patient populations who completed the full study period (completer population), in order to evaluate potential effects of early study withdrawal on analytic results. Results were similar between the completer and analysis populations. Also, since the exclusions criteria were only based on last DMT, the assessment may be limited if patients were on multiple DMTs and omitting the type or strength of DMT.

Conclusions

Overall, the results suggest that DMF may offer an effective treatment option for patients with RRMS, both from a clinical perspective and based on patients' satisfaction with DMF treatment in relation to their personal quality of life, health status, and physical abilities.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. Requests for data supporting this manuscript should be submitted to the Biogen Clinical Data Request Portal (www.biogenclinicaldatarequest.com).

Conflict of interests

TB: consulting/speaker fees from Almirall, AOP Pharma, Biogen, Bionorica, Celgene, MedDay, Merck, Novartis, Roche, Sanofi/Genzyme, and Teva; his institution (Universitätsklinik für Neurologie) has received honoraria for study participation and unrestricted research grants from Alexion, Bayer, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme, and Teva; **BB:** advisory boards for Biogen, Genzyme, Merck-Serono, Novartis, and Roche; his institution (Groupe Hospitalier Pellegrin)


Hôpital Pellegrin) has received support for clinical trials and research activities from Actelion, Bayer HealthCare, Biogen, Genzyme, Merck Serono, MedDay, Novartis, Roche, and Teva; **LB:** received honoraria for speaking from Novartis and for traveling from Sanofi-Genzyme and Roche; she acted as an Advisory Board member of Sanofi-Genzyme and principal investigator in clinical trials for Roche; sub-investigator in clinical trial for Novartis, Biogen, Sanofi-Genzyme, Merck; **XM:** received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Bayer, Biogen, Celgene, Excemed, Genzyme, Merck, MSIF, NMSS, Novartis, Roche, Sanofi-Genzyme, and Teva Pharmaceutical; **PSG:** consulting/speaker fees from/advisory boards for Actelion, Allergan, Bayer, Biogen, EMD Serono, Merz, Novartis, Pendopharm, Roche, Sanofi-Genzyme, and Teva Neuroscience; research support from Biogen; consultant for NeuroRx Research; principal investigator/sub-investigator for clinical trials for Actelion, Alexion, Bayer HealthCare, Biogen, Elan, EMD Serono, GlaxoSmithKline, MedImmune, Novartis, Ono, Roche-Genentech, Sanofi-Aventis, and Teva Neuroscience; **AVS:** consultant for Biogen, Merck Serono, Novartis, and Sanofi-Genentech; fees from Roche and Boehringer Ingelheim; **RS** and **AB:** employees of and hold stock/stock options in Biogen

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