Long-term safety and efficacy of dimethyl fumarate for up to 13 years in patients with relapsing-remitting multiple sclerosis: Final ENDORSE study results

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Abstract

Background: Dimethyl fumarate (DMF) demonstrated favorable benefit–risk in relapsing-remitting multiple sclerosis (RRMS) patients in phase-III DEFINE and CONFIRM trials, and ENDORSE extension.

Objective: The main aim of this study is assessing DMF safety/efficacy up to 13 years in ENDORSE.

Methods: Randomized patients received DMF 240 mg twice daily or placebo (PBO; Years 0–2), then DMF (Years 3–10; continuous DMF/DMF or PBO/DMF); maximum follow-up (combined studies), 13 years.

Results: By January 2020, 1736 patients enrolled/dosed in ENDORSE (median follow-up 8.76 years (ENDORSE range: 0.04–10.98) in DEFINE/CONFIRM and ENDORSE); 52% treated in ENDORSE for ⩾6 years. Overall, 551 (32%) patients experienced serious adverse events (mostly multiple sclerosis (MS) relapse or fall; one progressive multifocal leukoencephalopathy); 243 (14%) discontinued treatment due to adverse events (4% gastrointestinal (GI) disorders). Rare opportunistic infections, malignancies, and serious herpes zoster occurred, irrespective of lymphocyte count. For DMF/DMF ($n = 501$), overall annualized relapse rate (ARR) remained low (0.143 (95% confidence interval (CI), 0.120–0.169)), while for PBO/DMF ($n = 249$), ARR decreased after initiating DMF and remained low throughout (ARR 0–2 years, 0.330 (95% CI, 0.266–0.408); overall ARR (ENDORSE, 0.151 (95% CI, 0.118–0.194)). Over 10 years, 72% DMF/DMF and 73% PBO/DMF had no 24-week confirmed disability worsening.

Conclusion: Sustained DMF safety/efficacy was observed in patients followed up to 13 years, supporting DMF's positive benefit/risk profile for long-term RRMS treatment.

Keywords: Delayed-release dimethyl fumarate, efficacy, multiple sclerosis, newly diagnosed, safety

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Long-term Safety and Efficacy of Dimethyl Fumarate for up to 13 Years in Patients with Relapsing-Remitting Multiple Sclerosis: Final ENDORSE Study Results

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Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, inflammatory disease typically diagnosed at age 20–40 years.[1] As MS is a heterogeneous disease of long duration, treatment goals include prevention of relapses and disability accumulation.[2,3] Initial disease-modifying therapy (DMT) is critical for preventing confirmed disease worsening (CDW) and maintenance of low relapse rates to meet these goals.

Delayed-release dimethyl fumarate (DMF) is approved worldwide for the treatment of relapsing MS. As of 31 December 2020, more than 500,000 patients have received DMF, representing more than

1,000,000 patient-years of exposure. DMF demonstrated sustained efficacy on clinical and radiological measures and a favorable benefit–risk profile in two phase-III studies, DEFINE (NCT00420212) and CONFIRM (NCT00451451), in patients with relapsing forms of remitting MS.[4,5] Real-world trial data have also been consistent with the favorable efficacy and safety profile of DMF demonstrated in phase-III trials, in addition to demonstrating improvements on patient-reported outcomes (PROs).[6,7]

ENDORSE (NCT00835770) is a completed extension study of DEFINE/CONFIRM, designed to evaluate long-term safety and efficacy of DMF in patients with relapsing-remitting multiple sclerosis (RRMS). The ENDORSE study details the longest clinical follow-up of DMF exposure to date. Patients followed in extension studies also represent an aging patient population that may be more generalizable for the real-world population.

We report clinical and radiological efficacy and safety outcomes in patients treated in DEFINE/CONFIRM and ENDORSE, including a subgroup analysis of newly diagnosed patients.

Methods

Patients
Patients entered ENDORSE[8] following completion of DEFINE[4] or CONFIRM.[5] Patient details were reported previously.[8] In this report, newly diagnosed patients were defined as those diagnosed with MS within 1 year before DEFINE/CONFIRM study entry who were naïve to DMT for MS.

Study design
ENDORSE[8] was an extension of DEFINE[4] and CONFIRM,[5] with a minimum of 10 years (480 weeks) of planned follow-up (2 years in DEFINE/CONFIRM, plus ⩾8 years in ENDORSE). Patients randomized in DEFINE/CONFIRM to DMF 240 mg twice daily (BID) or thrice daily (TID) continued on the same dose at the start of ENDORSE; patients randomized to placebo (PBO) or glatiramer acetate (CONFIRM only) were re-randomized 1:1 to DMF BID or TID. Following the 2013 market authorization of DMF, patients receiving DMF TID switched to DMF BID (approved dose) at next study visit. Details of ENDORSE were reported previously.[8] The study was approved by local or central 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.

Safety and hematology assessments
Patients who received at least one dose of DMF (BID or TID) in ENDORSE were included in the safety analysis (Figure 1). Adverse events (AEs) were collected throughout the study. Laboratory assessments included blood and urine samples at baseline (every 4 weeks until week 24, then every 12 weeks thereafter) and hematologic parameters, including absolute lymphocyte count (ALC) at baseline and every ⩾12 weeks thereafter. All ALC analyses utilized the integrated analysis of the DEFINE/CONFIRM/ENDORSE trials (Figure 1) and were based on first exposure to DMF. Rate of ALC reconstitution in patients discontinuing DMF was assessed by linear mixed-model analysis in the integrated data set stated above.

Efficacy assessments
Annualized relapse rate (ARR) was assessed for Years 0–2 (DEFINE/CONFIRM) and 3–10 (ENDORSE). Disease worsening was measured every 24 weeks on the Expanded Disability Status Scale (EDSS). Time to 24-week CDW was defined as a ⩾1.0-point increase from a baseline EDSS score ⩾1 confirmed for 24 weeks or a ⩾1.5-point increase from a baseline EDSS score of 0 confirmed for 24 weeks. An EDSS score of 4 has been used as a milestone marker for onset of ambulation impairment.[9,10] PROs were assessed using the 36-item Short Form Health Survey (SF-36) and EuroQoL 5-dimensions (EQ-5D) Health Survey quality-of-life questionnaire.

Patients who received DMF TID in DEFINE/CONFIRM/ENDORSE or glatiramer acetate in CONFIRM were excluded for this efficacy analysis due to the potential for confounding effects.

Stability of efficacy was assessed in DMF/DMF and PBO/DMF patients (Figure 1) who, in the first 2 years of DMF BID treatment, had no protocol-defined relapses (relapse stability) or no 24-week CDW (disability stability). Baseline was defined as 2 years of DMF treatment (Week 0 DMF/DMF; Week 96 PBO/DMF); follow-up was up to 10 years from baseline (Week 480 DMF/DMF; Week 576 PBO/DMF).

Compliance with therapy
Compliance with DMF was assessed utilizing pill counts at each study visit.
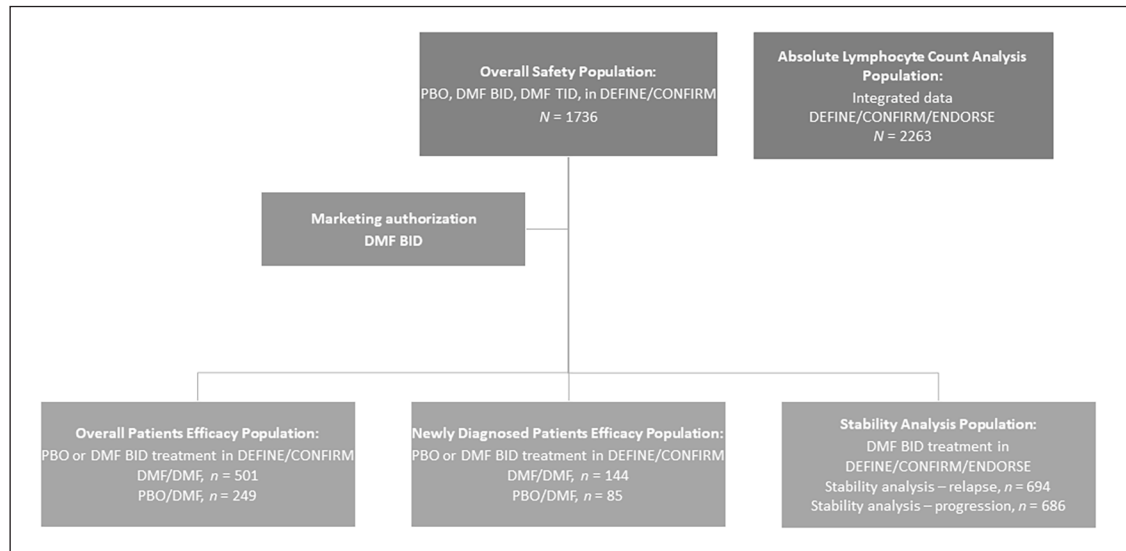
Figure 1. Patient populations for safety, efficacy, and lymphocyte analysis.
BID: twice daily; DMF: dimethyl fumarate; PBO: placebo.

Statistical analysis

Safety parameters were summarized using descriptive statistics; proportions of subjects developing lymphopenia relative to all DMF-treated subjects were shown. ALC was characterized using Common Terminology Criteria for Adverse Events: $<0.5 \times 10^9$/L (Grade 3 or 4, severe lymphopenia), ≥ 0.5 to $<0.8 \times 10^9$/L (Grade 2, moderate lymphopenia), and ≥ 0.8 to <0.91 (lower limit of normal (LLN)) $\times 10^9$/L (Grade 1, mild lymphopenia). In a linear mixed-effect model of post-DMF ALC reconstitution, patient groups were determined by the last ALC recorded at or before discontinuation. Median ALC at discontinuation was 0.75×10^9/L, and patients were grouped according to whether they had an ALC $\leq$ median ALC at discontinuation or >median ALC at discontinuation. Patients with ALC $< 0.91 \times 10^9$/L at DMF discontinuation and ≥ 1 post-DMF ALC value were included. Patients with $<0.5 \times 10^9$/L for ≥ 6 months were excluded.

ARR was defined as the total number of relapses divided by the number of patient-years in the study. Adjusted ARR was obtained from a negative binomial regression model adjusted for age, number of relapses in the year prior to study entry, baseline EDSS score, and region. The proportion of patients relapsed at 10 years and analysis of time to first relapse (TTFR) were based on the Kaplan–Meier product limit method.

For the stability analyses, descriptive statistics summarized relapse stability and ARR. Two-sample *t*-tests and chi-square tests compared ARR for those with/without stable outcomes. Restricted mean survival time estimated average TTFR, and time to first CDW for groups with and without stable outcomes.[11] Cox proportional hazards model assessed TTFR and time to first CDW. Poisson regression assessed the number of relapses, considering the follow-up length. Baseline variables in aforementioned models included 2-year stability since DMF initiation (stable vs unstable), patient group (DMF/DMF vs PBO/DMF), age, EDSS score, number of previous MS treatments 2 years prior to DMF initiation, region (US vs non-US), sex (female vs male), SF-36 physical component summary (PCS), SF-36 mental component summary (MCS), and visual function test (VFT) 2.5%.

For PROs, actual scores and change from baseline in SF-36 and EQ-5D were analyzed by an analysis of covariance (ANCOVA) model.

Results

Patients

Of 2079 patients who completed DEFINE/CONFIRM,[8] 1736 entered ENDORSE and received ≥ 1 dose of DMF (ENDORSE ITT and safety population; Figure 1). Overall, 501 patients were continuously treated DMF BID (DMF/DMF), and 249 patients received delayed DMF BID treatment (PBO/DMF). The newly diagnosed population comprised

Table 1. Baseline demographic and disease characteristics in ENDORSE.

Characteristic[a,b]	DMF/DMF[c] *n* = 501	PBO/DMF *n* = 249	Overall *N* = 1,736	Newly diagnosed *n* = 470
Age, years	39.8 (9.1)	39.9 (8.8)	39.8 (9.1)	38.0 (9.5)
Age < 40 years, *n* (%)	237 (47)	119 (48)	827 (48)	257 (55)
Female, *n* (%)	352 (70)	178 (71)	1,212 (70)	330 (70)
Race/ethnicity, *n* (%)				
White	162 (32)	82 (33)	594 (34)	138 (29)
Black or African American	4 (<1)	3 (1)	26 (1)	7 (1)
Asian	51 (10)	21 (8)	162 (9)	41 (9)
Other	21 (4)	8 (3)	56 (3)	22 (5)
Not reported	263 (52)	135 (54)	898 (52)	262 (56)
Time since first MS symptoms, years	10.0 (6.5)	10.1 (6.7)	9.6 (6.3)	6.1 (5.1)
Time since diagnosis of MS, years	6.9 (5.0)	6.8 (5.3)	6.7 (5.1)	2.4 (0.5)
Time on study, weeks	297.4 (139.5)	263.9 (157.0)	278.0 (152.3)	291 (149)
Time on treatment, weeks	287.1 (42.8)	251.4 (158.8)	267.4 (155.2)	280.5 (152.8)
EDSS score	2.42 (1.43)	2.58 (1.38)	2.49 (1.41)	2.04 (1.17)
Relapses in prior year (DEFINE/CONFIRM baseline)	1.3 (0.7)	1.3 (0.8)	1.3 (0.69)	1.4 (0.6)
EDSS score (DEFINE/CONFIRM baseline)	2.45 (1.25)	2.50 (1.14)	2.49 (1.20)	2.1 (1.1)

DMF: dimethyl fumarate; EDSS: Expanded Disability Status Scale; PBO: placebo.
[a]Values are mean (standard deviation) unless otherwise stated.
[b]Characteristics at ENDORSE baseline unless otherwise stated.
[c]Delayed-release dimethyl fumarate.

470 patients; 144 were continuously treated (DMF/DMF) and 85 received delayed DMF BID treatment (PBO/DMF).

The median (range) total follow-up time from randomization in DEFINE/CONFIRM and ENDORSE was 8.76 (2.04–12.98) years; time on treatment was 8.36 (2.00–12.25) years (1 year = 48 weeks). Approximately half of patients (*n* = 909 (52%) were treated in ENDORSE for ⩾6 years. Total median follow-up time and time on treatment for newly diagnosed patients were similar.

Overall, 759 (44%) patients completed ENDORSE. Patient baseline demographics are shown in Table 1. Common reasons for study treatment discontinuation were consent withdrawn (*n* = 288 (17%)), AEs (*n* = 243 (14%)), investigator decision (*n* = 83 (5%)), MS relapse (*n* = 39 (2%)), MS progression (*n* = 27 (2%)), lost to follow-up (*n* = 37 (2%)), subject non-compliance (*n* = 21 (1%)), death (*n* = 9 (<1%)), and other reasons (*n* = 216 (12%)). Baseline characteristics of patients who completed ENDORSE were similar to those who discontinued at any time over the course of the study (Table 2). Of the DMF/DMF and PBO/DMF cohorts, 236 (47%) and 100 (40%), respectively, completed ENDORSE

(Figure 2). During the first 3 months of DMF treatment in ENDORSE, 3% of DMF/DMF patients discontinued, compared with 13% of PBO/DMF patients, mainly due to AEs (DMF/DMF, *n* = 4 (<1%); PBO/DMF, *n* = 25 (10%) Beyond 3 months, the most common reason for discontinuation in both treatment groups was consent withdrawn (DMF/DMF, 15%; PBO/DMF, 14%).

Safety
AEs and serious adverse events (SAEs), experienced by ⩾5 patients in any treatment group, are summarized in Table 3. The most common AEs were MS relapse (*n* = 678 (39%)) and nasopharyngitis (*n* = 446 (26%)). The majority of AEs were mild (*n* = 84 (17%), *n* = 43 (17%)) to moderate (*n* = 283 (56%), *n* = 139 (56%)) in the DMF/DMF group and PBO/BID group, respectively. The most common SAEs were MS relapse (*n* = 238 (14%)) and fall (*n* = 31 (2%)). A case of progressive multifocal leukoencephalopathy (PML) occurred in a DMF-treated patient with prolonged, severe lymphopenia; details have been previously reported.[12] No other cases of PML occurred in this study. In addition, two (<1%) other opportunistic infections were observed. Overall incidence and type of AEs and SAEs were otherwise consistent with

Table 2. Baseline demographics of patients who completed or discontinued ENDORSE.

Characteristic	Patients who completed ENDORSE, $n = 759$	Patients who discontinued ENDORSE, $n = 977$
Age, years, mean (SD)	40.1 (8.8)	39.6 (9.3)
Age < 40 years, n (%)	348 (46)	479 (49)
Female, n (%)	510 (67)	702 (72)
Race/ethnicity, n (%)		
White	241 (32)	353 (36)
Black or African American	7 (< 1)	19 (2)
Asian	111 (15)	51 (5)
Other	23 (3)	33 (3)
Not reported	377 (50)	521 (53)
EDSS score, mean (SD)	2.51 (1.17)	2.47 (1.22)[a]
Number of relapses within the previous 12 months, mean (SD)	1.4 (0.7)	1.3 (0.7)
Months since most recent pre-study relapse, mean (SD)	6.5 (7.9)	6.4 (5.5)

EDSS: Expanded Disability Status Scale; SD: standard deviation.
[a]$n = 976$.
Age, sex, and ethnicity are at ENDORSE baseline. EDSS score, number of relapses within the previous 12 months, and time since most recent pre-study relapse are at DEFINE/CONFIRM baseline.
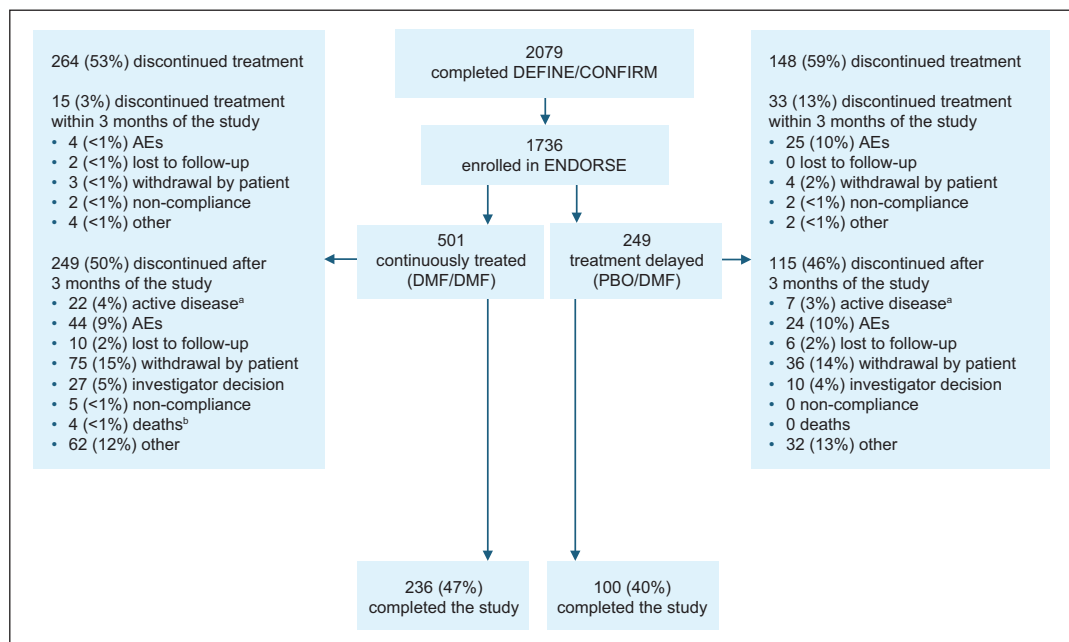
Figure 2. ENDORSE patient disposition.
AE: adverse event; DMF: dimethyl fumarate; PBO: placebo.
[a]MS relapse: $n = 11$ (2%), MS progression: $n = 11$ (2%).
[b]One additional death occurred during the study but was classified as an AE by the investigator. DMF/DMF-treated patients received 10 years of continuous DMF treatment; PBO/DMF-treated patients received 2 years of PBO (DEFINE/CONFIRM) followed by ~8 years of DMF (ENDORSE).

those reported in DEFINE and CONFIRM and were generally similar across treatment groups and the newly diagnosed population.

Gastrointestinal (GI) disorders were reported for 43% of patients and were higher for PBO/DMF (51%) compared with DMF/DMF (37%) (Table 4). These

Table 3. Most common AEs (incidence ⩾10% in any treatment group) and SAEs (experienced by ⩾5 patients in any treatment group) in ENDORSE.

AEs, *n* (%)	DMF/DMF[a] *n* = 501	PBO/DMF *n* = 249	Overall safety population *N* = 1,736	Newly diagnosed population *n* = 470
Any AE	474 (95)	242 (97)	1,638 (94)	435 (93)
MS relapse	206 (41)	92 (37)	678 (39)	175 (37)
Nasopharyngitis	143 (29)	56 (22)	446 (26)	134 (29)
Urinary tract infection	125 (25)	48 (19)	364 (21)	87 (19)
Flushing	60 (12)	81 (33)	335 (19)	108 (23)
Upper respiratory tract infection	91 (18)	39 (16)	280 (16)	91 (19)
Headache	96 (19)	35 (14)	277 (16)	80 (17)
Back pain	81 (16)	31 (12)	251 (14)	73 (16)
Diarrhea	60 (12)	40 (16)	230 (13)	67 (14)
Arthralgia	62 (12)	27 (11)	212 (12)	55 (12)
Pain in extremity	61 (12)	30 (12)	194 (11)	54 (11)
Depression	66 (13)	23 (9)	190 (11)	49 (10)
Bronchitis	50 (10)	21 (8)	180 (10)	53 (11)
Influenza	51 (10)	23 (9)	154 (9)	44 (9)
Proteinuria	44 (9)	26 (10)	157 (9)	46 (10)
Abdominal pain upper	25 (5)	33 (13)	145 (8)	43 (9)
Nausea	24 (5)	24 (10)	117 (7)	30 (6)
Any SAE	168 (34)	81 (33)	551 (32)	130 (28)
MS relapse	69 (14)	33 (13)	238 (14)	50 (11)
Fall	7 (1)	5 (2)	31 (2)	6 (1)

AE: adverse event; DMF: dimethyl fumarate; PBO: placebo; SAE: serious adverse event.
[a]Delayed-release dimethyl fumarate.

Table 4. AEs of interest in ENDORSE.

n (%)	DMF/DMF[a] *n* = 501	PBO/DMF *n* = 249	Overall population *N* = 1,736	Newly diagnosed population *n* = 470
Gastrointestinal disorders	184 (37)	128 (51)	748 (43)	210 (45)
Vascular disorders				168 (36)
Flushing[b]	77 (15)	94 (38)	419 (24)	133 (28)
Immune system disorders				15 (3)
Anaphylactic reaction	0	0	1 (<1)	1 (<1)
Potential hepatic disorders	45 (9)	27 (11)	198 (11)	48 (10)
ALT increased	22 (4)	19 (8)	112 (6)	24 (5)
AST increased	14 (3)	10 (4)	70 (4)	16 (3)
Renal and urinary disorders	143 (29)	66 (27)	443 (26)	122 (26)
Proteinuria	44 (9)	26 (10)	157 (9)	46 (10)
Microalbuminuria	35 (7)	13 (5)	116 (7)	29 (6)
Hematuria	32 (6)	13 (5)	111 (6)	29 (6)
Serious infections	28 (6)	14 (6)	81 (5)	25 (5)
Potential opportunistic infection	4 (<1)	0	7 (<1)	0
Opportunistic infections	1 (<1)	0	2 (<1)	0
Malignancy	16 (3)	8 (3)	49 (3)	16 (3)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DMF: dimethyl fumarate; PBO: placebo.
[a]Delayed-release dimethyl fumarate.
[b]Flushing consists of the preferred terms of flushing and hot flush.

differences were primarily driven by higher incidence rates in the first year of ENDORSE for the PBO/DMF group, which is consistent with the timing of GI AEs reported in DMF-treated patients in DEFINE and CONFIRM. Similar differences were seen for flushing AEs (defined as flushing or hot flush) between the PBO/DMF and DMF/DMF groups (38% and 15%, respectively). Consistent with DEFINE/CONFIRM, proteinuria, microalbuminuria, and hematuria were the most common renal AEs reported (Table 4). Renal or urinary disorders led to <1% of discontinuations. There was no evidence of increasing incidence of renal injury with long-term DMF treatment.

When safety was assessed annually, there was no increased incidence of infections, serious infections, (with the exception of PML), GI events, MS relapse, flushing, or malignancy over 10 years for either BID/BID or PBO/BID treated patients, relative to the prior time points (Table 5).

ALC

ALC analyses include all DMF-treated patients in ENDORSE and DMF-treated patients in DEFINE and CONFIRM who did not rollover into ENDORSE ($n = 2263$). Post-baseline lymphocyte measurements were available in 2222/2263 patients. ALC decreased over the first 48 weeks (mean percent change from baseline ALC, –27.7% at Week 48) and remained generally stable for the duration of the study (Figure 3), remaining above the LLN (0.91×10^9/L) for the majority of patients (59%). While on treatment, 235 (10.6%) and 53 (2.4%) of patients developed prolonged moderate or prolonged severe lymphopenia, respectively. When stratified by lymphocyte category, incidence of infection and malignancy was low across ALC groups (Table 6). Of 53 patients (2.8% of the total population) who developed prolonged severe lymphopenia over the study period, the majority did so in the first 3 years (Figure 4). Notably, nine patients (<1% of the total population) developed prolonged severe lymphopenia for the first time in Years 4–7. Of those, seven had an ALC below 0.8×10^9/L in the first year of treatment, and ALC remained low for several years until developing prolonged severe lymphopenia.

For the majority of patients with ALC < LLN at discontinuation, excluding patients with prolonged severe lymphopenia, predicted time to reconstitution to ⩾LLN was 4.7 weeks ($n = 228$) (Figure 5). For patients with mild, moderate, or severe lymphopenia at the time of discontinuation, predicted time to reconstitution to ⩾LLN was 0.7, 5.8, and 8.8 weeks, respectively. Predicted time to reach ⩾LLN in patients with

prolonged severe lymphopenia (2% of the total population) was 29 weeks ($n = 49$).

Clinical efficacy in the overall patient population

Overall, for patients continuously treated with DMF BID (DMF/DMF), the ARR (95% confidence interval (CI)), adjusted for baseline disease and demographic characteristics, remained consistent and low, ranging from 0.20 (0.16–0.25) in the first year to 0.11 (0.07–0.17) in Years 9–10 (Figure 6(a)).

To evaluate ARR in PBO/DMF patients, a repeated measures negative binomial model was used. The model-based ARR (95% CI) was 0.35 (0.29–0.43) during the PBO treatment period (Years 0–2 (DEFINE/CONFIRM) and decreased to 0.15 (0.12–0.19) during Years 3–10 (ENDORSE) after initiating DMF treatment (rate ratio (95% CI) = 0.44 (0.34–0.56) a 56% reduction ($p < .0001$; Figure 7(a)). The estimated proportion (95% CI) of patients with relapses at 10 years was 54.9% (50.0–59.8%) for DMF/DMF and 58.1% (51.4–64.9%) for PBO/DMF treatment groups (Figure 8).

After ~8 years of DMF treatment in ENDORSE (Year 10), mean (SD) EDSS scores were low (DMF/DMF, 2.0 (1.4) PBO/DMF, 1.5 (0) Rates of CDW were low over 10 years; proportion of patients with no CDW was 72% and 73% of DMF/DMF and PBO/DMF patients, respectively. EDSS scores were ⩽3.5 at Year 2 and Year 10, respectively, for 86% (413/479) and 77% (173/226) of DMF/DMF patients and 82% (179/217) and 74% (67/90) of PBO/DMF patients.

Clinical efficacy in the newly diagnosed patient population

Relapse rates in newly diagnosed patients were consistent with the overall patient population (Figure 6(b)). In the PBO/DMF group, the model-based ARR (95% CI) was 0.25 (0.17–0.36) during the PBO treatment period (Years 0–2 (DEFINE/CONFIRM) and decreased to 0.09 (0.06–0.13) during the DMF treatment period (Years 3–10 (ENDORSE) rate ratio = 0.36 (0.24–0.55) a 64% decrease ($p < .0001$; Figure 7(b)).

Mean (SD) EDSS scores in newly diagnosed patients were low (2.0 (2.0) for DMF/DMF and 2.0 (0.9) for PBO/DMF) after ~8 years DMF treatment. The proportion of patients with no CDW (combined DEFINE/CONFIRM and ENDORSE data) at Year 10 was 81% and 75% for DMF/DMF and PBO/DMF, respectively.

Table 5. Incidence of adverse events of interest over 10 years in continuously treated patients (DMF/DMF) and in patients who were treated with placebo in DEFINE/CONFIRM and re-randomized to DMF twice daily in ENDORSE (delayed DMF; PBO/DMF).

Event, n (%)	Incidence, years[a]										
	0–1	>1–2	>2–3	>3–4	>4–5	>5–6	>6–7	>7–8	>8–9	>9–10	>10
DMF/DMF	*n* = 501	*n* = 472	*n* = 445	*n* = 394	*n* = 370	*n* = 338	*n* = 295	*n* = 261	*n* = 231	*n* = 73	*n* = 5
Infections	231 (46)	151 (32)	132 (30)	141 (36)	118 (32)	90 (27)	77 (26)	74 (28)	41 (18)	10 (14)	1 (20)
Serious infections	8 (2)	5 (1)	4 (<1)	4 (1)	3 (<1)	4 (1)	2 (<1)	1 (<1)	2 (<1)	0	0
GI disorders	84 (17)	43 (9)	44 (10)	37 (9)	33 (9)	20 (6)	19 (6)	18 (7)	7 (3)	4 (5)	0
MS relapse	59 (12)	59 (13)	59 (13)	62 (16)	37 (10)	37 (11)	28 (9)	31 (12)	15 (6)	1 (1)	0
Flushing	43 (9)	4 (<1)	9 (2)	6 (2)	5 (1)	2 (<1)	2 (<1)	1 (<1)	0	0	0
Malignancy	1 (<1)	3 (<1)	4 (<1)	3 (<1)	1 (<1)	2 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (1)	0
PBO/DMF	*n* = 249	*n* = 208	*n* = 195	*n* = 176	*n* = 160	*n* = 148	*n* = 131	*n* = 112	*n* = 95	*n* = 34	*n* = 1
Infections	102 (41)	75 (36)	61 (31)	55 (31)	40 (25)	40 (27)	32 (24)	25 (22)	10 (11)	3 (9)	0
Serious infections	4 (2)	1 (<1)	2 (1)	2 (1)	1 (<1)	0	1 (<1)	2 (2)	0	1 (3)	0
GI disorders	96 (39)	30 (14)	25 (13)	20 (11)	11 (7)	5 (3)	10 (8)	2 (2)	3 (3)	0	0
MS relapse	40 (16)	27 (13)	20 (10)	23 (13)	20 (13)	17 (11)	19 (15)	11 (10)	5 (5)	2 (6)	0
Flushing	73 (29)	5 (2)	2 (1)	3 (2)	0	1 (<1)	0	1 (<1)	0	0	0
Malignancy	1 (<1)	2 (<1)	1 (<1)	0	0	1 (<1)	2 (2)	0	1 (1)	0	0

DMF: dimethyl fumarate; GI: gastrointestinal; PBO: placebo.
[a]1 year = 48 weeks.

Figure 3. Lymphocyte mean values over time by ALC subgroup.
ALC: absolute lymphocyte count; DMF: dimethyl fumarate; LLN: lower limit of normal; SD: standard deviation.

Table 6. Incidence of infection and malignancy by lymphocyte category.

	Prolonged severe lymphopenia	Prolonged moderate lymphopenia	Mild lymphopenia	Always ⩾ LLN	Total
Patients, n	53	235	620	1,300	2,208
Total patient-years	315.4	1,763.2	4,005.9	5,581.2	11,666
Serious infections/patient-year	0.01	0.01	0.01	0.01	0.01
Opportunistic infections/patient-year	<0.01	0	<0.01	0	<0.01
Malignancies/patient-year	0.01	0.01	<0.01	<0.01	<0.01
Serious herpes zoster infections/patient-year	0	<0.01	0	<0.01	<0.01

LLN: lower limit of normal (0.91×10^9/L).
Patient-year = ((last date in study) − (date of first exposure to delayed-release dimethyl fumarate) + (1))/365.25. Incidence = (number of patients with specific adverse events)/(total patient-years of follow-up). Prolonged severe lymphopenia = $<0.5 \times 10^9$/L for ⩾6 months; prolonged moderate lymphopenia = $⩾0.5$ to $<0.8 \times 10^9$/L for ⩾6 months; mild lymphopenia = <LLN at any time.

Stability analysis: relapse
Approximately 75% (519/694) of patients were relapse-free within the first 2 years of DMF BID treatment. During subsequent years (up to 12 years treatment), 37% (258/694) of DMF BID patients relapsed. Relapse rate was lower for patients without a relapse in the first 2 years of DMF BID treatment versus those with a relapse in the first 2 years (28.7% vs 62.3%). Mean number of relapses and ARR were both lower for patients with no relapses in the first 2 years ($p < .001$), suggesting early relapses may be predictive of more relapses in the future.

TTFR during subsequent years of treatment (3–12 years) was longer for patients without a relapse in the first 2 years versus those with a relapse-estimated restricted mean survival time (TTFR (95% CI) = 6.9 (6.56–7.15) versus 3.9 (3.30–4.42) years; $p < .001$). After adjusting for baseline covariates, the estimated difference remains significant ($p = .013$), indicating that an early relapse may be predictive of earlier future relapses. After adjusting for follow-up length, fewer relapses in Years 3–12 were associated with no relapses in the first 2 years, older age, lower EDSS score, higher SF-36 PCS, and lower SF-36 MCS score.
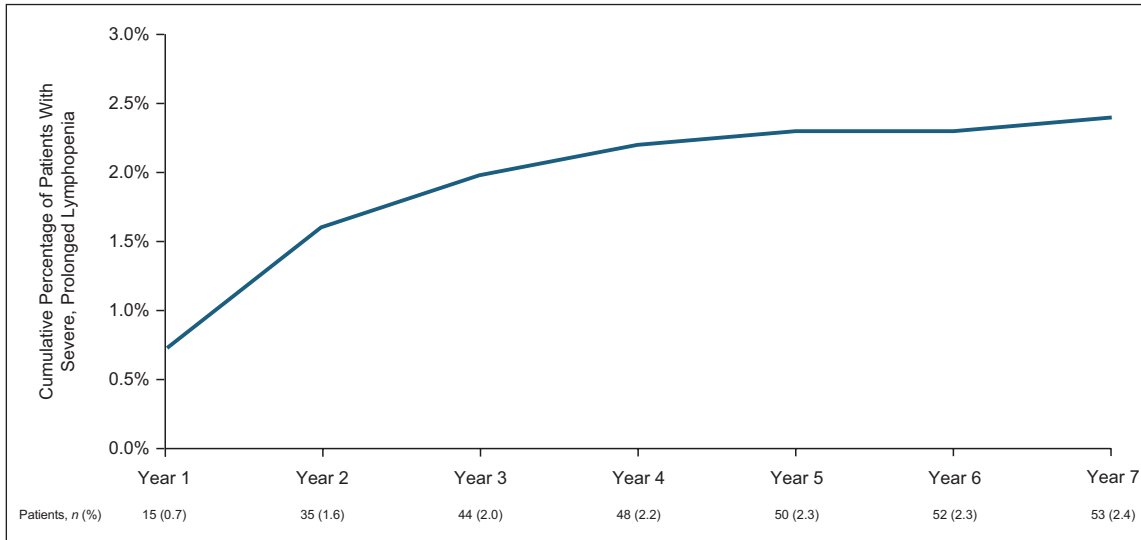
Figure 4. Prevalence of prolonged severe lymphopenia[a] by year ($N = 2222$).
[a]Prolonged severe lymphopenia defined as an ALC of $<0.5 \times 10^9$/L for $\geqslant 6$ months.
Over the course of the ENDORSE trial, one new confirmed safety signal was identified (PML in the setting of lymphopenia, as previously reported), which resulted in updated risk mitigation strategies, introducing ALC discontinuation criteria.
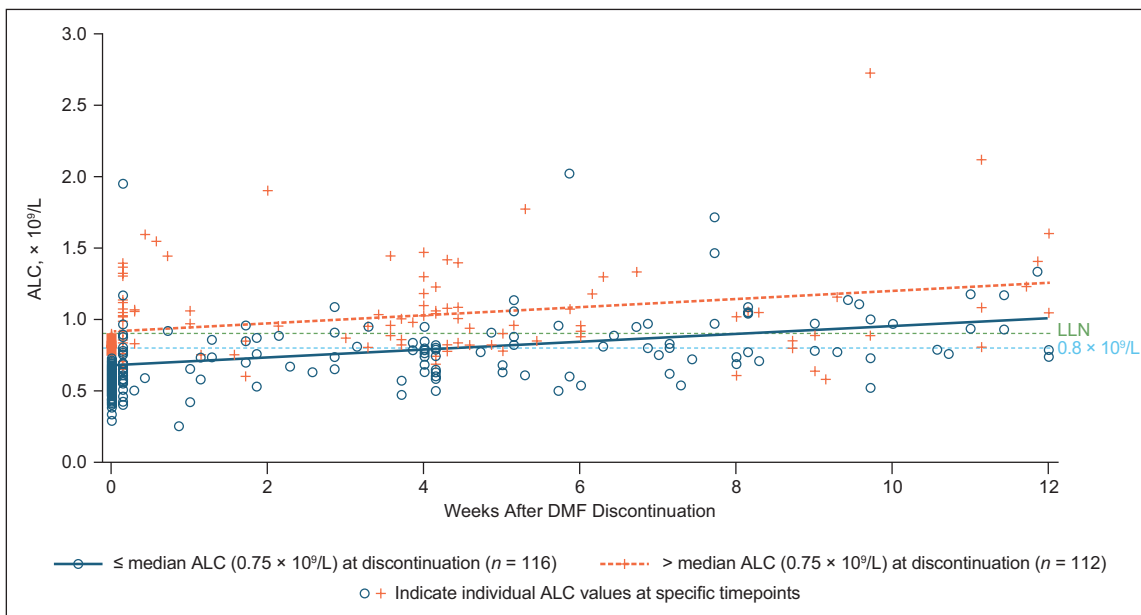

Figure 5. ALC reconstitution post-DMF discontinuation.
ALC = absolute lymphocyte count; DMF = dimethyl fumarate; LLN = lower limit of normal (0.91×10^9/L).
In a linear mixed-effect model of post-DMF ALC reconstitution, groups were determined by the last ALC recorded at or before discontinuation. Patients with ALC $< 0.91 \times 10^9$/L at DMF discontinuation and $\geqslant 1$ post-DMF ALC value were included. Patients with $<0.5 \times 10^9$/L for $\geqslant 6$ months were excluded. The median ALC at discontinuation was 0.75×10^9/L.

Stability analysis: progression

Approximately 92% (632/686) of patients had no CDW progression during the first 2 years of DMF BID. The estimated restricted mean survival time (95% CI) to subsequent CDW in Years 3–12 for patients with CDW during the first 2 years of treatment was 5.3 (4.14–6.38) years, while the time was significantly longer ($p = .002$) for patients without CDW in the first 2 years (7.1 (6.82–7.29) years). After adjusting for baseline covariates, the estimated
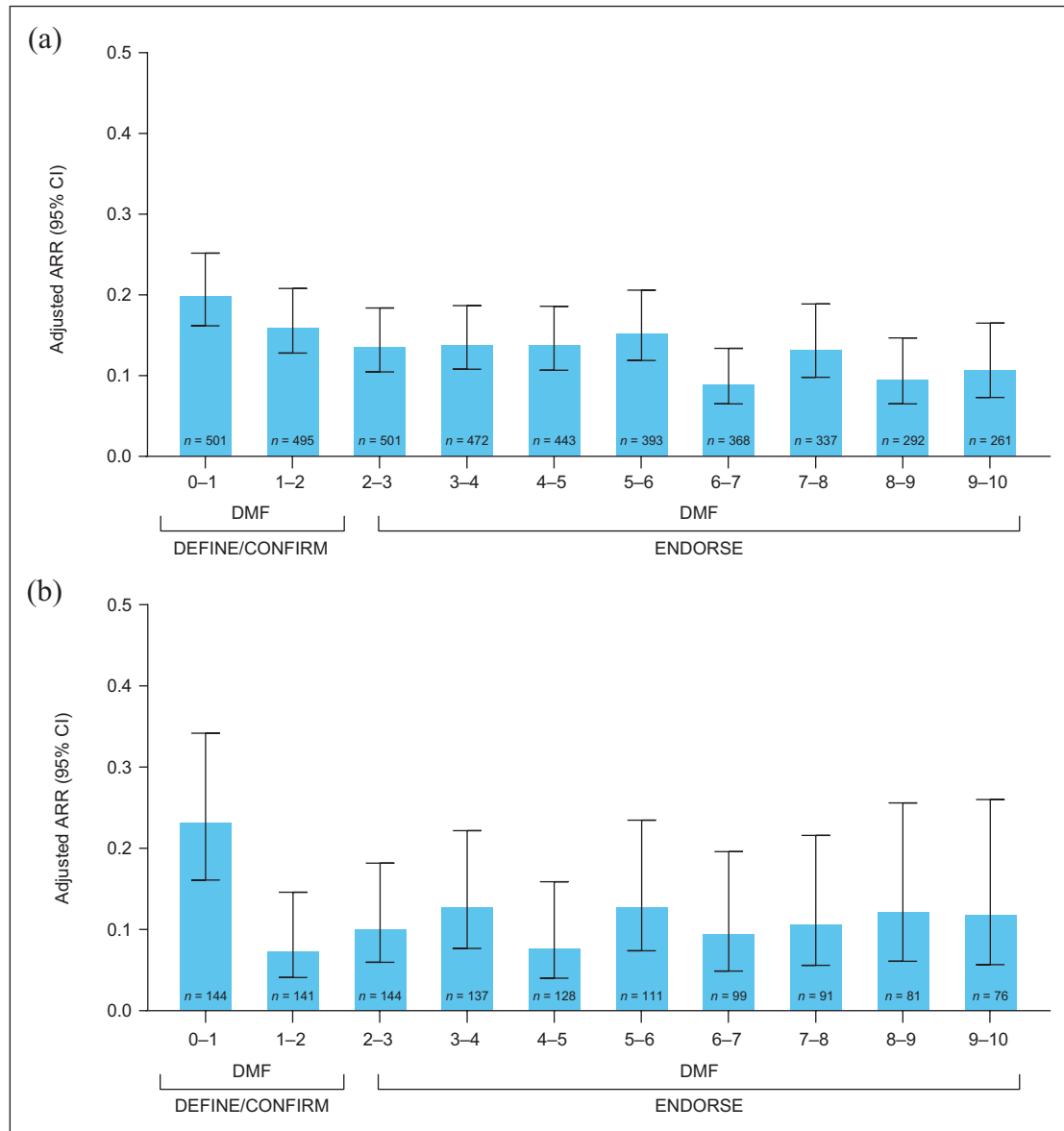
Figure 6. Adjusted ARR (objective relapses) by yearly interval for the DMF/DMF group in the (a) overall ENDORSE population and (b) newly diagnosed patient population over 10 years (ENDORSE 8 years).
ARR: annualized relapse rate; CI: confidence interval; DMF: dimethyl fumarate.
Adjusted ARR is shown for all patients treated with DMF continuously (DMF/DMF). Adjusted ARR and 95% CI are based on negative binomial regression, except for Years 4–5, 5–6, 6–7, 7–8, and 8–9 (third, fourth, fifth, sixth, and seventh, and eighth years of ENDORSE), which are based on Poisson regression. The model was based on the overall ENDORSE intention-to-treat population and adjusted in each yearly interval for baseline Expanded Disability Status Scale score ($\leqslant$2.0 vs >2.0), baseline age (<40 vs $\geqslant$40 years), region, and number of relapses in the year before DEFINE/CONFIRM study entry. Relapse, confirmed by an independent neurologic evaluation committee, was defined as new or recurrent neurologic symptoms lasting $\geqslant$24 hours accompanied by new objective neurologic findings.

difference between groups was not significant ($p = .06$), though sample size was small for patients with CDW during Years 0–2 ($n = 54$).

Overall compliance to therapy

Among patients continuously treated DMF/DMF ($n = 501$), $\geqslant$94% patients were $\geqslant$90% compliant to therapy. For PBO/DMF ($n = 249$), $\geqslant$90% of patients were $\geqslant$90% compliant to therapy, and 1 patient was <10% compliant to last dose of DMF. Baseline characteristics were similar for patients continuously treated with DMF 240-mg BID and stratified by compliance category (Table 7), though the sample size for patients with <90% non-compliance was small ($n = 53$).
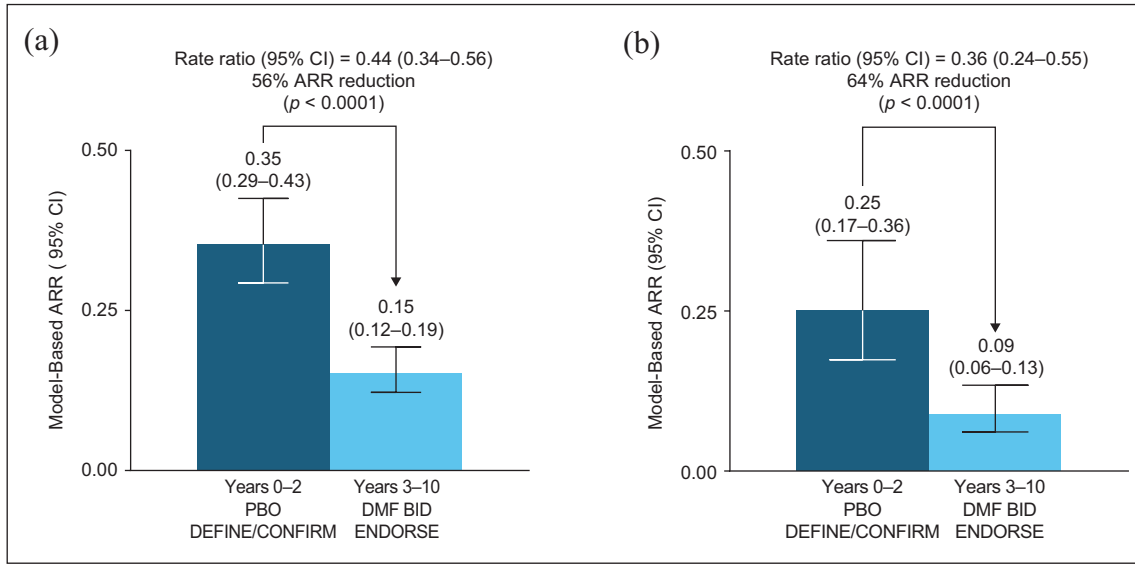
Figure 7. Model-based ARR during treatment with PBO (Years 0–2 in DEFINE/CONFIRM) and DMF (Years 3–10 in ENDORSE) in PBO/DMF patients: (a) overall population and (b) newly diagnosed patients.
ARR: annualized relapse rate; BID: twice daily; CI: confidence interval; DMF: dimethyl fumarate; PBO: placebo.
The ARR is from the repeated measures negative binomial model, which included periods for Years 0–2 and Years 3–10.
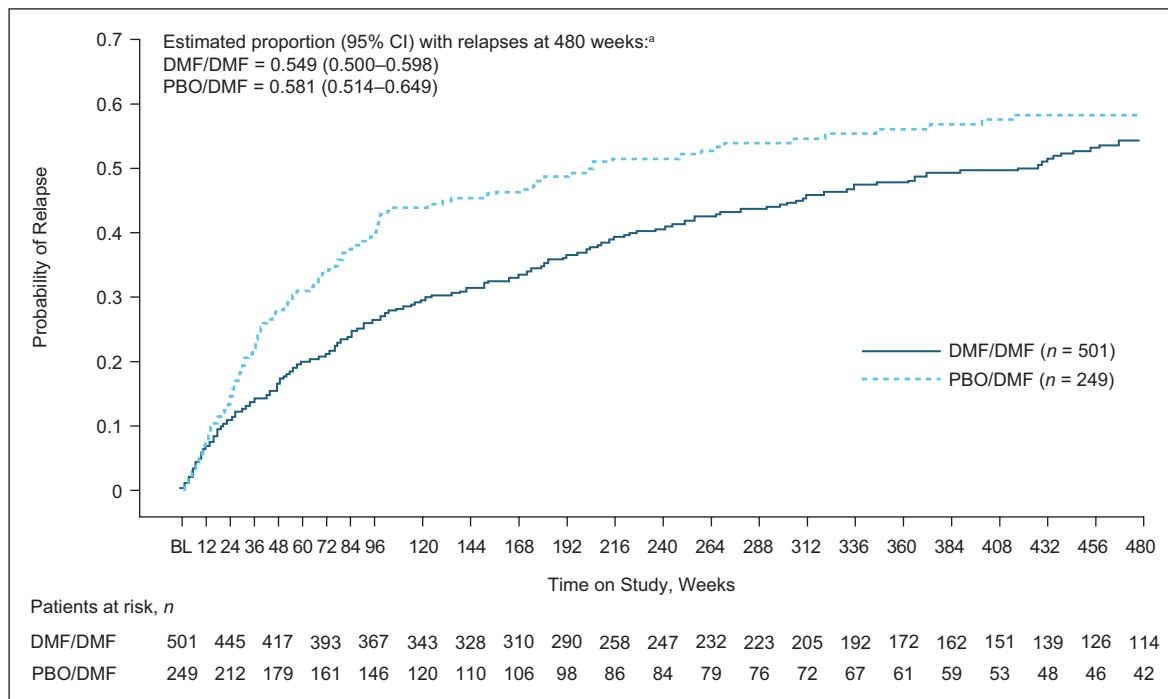

Figure 8. Kaplan–Meier estimated proportion of patients with relapses at 480 weeks.
BL: baseline; CI: confidence interval; DMF: dimethyl fumarate; PBO: placebo.
[a]Kaplan–Meier estimate (not calculated if the number of patients is <30); only objective relapses are included in the analysis.

PROs

For the overall population, PROs (SF-36 and EQ-5D) generally remained stable during ENDORSE (Figure 9).

Discussion

ENDORSE, a phase-III extension of DEFINE/CONFIRM, established the long-term safety and sustained efficacy profile of DMF with up to 13 years of

Table 7. Summary of baseline characteristics, relapse outcomes, and EDSS scores at 10 years in patients continuously treated with DMF[a] 240-mg BID stratified by compliance category.

	Continuous treatment group (DMF/DMF)	
	≥90% compliance n = 448	<90% non-compliance n = 53
Age, years (mean (SD))	39.9 (9.0)	38.3 (9.7)
Age < 40 years (n, %)	208 (46)	29 (55)
Female (n, %)	307 (69)	45 (85)
Race/ethnicity		
White (n, %)	141 (31)	21 (40)
Black or African American	1 (<1)	3 (6)
Asian	49 (11)	2 (4)
Other	18 (4)	3 (6)
Not reported	239 (53)	24 (45)
Number of relapse-free patients (Years 0–10), n (%)	224 (50)	32 (60)
Adjusted ARR (95% CI) (Years 0–10)	0.15 (0.12–0.18)	0.15 (0.10–0.25)
Time to first relapse, weeks (median (range))	417.14	NA[b]
EDSS score, mean (SD)	2.33	1.00

ARR: annualized relapse rate; DMF: dimethyl fumarate; EDSS: Expanded Disability Status Scale; NA: not available; SD: standard deviation.
[a]Delayed-release dimethyl fumarate.
[b]The proportion of patients who relapsed within the 10 year follow-up is less than the specified percentage.
Compliance was calculated as: (((total number of capsules the patient was expected to take) – (total number of capsules not taken))/ (total number of capsules expected to be taken)) × 100. Patients with missing data for number of capsules not taken since the previous visit were excluded.
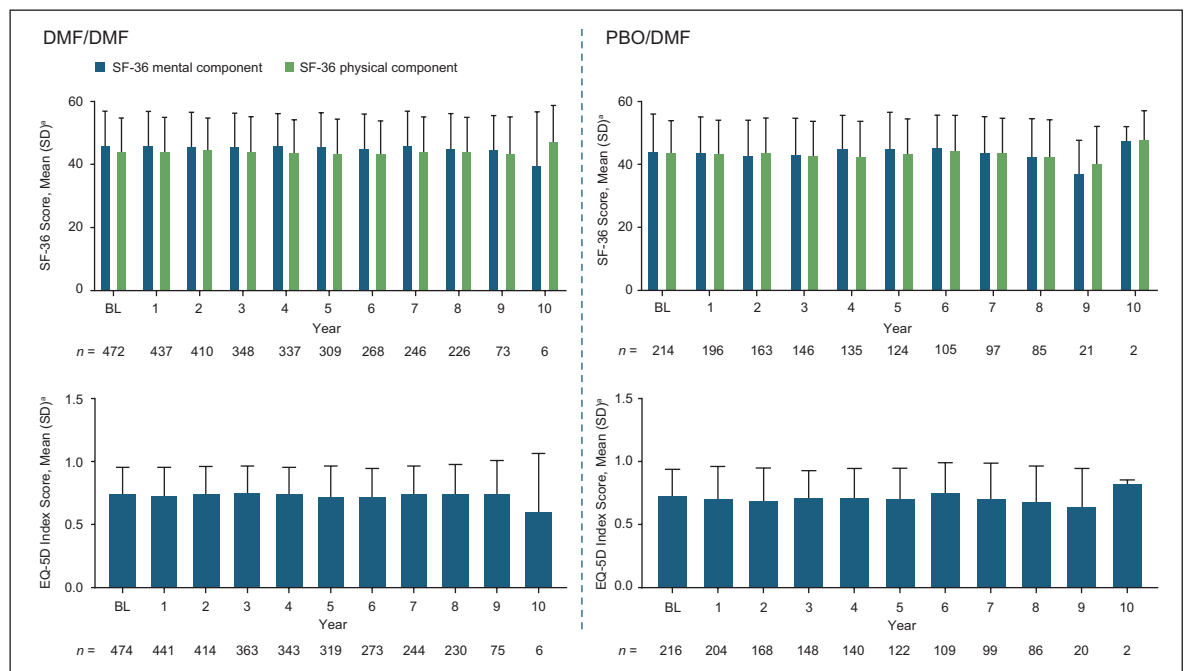

Figure 9. Patient-reported outcome scores from ENDORSE baseline to Year 10.
BL: baseline; EQ-5D: EuroQoL 5-dimensions; SD: standard deviation; SF-36: 36-Item Short Form Health Survey.
[a]Higher score indicates better health status.

follow-up. The data support a favorable benefit-risk profile of DMF, as evidenced by well-characterized safety, sustained efficacy, and stable PROs. In this study, more than 1000 patients were treated with DMF for ≥5 years, suggesting continuous favorable long-term outcomes for persistent patients (summarized in infographic).

Aside from PML, the incidence of AEs and SAEs were similar to those observed in DEFINE/CONFIRM and real-world data sets. Most AEs were mild to moderate in severity, and incidence did not increase over time. One new confirmed safety signal was identified (PML in the setting of lymphopenia, as previously reported), which resulted in updated risk mitigation strategies, introducing ALC discontinuation criteria. Notably, in the post-marketing setting, PML remains a very rare event (estimated reporting rate of 1.07 cases per 100,000 person-years of post-marketing exposure, as of 31 December 2020). Prolonged severe lymphopenia occurring after Year 3 was very rare, occurring in 9 of 2263 patients (<1%).

The incidence of serious infections, hepatic and renal disorders, and malignancies remained low. The incidence rate of malignancy (95% CI) reported in the overall ENDORSE population was 459 (344–601) per 100,000 persons per year, consistent with the background rate of the general US population (442 per 100,000 persons per year).[13]

As expected in a long-term study, discontinuation rates were higher than in a 2-year study; however, this was not primarily driven by efficacy. Discontinuations observed within the first 3 months were related to GI AEs, in contrast with late discontinuations, which were related to patient preference or other reasons.

ARR remained stable and low over 10 years, and most patients did not experience a relapse. Patients who had a delayed start to DMF treatment (PBO/DMF) experienced a significant decrease in ARR after starting DMF and maintained a low ARR thereafter. Disability scores remained stable during ENDORSE, and most patients maintained walking ability over 10 years. Newly diagnosed patients treated with DMF responded to therapy similarly to the overall population, highlighting the effectiveness of DMF in this specific population. Annual magnetic resonance imaging (MRI) efficacy outcomes in the MRI cohort of the ENDORSE study have been previously published.[14]

Disability stability and absence of relapses in the first 2 years on treatment were a predictive indicator of long-term stability. Patients who did not relapse or who had low CDW in the first 2 years of treatment tended to have significantly fewer relapses and later onset of relapse and CDW in the subsequent decade compared with those who relapsed and/or had CDW in the first 2 years.

PROs assessed throughout DEFINE/CONFIRM and ENDORSE were generally stable with continuous DMF treatment. We observed that relapses were associated with lower SF-36 MCS scores, which was an unexpected finding. Once a sensitivity analysis was conducted to remove three patients with small SF-36 MCS scores, there was no significance for SF-36 MCS, suggesting the small effect size possibly influenced the results.

Limitations associated with a long-term follow-up study such as this include attrition, informative censoring secondary to attrition, selective dropout, discontinuation secondary to AEs, and the lack of a control group. Inherent of long-term extension studies, these observations demonstrate the effectiveness of DMF over time, but the observations are relevant for the population who remained on the study, which represents a small proportion of the initial trial enrollment from DEFINE/CONFIRM. Of note, due to the broad commercial availability of DMF, multiple real-world studies corroborate our findings.[6,7,15] ENDORSE indicates that long-term treatment with DMF was associated with a sustained clinical profile and favorable safety profile.

Declaration of Conflicting Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: R.G. reports honoraria/research support from Bayer, Biogen, Merck Serono, Novartis, and Teva Neuroscience; and compensation from Sage for serving as editor of *Therapeutic Advances in Neurological Disorders*. D.L.A. reports consultant fees and/or grants from Acorda, Adelphi, Alkermes, Biogen, Celgene, Genentech, Genzyme, Hoffman-La Roche, Immune Tolerance Network, Immunotec, MedDay, Novartis, Pfizer, Receptos, Roche, Sanofi-Aventis, Canadian Institutes of Health Research, MS Society of Canada, and International Progressive MS Alliance; and equity

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