Time course of clinical and neuroradiological effects of delayed-release dimethyl fumarate in multiple sclerosis

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Background and purpose: Delayed-release dimethyl fumarate (DMF, also known as gastro-resistant DMF), demonstrated efficacy and safety in relapsing−remitting multiple sclerosis in the 2-year, randomized, placebo-controlled, phase 3 DEFINE and CONFIRM trials. A *post hoc* analysis of integrated data from DEFINE and CONFIRM was conducted to determine the temporal profile of the clinical and neuroradiological effects of DMF.

Methods: Eligible patients were randomized to receive placebo, DMF 240 mg twice (BID) or three times (TID) daily or glatiramer acetate (GA; reference comparator; CONFIRM only) for up to 96 weeks. Patients in the GA group were excluded from this analysis.

Results: A total of 2301 patients were randomized and received treatment with placebo ($n = 771$) or DMF BID ($n = 769$) or TID ($n = 761$). DMF significantly reduced the annualized relapse rate beginning in weeks 0–12 (BID, $P = 0.0159$; TID, $P = 0.0314$); the proportion of patients relapsed beginning at week 10 (BID, $P = 0.0427$) and week 12 (TID, $P = 0.0451$); and the proportion of patients with 12-week confirmed disability progression beginning at week 62 (BID, $P = 0.0454$) and week 72 (TID, $P = 0.0399$), compared with placebo. These effects were sustained throughout the 2-year study period. DMF significantly reduced the odds of having a higher number of gadolinium-enhancing lesions by 88% (BID) and 75% (TID) and the mean number of new or enlarging T2 lesions by 72% (BID) and 67% (TID), from the first post-baseline magnetic resonance imaging assessment at 24 weeks (all $P < 0.0001$ versus placebo).

Conclusions: In phase 3 clinical trials, DMF demonstrated rapid and sustained clinical and neuroradiological efficacy in relapsing−remitting multiple sclerosis.

Introduction

In clinical practice, when choosing amongst treatment options for multiple sclerosis (MS), it is important to know how quickly these therapeutics can be expected

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to control disease activity [1]. This is true not only for treatment-naive patients but also for patients looking to transition from one therapeutic to another for safety, tolerability or efficacy reasons. Yet, because clinical studies generally examine efficacy over a period of years, little is known about the time course of the effects of most MS therapeutics [2].

Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) is a novel oral therapeutic indicated for the treatment of patients with

relapsing MS. In the phase 3 DEFINE [3] and CONFIRM [4] trials in people with relapsing−remitting MS (RRMS), DMF demonstrated significant efficacy on clinical and neuroradiological measures, coupled with an acceptable safety profile, over a 2-year period. In a phase 2b study, DMF significantly reduced magnetic resonance imaging (MRI) activity compared with placebo from 12 weeks after initiation, suggesting a rapid onset of neuroradiological efficacy [5].

A pre-specified integrated analysis of DEFINE and CONFIRM was conducted to assess DMF's effects on end-points including annualized relapse rate (ARR), proportion of patients relapsed, disability as measured by 12-week confirmed Expanded Disability Status Scale (EDSS) progression, number of gadolinium-enhancing (Gd+) lesions and number of T2 lesions, at 2 years [6]. Here a *post hoc* analysis of integrated data is presented, focusing on the time to onset and maintenance over time of DMF's effects on clinical and neuroradiological end-points, to further characterize the temporal profile of DMF's effects.

Methods/patients

Patients, study design and trial registration

The designs of the DEFINE (ClinicalTrials.gov identifier NCT00420212) and CONFIRM (ClinicalTrials.gov identifier NCT00451451) trials have been described previously [3,4]. Briefly, eligible patients were aged 18–55 years; were diagnosed with RRMS according to the McDonald criteria [7]; had an EDSS score [8] of 0–5.0, inclusive; and had experienced at least one clinically documented relapse within 1 year prior to randomization or had at least one Gd+ lesion on a brain MRI scan obtained within 6 weeks prior to randomization. Key exclusion criteria included relapse or corticosteroid treatment within 50 days prior to randomization or prior treatment with glatiramer acetate (GA) within the 3 months prior to randomization (DEFINE) or at any time (CONFIRM).

In DEFINE, patients were randomized 1:1:1 to receive placebo, DMF 240 mg twice daily (BID) or DMF 240 mg three times daily (TID) for up to 96 weeks. In CONFIRM, patients were randomized 1:1:1:1 to receive treatment with placebo, DMF 240 mg BID or TID, or GA (reference comparator) for up to 96 weeks. Neurological examinations were conducted every 12 weeks for efficacy assessments and at the time of suspected relapse. MRI assessments were conducted at baseline and at weeks 24, 48 and 96.

Magnetic resonance imaging was performed in a subset of the intention-to-treat (ITT) population (MRI cohort; $n = 1221$ patients), based on case number calculations for the MRI outcomes and the availability of MRI equipment at the sites to perform the assessments required for the study, including magnetization transfer ratio measurements.

The primary end-point of DEFINE was the proportion of patients relapsed at 2 years. The primary end-point of CONFIRM was the ARR at 2 years. Additional end-points included the time to 12-week confirmed disability progression, number of Gd+ lesions, and number of new or enlarging T2 lesions, all at 2 years. Relapses were defined as new or recurrent neurological symptoms, not associated with fever or infection, lasting at least 24 h, and accompanied by new objective neurological findings. Relapses were confirmed by an Independent Neurological Evaluation Committee.

Patients had the option of discontinuing study treatment and initiating treatment with an approved, open-label, alternative MS medication if they experienced disability progression at any time (both studies), if they completed 48 weeks of study treatment and experienced one or more relapses after 24 weeks (DEFINE) or if they completed 48 weeks of study treatment and experienced two confirmed relapses at any time (CONFIRM).

Statistical analysis

As described elsewhere [6], a pre-specified, integrated analysis of DEFINE and CONFIRM was conducted to assess DMF's efficacy on clinical and neuroradiological end-points including ARR, proportion of patients relapsed, number of Gd+ lesions and number of T2 lesions, at 2 years. The integrated analysis plan was finalized prior to the unblinding of CONFIRM and was to be conducted only if baseline characteristics and treatment effects were homogeneous across the studies.

The integrated analysis was performed on data from the ITT population, which included patients who were randomized and received at least one dose of placebo, DMF BID or DMF TID. Patients receiving GA were excluded because there was no GA arm in DEFINE and because CONFIRM was not powered to test the superiority or non-inferiority of DMF compared with GA. The MRI cohort consisted of patients in the ITT population for whom at least one MRI scan (baseline or any other time point) was available for analysis. Data from patients who elected to switch to alternative MS treatment (not those who discontinued study medication without switching to another disease-modifying therapy) were censored as of the date of the switch.

A modeling approach was used to analyze each efficacy end-point. For ARR, rate ratios (DMF/placebo) and 95% confidence intervals (CI) were calculated using Poisson regression adjusted for baseline age (<40 vs. ≥40 years), baseline EDSS score (≤2.0 vs. >2.0), region [1 (USA), 2 (Western European countries, Canada, Costa Rica, Australia, New Zealand, Israel and South Africa) or 3 (Eastern European countries, India, Guatemala and Mexico)], study (DEFINE versus CONFIRM) and number of relapses in the year prior to study entry. The proportion of patients relapsed was derived using Kaplan–Meier analysis; hazard ratios (delayed-release DMF/placebo) and 95% CI were based on a Cox proportional hazards model adjusted for region (1, 2 or 3), study, baseline age (<40 vs. ≥40 years), baseline EDSS score (≤2.0 vs. >2.0) and number of relapses in the year prior to study entry. Disability as measured by 12-week confirmed EDSS progression was analyzed using a Cox proportional hazards model with study as a stratifying factor, and adjusted for the following covariates: baseline EDSS score (as a continuous variable), baseline age (<40 vs. ≥40) and region. The odds of having a higher number of Gd+ lesions was analyzed using ordinal logistic regression adjusted for region (1, 2 or 3), study and baseline number of Gd+ lesions. The number of new or enlarging T2-hyperintense lesions was analyzed using negative binomial regression adjusted for region (1, 2 or 3), study and baseline T2-hyperintense volume. As these were *post hoc* analyses, no adjustment for multiplicity was made.

Standard protocol approvals, registrations and patient consents

The DEFINE (ClinicalTrials.gov identifier NCT00 420212) and CONFIRM studies (ClinicalTrials.gov identifier NCT00451451) were approved by central and local ethics committees and performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice [9] and the ethical principles outlined in the Declaration of Helsinki [10]. Written informed consent was obtained from all patients before evaluations were performed to determine eligibility.

Results

Study population

A total of 2301 patients (ITT population) were randomized and received treatment with placebo (n = 771), DMF BID (n = 769) or DMF TID (n = 761) (Fig. 1). The subset of patients comprising the MRI cohort included 347 placebo-treated patients and 345 and 354 patients treated with DMF BID and TID, respectively. Demographics and baseline characteristics were well balanced across treatment groups, as reported elsewhere [3,4].
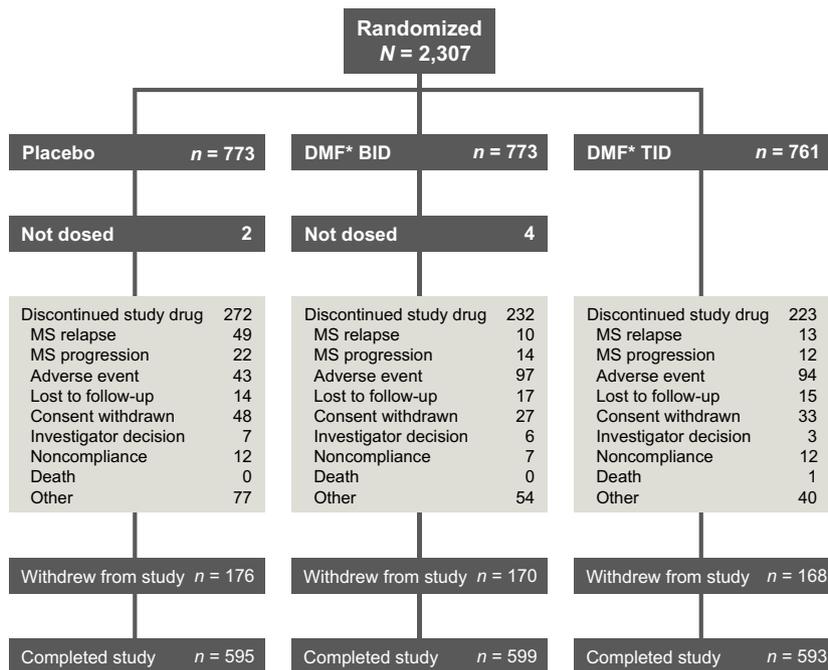
Figure 1 Patient disposition. The ITT population, defined as all subjects who were randomized and received at least one dose of study treatment, comprised 2301 subjects.

*DMF, delayed-release DMF (also known as gastro-resistant DMF)

A total of 1787 patients (78%) completed the studies (77%, 78% and 78% in the placebo, DMF BID and DMF TID groups, respectively). The rate of study drug discontinuation was 35% in the placebo group, 30% in the DMF BID group and 29% in the DMF TID group. The percentage of patients who switched to alternative MS therapies was 12% in the placebo group, 7% in the DMF BID group and 6% in the DMF TID group.

Clinical end-points

The ARR was significantly reduced by DMF BID and TID compared with placebo beginning at weeks
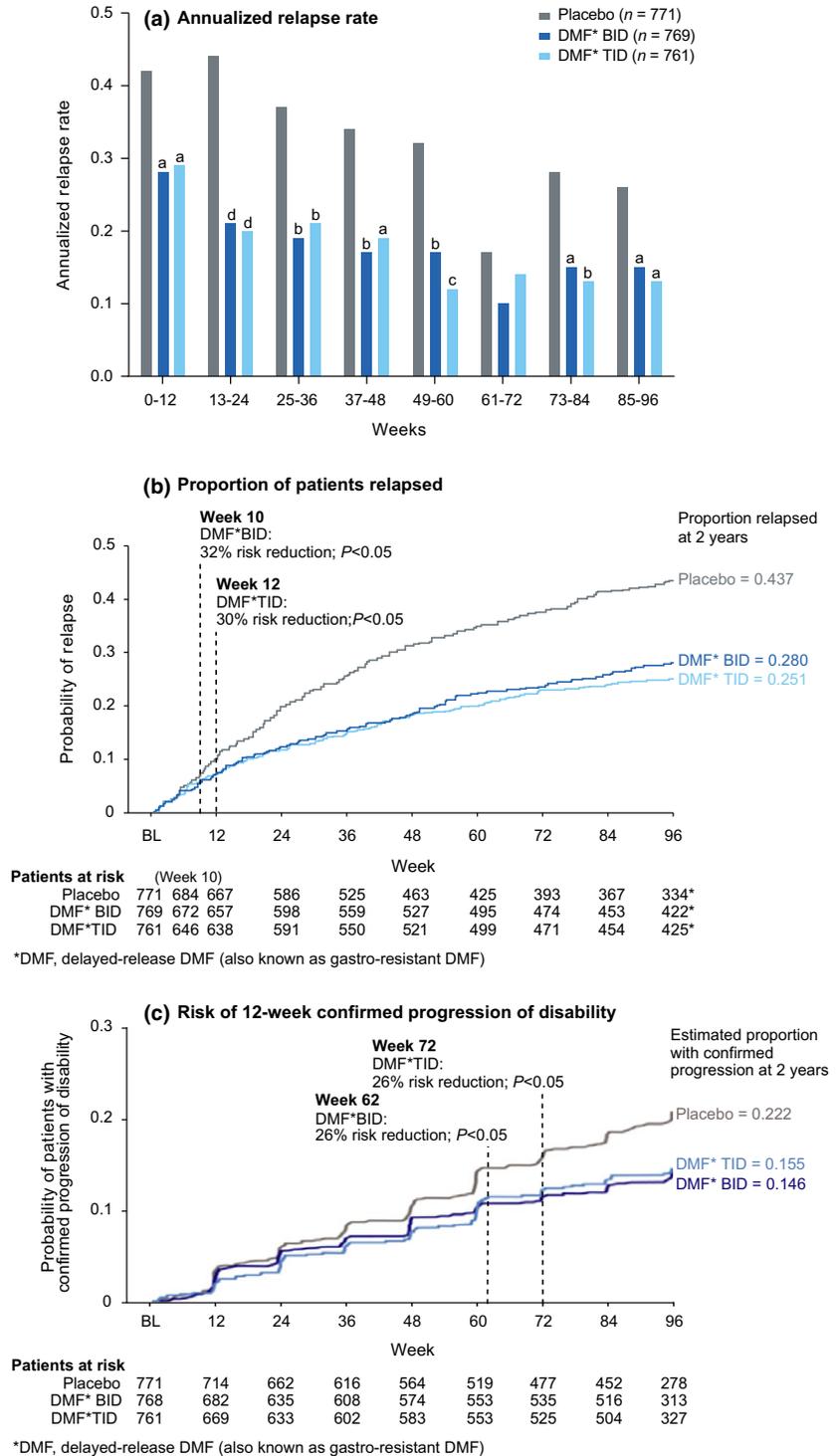
Figure 2 ARR, risk of relapse and risk of 12-week confirmed disability progression over 2 years. (a) Rate ratios were analyzed based on confirmed relapses. (b) Proportion of patients relapsed, by time to first relapse. (c) Disability as measured by 12-week confirmed EDSS progression. *Week 96 numbers of patients at risk are numbers 5 days prior to week 96. BID, twice daily; BL, baseline; TID, three times daily. $^a P < 0.05$; $^b P < 0.01$; $^c P < 0.001$; $^d P < 0.0001$ versus placebo.

0–12 and continuing through the duration of the 2-year study, with the exception of weeks 61–72 when the ARR in the placebo group was low (Fig. 2a). The ARR in weeks 0–12 was 0.42 in the placebo group, 0.28 in the DMF BID group and 0.29 in the DMF TID group, representing relative reductions of 34% ($P = 0.0159$) and 31% ($P = 0.0314$), respectively. Across the remaining 12-week time periods, with the exception of weeks 61–72, the range of ARRs was 0.26–0.44 in the placebo group, 0.15–0.21 in the DMF BID group and 0.12–0.21 in the DMF TID group, representing relative reductions of 42%–53% (BID) and 43%–61% (TID). ARRs, rate ratios, relative reductions and P values for each 12-week time period are presented in Table 1.

The proportion of patients relapsed was significantly reduced by DMF beginning at week 10 in the BID group and week 12 in the TID group, compared with placebo (Fig. 2b). On the basis of Kaplan–Meier estimates, the proportion of patients relapsed by week 10 was 8.9% in the placebo group and 6.0% in the DMF BID group, representing a relative reduction of 32% ($P = 0.0427$), and the proportion of patients relapsed by week 12 was 10.8% in the placebo group and 7.5% in the TID group, representing a relative reduction of 30% ($P = 0.0451$).

The risk of 12-week confirmed progression of disability was significantly reduced by DMF beginning at week 62 in the BID group, compared with placebo (Fig. 2c). In the TID group, the risk of 12-week confirmed progression of disability was significantly reduced at week 60 and at weeks 72–96, compared with placebo (Fig. 2c). On the basis of Kaplan–Meier estimates, the proportion of patients with confirmed 12-week disability progression at week 62 was 15.7% in the placebo group and 11.6% in the DMF BID group, representing a relative reduction of 26% ($P = 0.0454$ versus placebo), and at week 72 was 16.8% in the placebo group and 12.7% in the DMF TID group, representing a relative reduction of 26% ($P = 0.0399$ versus placebo).

Magnetic resonance imaging end-points

The odds of having a higher number of Gd+ lesions and the adjusted mean number of new or enlarging T2 lesions were significantly reduced by DMF BID and TID compared with placebo beginning at the first post-treatment assessment of MRI activity at week 24 (Fig. 3). The odds of having a higher number of Gd+ lesions was reduced by 88% (BID) and 75% (TID) at week 24, by 90% (BID) and 82% (TID) at week 48, and by 83% (BID) and 70% (TID) at week 96, compared with placebo ($P < 0.0001$ for all comparisons). The adjusted mean number of T2 lesions was reduced by 72% (BID) and 67% (TID) at week 24, by 79% (BID) and 76% (TID) from week 24 to week 48, and by 82% (BID) and 76% (TID) from week 48 to week 96, compared with placebo ($P < 0.0001$ for all comparisons).

Discussion

In this *post hoc* analysis of integrated data from DEFINE and CONFIRM, DMF significantly reduced the ARR within the first 12 weeks of initiation (BID and TID), the cumulative risk of relapse within 10 weeks (BID) to 12 weeks (TID) of initiation, and the 12-week confirmed disability progression beginning at week 62 (BID) and week 72 (TID), compared with placebo. The effects on relapse rates further increased during the second trimester and were generally sustained throughout the 2-year study period, with the exception of one 12-week interval (weeks 61–72) in which the reduction in ARR with DMF was not statistically significant, probably due to a transient decrease in the ARR in the placebo group. On neuroradiological measures, DMF BID and TID

Table 1 Annualized relapse rate (ARR), rate ratio and relative reduction

Week	ARR			Rate ratio (95% CI)		Relative reduction	
	Placebo	DMF[a] BID	DMF[a] TID	DMF[a] BID	DMF[a] TID	DMF[a] BID (%)	DMF[a] TID (%)
0–12	0.42	0.28	0.29	0.66 (0.47, 0.93)[b]	0.69 (0.49, 0.97)[b]	34	31
13–24	0.44	0.21	0.20	0.47 (0.32, 0.70)[e]	0.47 (0.32, 0.69)[e]	53	53
25–36	0.37	0.19	0.21	0.51 (0.34, 0.77)[c]	0.55 (0.36, 0.83)[c]	49	45
37–48	0.34	0.17	0.19	0.51 (0.32, 0.82)[c]	0.57 (0.37, 0.90)[b]	49	43
49–60	0.32	0.17	0.12	0.53 (0.34, 0.84)[c]	0.39 (0.24, 0.65)[d]	47	61
61–72	0.17	0.10	0.14	0.59 (0.34, 1.03)	0.80 (0.48, 1.32)	41	20
73–84	0.28	0.15	0.13	0.54 (0.33, 0.90)[b]	0.46 (0.27, 0.79)[c]	46	54
85–96	0.26	0.15	0.13	0.58 (0.35, 0.97)[b]	0.51 (0.30, 0.88)[b]	42	49

BID, twice daily; CI, confidence interval; TID, three times daily. [a]DMF, delayed-release DMF (also known as gastro-resistant DMF); [b]$P < 0.05$, [c]$P < 0.01$, [d]$P < 0.001$, [e]$P < 0.0001$ versus placebo.
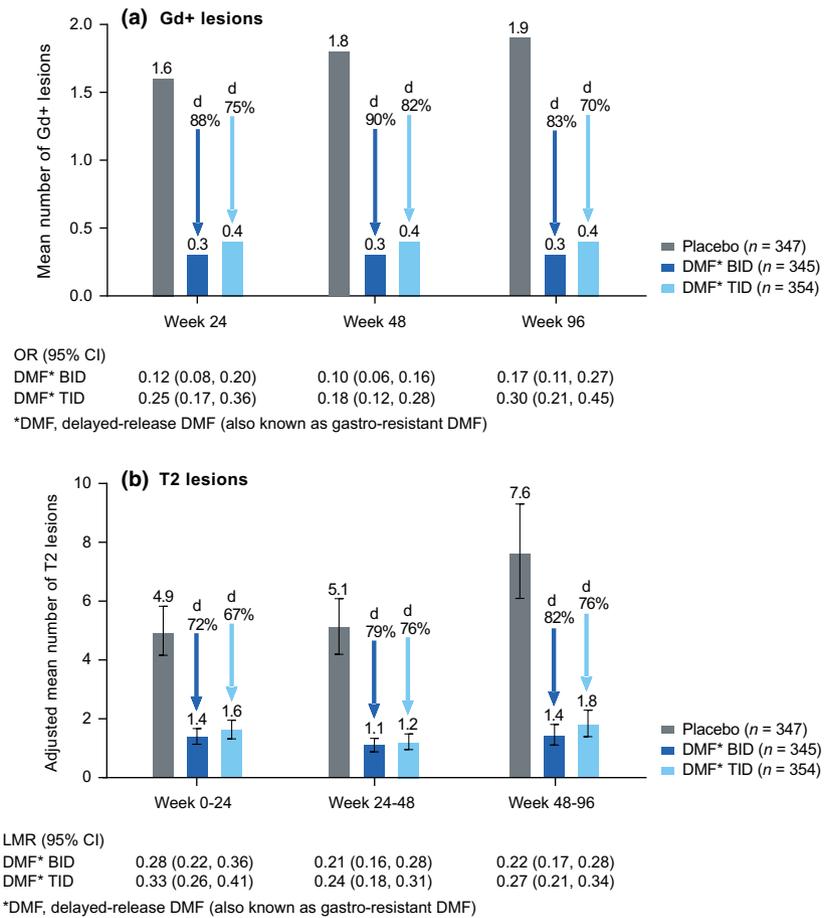
Figure 3 Gd+ and T2 lesions at weeks 24, 48 and 96. (a) Mean number of Gd+ lesions at weeks 24, 48 and 96. (b) Adjusted mean number of new and enlarging T2 lesions from week 0 to week 24, week 24 to week 48 and week 48 to week 96. BID, twice daily; CI, confidence interval; Gd+, gadolinium-enhancing; LMR, lesion mean ratio; OR, odds ratio; TID, three times daily.
[a]P < 0.05; [b]P < 0.01; [c]P < 0.001; [d]P < 0.0001 versus placebo.

significantly reduced the odds of having a higher number of Gd+ lesions and the mean number of T2 lesions at week 24 (the first post-treatment assessment of MRI activity), compared with placebo. These effects were sustained at weeks 48 and 96. Although based on a group analysis, this is important information that informs treating physicians and patients about when the effect of DMF treatment should be expected.

Rapid control of MS disease activity is critical for slowing disease progression, irreversible damage and associated disability [1]. Early in the course of MS, a greater frequency of relapses, a shorter interval between relapses and a higher number of new lesions on MRI are predictive of later disability progression [11–13]. Regarding disability progression, a nominal effect of DMF on 12-week confirmed disability progression was seen as early as weeks 36–48 and a statistically significant effect emerged at weeks 62–72 (Fig. 2c). Longer-term efficacy (beyond 2 years) on disability and other measures is being examined in ENDORSE (ClinicalTrials.gov identifier NCT00835770), an ongoing extension of DEFINE and CONFIRM.

The effects of DMF on MRI measures in the integrated analysis were consistent with those observed in a phase 2b trial [5] and follow-up analyses [14,15]. In the phase 2b study, DMF 240 mg TID reduced Gd+ lesion activity, the number of new or enlarging T2-hyperintense and T1-hypointense lesions, and the percentage of Gd+ lesions that evolved to T1-hypointense lesions, over 24 weeks [5,14,15]. The reduction in Gd+ lesion activity was evident by 8 weeks and was statistically significant by 12 weeks after initiation of DMF treatment [14]. The phase 2b trial did not include a DMF 240 mg BID arm. Effects on clinical end-points including ARR, risk of relapse and risk of 12-week confirmed disability progression were similar in the MRI cohort compared with the overall ITT population in both DEFINE [16] and CONFIRM [17].

It is important to note that the P values reported here should be interpreted with a certain degree of caution. As the analyses were post hoc, no adjustment for multiplicity was made.

DMF has an acceptable safety and tolerability profile. In clinical trials, the most common adverse events associated with DMF treatment were flushing and gastrointestinal events (nausea/vomiting, abdominal

pain and diarrhea) [3,4]. For most patients with events, these events were of mild or moderate severity. Other safety signals of note included a decrease in mean white blood cell and lymphocyte counts and a transient increase in mean liver transaminases. There was no increased risk of infection, serious infection, opportunistic infection or malignancy in DMF-treated patients.

In summary, the results of the present analysis suggest that DMF showed early and sustained clinical and neuroradiological activity in phase 3 clinical trials.

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Disclosure of conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Additional authors.

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