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Original Research Paper

Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: Interim analysis of ENDORSE, a randomized extension study

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Abstract

Background: Delayed-release dimethyl fumarate (DMF) demonstrated strong efficacy and a favorable benefit–risk profile for patients with relapsing–remitting multiple sclerosis (RRMS) in phase 3 DEFINE/CONFIRM studies. ENDORSE is an ongoing long-term extension of DEFINE/CONFIRM.

Objective: We report efficacy and safety results of a 5-year interim analysis of ENDORSE (2 years DEFINE/CONFIRM; minimum 3 years ENDORSE).

Methods: In ENDORSE, patients randomized to DMF 240 mg twice (BID) or thrice daily (TID) in DEFINE/CONFIRM continued this dosage, and those initially randomized to placebo (PBO) or glatiramer acetate (GA) were re-randomized to DMF 240 mg BID or TID.

Results: For patients continuing DMF BID (BID/BID), annualized relapse rates were 0.202, 0.163, 0.139, 0.143, and 0.138 (years 1–5, respectively) and 63%, 73%, and 88% were free of new or enlarging T2 hyperintense lesions, new T1 hypointense lesions, and gadolinium-enhanced lesions, respectively, at year 5. Adverse events (AEs; serious adverse events (SAEs)) were reported in 91% (22%; BID/BID), 95% (24%; PBO/BID), and 88% (16%; GA/BID) of the patients. One case of progressive multifocal leukoencephalopathy was reported in the setting of severe, prolonged lymphopenia.

Conclusion: Treatment with DMF was associated with continuously low clinical and magnetic resonance imaging (MRI) disease activity in patients with RRMS. These interim data demonstrate a sustained treatment benefit and an acceptable safety profile with DMF.

Keywords: Relapsing–remitting multiple sclerosis, delayed-release dimethyl fumarate (DMF), Expanded Disability Status Scale, ENDORSE, DEFINE

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Introduction

Delayed-release dimethyl fumarate (DMF) is an oral treatment for patients with relapsing–remitting multiple sclerosis (RRMS).[1,2] In two 2-year pivotal phase 3 trials (DEFINE and CONFIRM) in patients with RRMS, DMF significantly reduced clinical and magnetic resonance imaging (MRI) activity and demonstrated an acceptable safety profile.[3,4] ENDORSE is an ongoing 12-year extension of DEFINE/CONFIRM designed to evaluate the long-term efficacy and safety of DMF. We report a 5-year interim analysis (2 years DEFINE/CONFIRM; 3 years ENDORSE) of clinical and MRI outcomes and safety from ENDORSE. This report focuses on data for DMF 240 mg twice daily (BID; the approved dosage); however, data for all treatment groups are presented in figures or tables.

Methods

Patients and study design

In DEFINE/CONFIRM, eligible patients were of age 18–55 years, had a diagnosis of RRMS,[5] an Expanded

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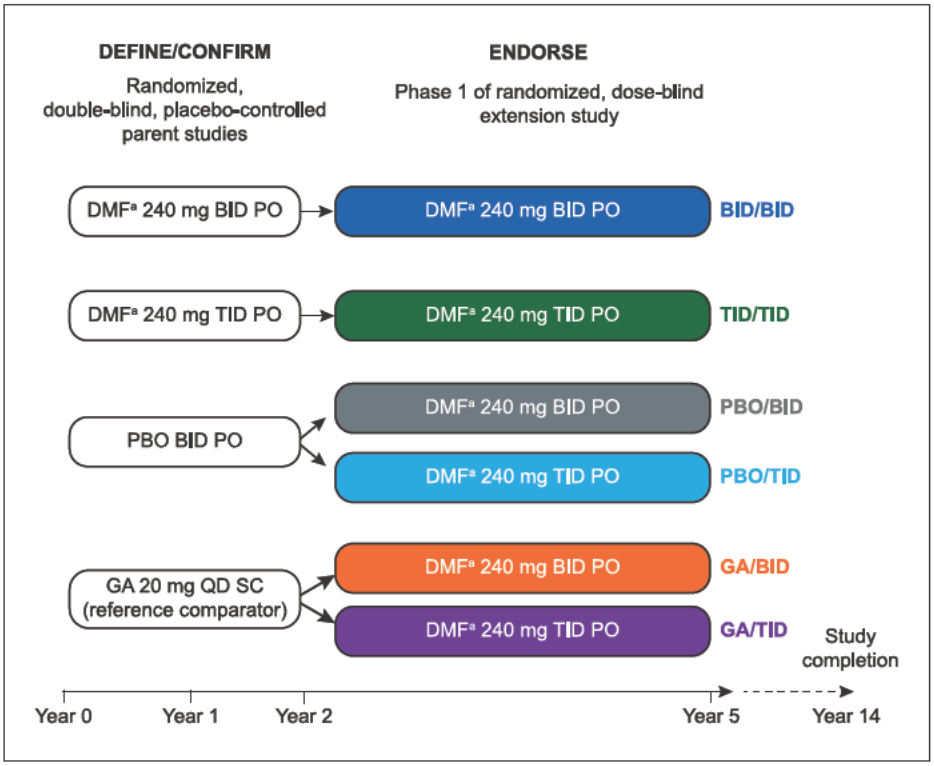

Figure 1. Design of ENDORSE extension study (phase 1).
BID: twice daily; DMF: dimethyl fumarate; GA: glatiramer acetate; PBO: placebo; PO: by mouth; QD: once daily; SC: subcutaneous; TID: thrice daily.
[a]DMF: delayed-release DMF.

Disability Status Scale (EDSS)[6] score of 0–5.0, and ⩾1 relapse within 1 year before randomization or ⩾1 gadolinium-enhanced (Gd+) lesion 0–6 weeks before randomization. Key exclusion criteria included relapse or corticosteroid treatment within 50 days before randomization or prior treatment with glatiramer acetate (GA) within 3 months before randomization (DEFINE) or at any time (CONFIRM). Patients were randomized to DMF 240 mg BID or thrice daily (TID) or placebo (PBO; 1:1:1 in DEFINE) or daily GA 20 mg (1:1:1:1 in CONFIRM) for 96 weeks.[3,4]

ENDORSE enables up to 14 years of follow-up (2 years DEFINE/CONFIRM + 12-year extension; Figure 1). Originally designed as a multicenter, randomized, dose-blind, dose-comparison study, patients who received DMF 240 mg BID or TID in either parent study remained on the same dosage in ENDORSE. Patients who received PBO or GA were randomized 1:1 to DMF 240 mg BID or TID. After initiation of ENDORSE, DMF was approved for RRMS in several countries at 240 mg BID. A protocol amendment (approved March 2014) outlines a second, open-label phase (beyond year 5), in which all participants receiving DMF 240 mg TID are switched to BID dosing.

ENDORSE enrolled eligible patients who completed DEFINE/CONFIRM, excluding those who experienced significant changes in medical history, withdrew consent; discontinued study treatment; or if alanine transaminase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transpeptidase increased to >3 times the upper limit of normal (ULN). The final (week 96) visit of DEFINE/CONFIRM served as the baseline for ENDORSE; patients were followed every 4 weeks for 24 weeks and every 12 weeks thereafter for up to 12 years.

Efficacy assessments

The primary efficacy endpoint was the proportion of patients relapsed at 2 years (DEFINE) and annualized relapse rate (ARR) at 2 years (CONFIRM). Additional endpoints included time to 12-week sustained disability progression and number of new T1 hypointense lesions (T1), new or enlarging T2 hyperintense lesions (T2), and Gd+ lesions at 2 years. Relapse (confirmed by an Independent Neurologic Evaluation Committee) was defined as new or recurrent neurologic symptoms lasting ⩾24 hours, accompanied by new objective neurologic findings.

Secondary objectives of ENDORSE include assessment of long-term ARR, proportion of patients relapsed, disability progression (measured every 6 months by EDSS), and MRI assessments of brain lesions. Patients at sites with validated MRI capability were eligible to participate in the MRI portion of DEFINE/CONFIRM and could continue in the MRI cohort at the same ENDORSE site.[3,4] MRI scans were performed yearly for each patient by the same reading center as that of the parent study. MRI endpoints included number of T1, T2, and Gd+ lesions and percentage of patients free of these lesions. Normalized brain volume was determined at baseline of DEFINE/CONFIRM and ENDORSE, and percent brain volume change (PBVC) was calculated automatically for each post-baseline MRI visit relative to baseline.

Safety assessments

The primary objective of ENDORSE was evaluation of long-term safety of DMF in patients with RRMS. Adverse events (AEs) and concomitant medications were monitored and recorded continuously. Laboratory assessments were performed on a schedule: blood chemistry and urinalysis at baseline, every 4 weeks until week 24, and every 12 weeks thereafter and hematological parameters at baseline and every 12 weeks for up to 12 years. On initiation of the amended protocol, the frequency of some study procedures was decreased to every 24 weeks; however, patients continued visits every 12 weeks for drug dispensing and vital signs assessment.

Patients who completed or discontinued DMF and had a lymphocyte count less than the lower limit of normal (LLN) were followed at least every 12 weeks until lymphocyte counts recovered or until 48 weeks after the last dose (whichever came sooner). Unscheduled relapse assessment was performed as necessary.

Statistical analysis

This 5-year interim analysis (data cutoff date: 14 May 2014) included patients who received ⩾1 dose of DMF in ENDORSE. Results are summarized throughout DEFINE/CONFIRM (years 1–2) and ENDORSE (years 3–5). Data are presented according to treatment received in the parent or extension study: continuing DMF (BID/BID and TID/TID) and new to DMF (PBO/BID, PBO/TID, GA/BID, and GA/TID). To increase sample size in the brain atrophy analysis, DMF BID/TID dosing was pooled from the groups new to DMF.

A Poisson or negative binomial regression model was used to analyze ARR. The proportion of patients relapsed or with progression was estimated based on the Kaplan–Meier product limit method. Disability progression was defined as ⩾1.0-point increase in EDSS from baseline EDSS = 1.0 sustained for 24 weeks or ⩾1.5-point increase in EDSS from baseline EDSS = 0 sustained for 24 weeks. Numbers of T1 and T2 lesions were analyzed by negative binomial regression model, adjusted for region and lesion volume at DEFINE/CONFIRM baseline. Number of Gd+ lesions was analyzed by logit regression.

Comparisons of brain atrophy between BID/BID and PBO/DMF and GA/DMF were based on the analysis of covariance of ranked data, adjusted for DEFINE/CONFIRM or ENDORSE baseline number of Gd+ lesions and T2 lesion volume.

No sample size was calculated for ENDORSE; number of eligible patients was determined by the number of DEFINE/CONFIRM participants.

Safety parameters were tabulated according to the treatment received during parent study or extension phase 1, continuing DMF (BID/BID and TID/TID) and new to DMF (PBO/BID, PBO/TID, GA/BID, and GA/TID), and summarized using descriptive statistics.

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

Efficacy data are described below for the DMF BID dosage and reported for DMF TID in tables or figures; safety data for both dosages are summarized below.

Patients

Of 2651 patients randomized and dosed in DEFINE/CONFIRM, 2079 completed these studies and 1736 were enrolled and dosed in ENDORSE (intention-to-treat (ITT) population): BID/BID, $n = 501$; TID/TID, $n = 502$; PBO/BID, $n = 249$; PBO/TID, $n = 248$; GA/BID, $n = 118$; and GA/TID, $n = 118$. As of 14 May 2014, total follow-up for this 5-year interim analysis was 4981 patient-years. Follow-up of patients

continuing and new to DMF was 3058 and 1923 patient-years, respectively. For BID/BID patients remaining on study ($n=364$), minimum follow-up was ~5 years. Among patients new to DMF BID in ENDORSE, minimum follow-up for those remaining on study ($n=163$) was ~3 years (Supplementary Table e-1). Of the DEFINE/CONFIRM MRI cohort ($n=1221$), 746 were treated in ENDORSE: 363 received DMF BID and 383 DMF TID. Patient disposition is presented in Figure 2. Baseline demographic and disease characteristics at the start of DEFINE/CONFIRM were generally well balanced across treatment groups and were similar between the ENDORSE ITT population (Table 1) and MRI cohort (Supplementary Table e-2).

Efficacy

Relapses. Cumulative ARR for ENDORSE BID/BID patients during years 0–5 was 0.163 (95% confidence interval (95% CI): 0.140, 0.190; Figure 3(a) presents ARRs by yearly interval), and the estimated proportion relapsed at 5 years was 40.1% (95% CI: 35.9%, 44.7%; Figure 3(b)).

Cumulative ARR for ENDORSE PBO/BID patients during years 0–5 was 0.240 (95% CI: 0.196, 0.296). Improvements were generally observed following the switch from PBO to DMF after year 2 (Figure 3(a)). The estimated proportion of PBO/BID patients relapsed at 5 years was 51.5% (95% CI: 45.2%, 58.1%; Figure 3(b)).

Cumulative ARR for ENDORSE GA/BID patients during years 0–5 was 0.199 (95% CI: 0.148, 0.269; Figure 3(a) presents data by yearly interval), and the estimated proportion relapsed at 5 years was 42.1% (95% CI: 33.5%, 52.0%; Figure 3(b)).

Disability progression. An estimated 18.6% (95% CI: 15.3%, 22.4%) of ENDORSE BID/BID patients had confirmed 24-week EDSS progression after 5 years (Figure 3(c)). For PBO/BID patients, the estimated proportion with disability progression after 5 years was 21.1% (95% CI: 16.2%, 27.1%; Figure 3(c)); for GA/BID patients, the corresponding proportion was 25.7% (95% CI: 18.4%, 35.2%; Figure 3(c)).

MRI outcomes

Patients continuing DMF in ENDORSE. Among ENDORSE BID/BID patients, 73% and 63% were free of T1 and T2 lesions, respectively, during years 4–5; 88% were free of Gd+ lesions (year 5 scan). For BID/BID patients, adjusted mean number of T1 and T2 lesions during years 4–5 was 0.5 (95% CI: 0.3, 0.7) and 1.2 (95% CI: 0.8, 1.8), respectively (Figure 4(a) and (b)); mean (±standard error (SE)) number of Gd+ lesions at year 5 was 0.2 ± 0.05 (Figure 4(c)).

Patients new to DMF in ENDORSE. Of ENDORSE PBO/BID patients, 85% and 68% were free of T1 and T2 lesions, respectively, during years 4–5; 82% were free of Gd+ lesions (year 5 scan). For PBO/BID patients, adjusted mean number of T1 and T2 hyperintense lesions during years 4–5 was 0.2 (95% CI: 0.1, 0.5) and 0.8 (95% CI: 0.4, 1.5), respectively (Figure 4(a) and (b)); mean (±SE) number of Gd+ lesions at year 5 was 0.2 ± 0.06 (Figure 4(c)).

Of ENDORSE GA/BID patients, 64% and 62% were free of T1 and T2 lesions, respectively, during years 4–5 and 86% were free of Gd+ lesions (year 5 scan). For GA/BID patients, adjusted mean number of T1 and T2 lesions during years 4–5 was 0.7 (95% CI: 0.3, 1.7) and 1.6 (95% CI: 0.7, 3.8), respectively, and mean (±SE) number of Gd+ lesions at year 5 was 0.6 ± 0.48.

Brain atrophy. At year 2 of DEFINE/CONFIRM, among patients in ENDORSE, adjusted PBVC from baseline was significantly lower with DMF BID versus PBO ($p=0.0070$); in post hoc exploratory analyses, significantly lower PBVC was observed versus GA ($p=0.0035$; Table 2). Adjusted PBVC relative to ENDORSE baseline at years 3, 4, and 5 was not significantly different in BID/BID patients compared with the PBO/DMF or GA/DMF groups (Table 2). Annualized rate of adjusted mean PBVC calculated throughout 5 years of follow-up was −0.32 per year (95% CI: −0.37, −0.27)) in BID/BID patients, comparable with that of healthy volunteers.[7]

Safety. The overall incidence of AEs, serious AEs (SAEs), and discontinuations due to AEs (Supplementary Table e-3) was similar among the treatment groups who continued DMF from DEFINE/CONFIRM and those new to DMF; however, a higher proportion of patients new to DMF discontinued due to AEs, largely from flushing and gastrointestinal (GI) events that tend to occur early in DMF therapy.[3,4,8] The most common individual AEs and SAEs are summarized in Table 3. Multiple sclerosis (MS) relapse and nasopharyngitis were most common in patients continuing DMF. Flushing and GI-related events were more common among patients new to DMF, with incidences highest during the first year of ENDORSE (Supplementary Figure e-1) and generally consistent with those of DMF-treated patients in the parent studies, wherein incidences were highest during the first month and decreased substantially thereafter.[3,4,8]

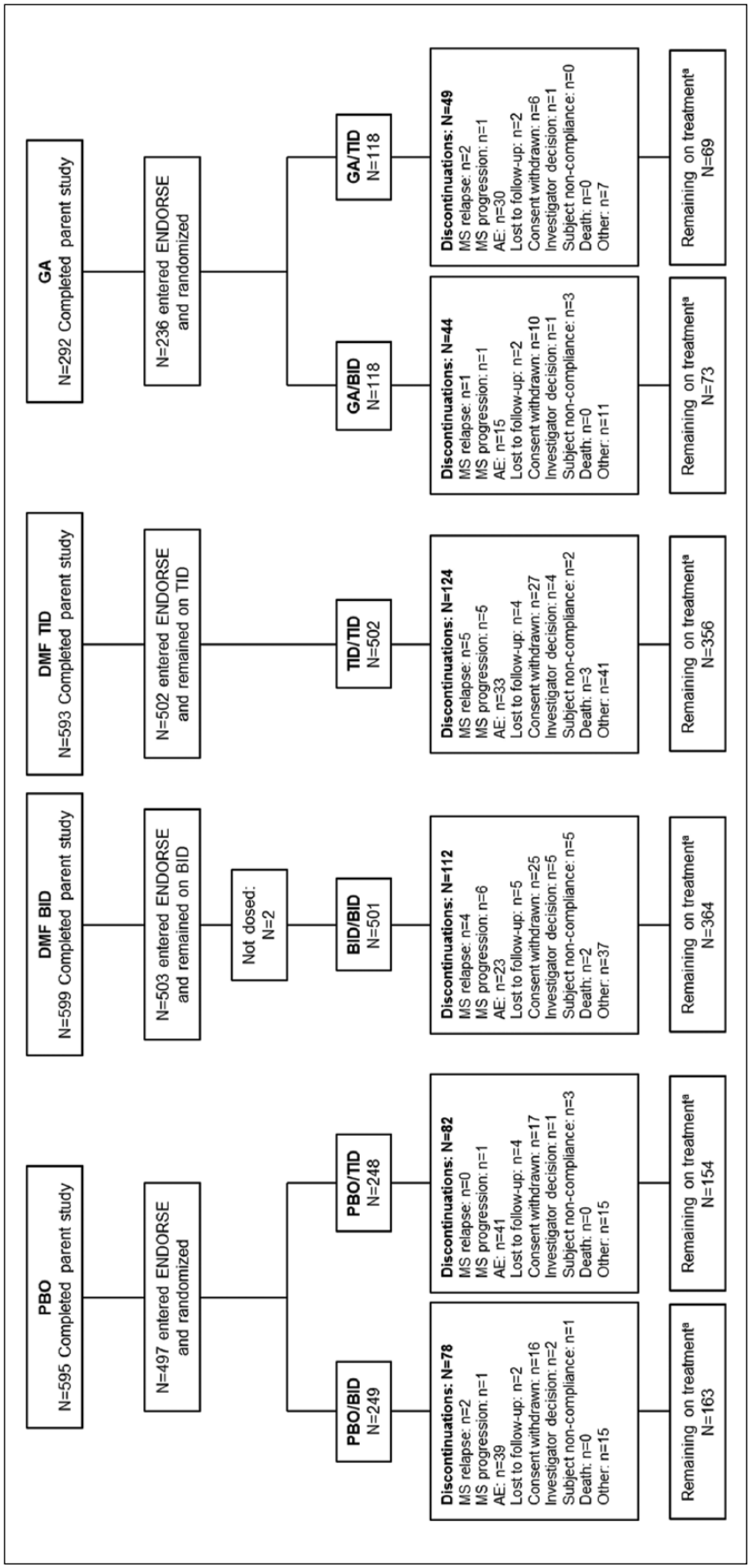

Figure 2. Patient disposition.
AE: adverse event; BID: twice daily; DMF: dimethyl fumarate; GA: glatiramer acetate; MS: multiple sclerosis; PBO: placebo; TID: thrice daily.
[a]Some additional patients ($n=68$ across treatment groups) completed ENDORSE at year 2, prior to the protocol amendment extending the study duration.

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