



Efficacy of Dimethyl Fumarate in Young Adults with Relapsing-Remitting Multiple Sclerosis: Analysis of the DEFINE, CONFIRM, and ENDORSE Studies

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ABSTRACT

Introduction: Dimethyl fumarate (DMF) showed favorable benefit-risk in patients with relapsing-remitting multiple sclerosis (MS) in phase 3 DEFINE and CONFIRM trials and in the ENDORSE extension study. Disease activity can differ in younger patients with MS compared with the overall population.

Methods: Randomized patients received DMF 240 mg twice daily or placebo (PBO; years 0–2

DEFINE/CONFIRM), then DMF (years 3–10; continuous DMF/DMF or PBO/DMF; ENDORSE); maximum follow-up (combined studies) was 13 years. This integrated post hoc analysis evaluated safety and efficacy of DMF in a subgroup of young adults aged 18–29 years.

Results: Of 1736 patients enrolled in ENDORSE, 125 were young adults, 86 treated continuously with DMF (DMF/DMF) and 39 received delayed DMF (PBO/DMF) in DEFINE/CONFIRM. Most ($n = 116$ [93%]) young adults completed DMF treatment in DEFINE/CONFIRM. Median (range) follow-up time in ENDORSE was 6.5 (2.0–10.0) years. Young adults entering ENDORSE who had been treated with DMF in DEFINE/CONFIRM had a model-

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based Annualized Relapse Rate (ARR; 95% CI) of 0.24 (0.16–0.35) vs. 0.56 (0.35–0.88) in PBO patients. ARR remained low in ENDORSE: 0.07 (0.01–0.47) at years 9–10 (DMF/DMF group). At year 10 of ENDORSE, EDSS scores were low in young adults: DMF/DMF, 1.9 (1.4); PBO/DMF, 2.4 (1.6). At ~ 7 years, the proportion of young adults with no confirmed disability progression was 81% for DMF/DMF and 72% for PBO/DMF. Patient-reported outcomes (PROs) (SF-36 and EQ-5D) generally remained stable during ENDORSE. The most common adverse events (AEs) in young adults during ENDORSE were MS relapse ($n = 53$ [42%]). Most AEs were mild ($n = 20$ [23.3%], $n = 7$ [17.9%]) to moderate ($n = 45$ [52.3%], $n = 23$ [59.0%]) in the DMF/DMF and PBO/DMF groups, respectively. The most common serious AE (SAE) was MS relapse ($n = 19$ [15%]).

Conclusion: The data support a favorable benefit-risk profile of DMF in young adults, as evidenced by well-characterized safety, sustained efficacy, and stable PROs.

Clinical Trial Information: Clinical trials.gov, DEFINE (NCT00420212), CONFIRM (NCT00451451), and ENDORSE (NCT00835770).

Keywords: Dimethyl fumarate; DMT; Efficacy; Multiple sclerosis; Safety; Young adults

Key Summary Points

Why carry out this study?

Patients with early onset MS are reported to relapse more frequently and have significant disability at an earlier age; therefore, disease-modifying therapy initiated early in the disease course is critical for preventing disease worsening

This study investigates the relationship between MS disease activity and effect of DMF treatment on efficacy and safety outcomes in young adults aged between 18 and 29 years compared with the overall ENDORSE population (ages 18–55)

What was learned from the study?

This study supports a favorable benefit-risk profile of DMF in young adults, with incidence of AEs and SAEs consistent with those observed in the adult population and most AEs being mild to moderate in severity

Young adults taking DMF during DEFINE/CONFIRM showed reductions in ARR and number of Gd+ lesions relative to PBO patients and consistent with the overall population

DMF demonstrated sustained efficacy in the young adult population in the ENDORSE extension study: ARR remained stable and low over 10 years, with most patients not experiencing a relapse, and PROs remained stable

INTRODUCTION

Multiple sclerosis (MS) is a chronic, demyelinating, inflammatory disease typically diagnosed at age 20–40 years [1, 2]. In young adults, MS is a major cause of non-traumatic disability [2], placing a substantial burden on individuals and society due to the long-term loss of productivity, physical and cognitive disability, fatigue, comorbidity, assistance with daily living, and multidisciplinary healthcare requirements [3]. Patients with early-onset MS are reported to relapse more frequently, with higher disease activity compared with their adult counterparts; although disability accumulation occurs at a slower rate, younger patients eventually have significant disability at an earlier age [4–7]. These features suggest that younger patients with MS experience a more inflammatory disease course than older patients [6, 8]. As a heterogeneous chronic disease, treatment goals for MS among younger patients therefore include prompt intervention for prevention of relapses and disability accumulation [2, 9]. A disease-modifying therapy (DMT), initiated early in the disease course [10, 11], is critical for preventing confirmed disability worsening

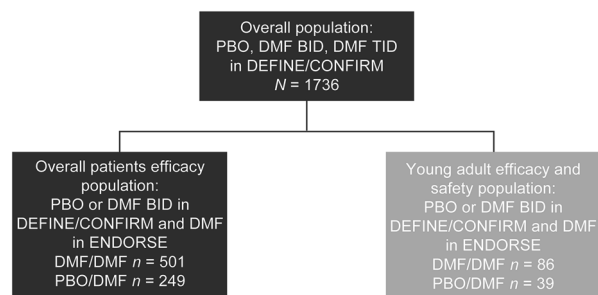


Fig. 1 Patient populations for safety, efficacy, and lymphocyte analysis. *BID* twice daily, *DMF* dimethyl fumarate, *PBO* placebo, *TID* three times daily

(CDW) and maintenance of low relapse rates to meet these goals.

Dimethyl fumarate (DMF; Tecfidera, BG00012) is approved worldwide for the treatment of relapsing forms of MS [12]. As of December 31, 2022, > 585,000 patients have received DMF, representing > 1,333,000 patient-years of exposure. In two pivotal phase 3 studies, DEFINE (NCT00420212) and CONFIRM (NCT00451451), and the completed long-term extension study, ENDORSE (NCT00835770), DMF demonstrated strong efficacy on clinical and radiologic measures and a favorable benefit-risk profile in patients with relapsing-remitting MS [13–15]. Real-world trial data have also been consistent with the favorable efficacy and safety profile of DMF demonstrated in phase 3 trials [16, 17], in addition to demonstrating improvements on patient-reported outcomes (PROs) [18–20].

We report the results of an integrated post hoc analysis of the two pivotal phase 3 studies, DEFINE and CONFIRM, and their long-term extension study, ENDORSE, investigating the relationship between MS disease activity and effect of DMF treatment on efficacy and safety outcomes in young adults aged between 18 and 29 years compared with the overall ENDORSE population (ages 19–58) [21].

METHODS

Patients

Patients entered ENDORSE [21] following completion of DEFINE [15] or CONFIRM [14]. Patient details for DEFINE and CONFIRM were reported previously [21]. In this report, young adult patients were defined as adults aged 18–29 years [6].

Study Design

ENDORSE [21] was an extension of DEFINE [15] and CONFIRM [14], 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 three times daily (TID) continued on the same dosage at the start of ENDORSE; patients randomized in the parent studies to placebo (PBO) or glatiramer acetate (GA; in 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 [13]. TID-treated patients were excluded from this analysis. 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) in ENDORSE were included in the safety analysis (Fig. 1). Data on adverse events (AEs) were collected throughout the study. Laboratory assessments included blood and urine samples at baseline (every 4 weeks until week

Table 1 Baseline demographic and disease characteristics in the ENDORSE young adult and overall populations

Characteristic ^{a,b}	DMF/DMF ^c <i>n</i> = 86	PBO/DMF <i>n</i> = 39	Overall YA <i>n</i> = 125	Overall ENDORSE <i>N</i> = 1736
Age, years ^d	24.2 (2.7)	23.6 (2.9)	24.0 (2.8)*	37.9 (9.1)
Age at diagnosis, years	21.9 (3.5)	21.3 (3.6)	21.7 (3.6)*	33.1 (8.9)
Childhood MS diagnosis, <i>n</i> (%)	9 (10.5)	6 (15.4)	15 (12.0)*	47 (2.7)
Female, <i>n</i> %	54 (62.8)	26.0 (66.7)	80.0 (64.0)	1212 (70)
Race/ethnicity, <i>n</i> %				
White	60 (69.8)	26 (66.7)	86 (68.8)	1417 (81.6)
Black or African American	1 (1.2)	1 (2.6)	2 (1.6)	26 (1.5)
Other ^e	24 (27.9)	10 (25.6)	34 (27.2)	224 (12.9)
Not reported	1 (1.2)	2 (5.1)	3 (2.4)	69 (4.0)
Time since first MS symptoms, years	3.7 (2.7)	3.7 (2.7)	3.7 (2.7)*	7.7 (6.3)
Time since diagnosis of MS, years	2.3 (2.4)	2.2 (2.2)	2.3 (2.3)*	4.8 (5.1)
Time on study, years ^e	4.7 (2.8)	4.2 (2.8)	4.5 (2.8)*	5.3 (2.9)
EDSS score	2.2 (1.26)	1.9 (0.93)	2.1 (1.17)*	2.5 (1.2)
Relapses in prior year	1.5 (0.8)	1.5 (0.8)	1.5 (0.8)*	1.3 (0.7)
No. of Gd+ lesions, <i>n</i> (%)				
0	15 (17.4)	7 (17.9)	22 (17.6)	470 (27.1)
1	7 (8.1)	4 (10.3)	11 (8.8)	118 (6.8)
2	3 (3.5)	3 (7.7)	6 (4.8)	71 (4.1)
3	3 (3.5)	3 (7.7)	6 (4.8)	41 (2.4)
≥ 4	9 (10.5)	2 (5.1)	11 (8.8)	95 (5.5)

Overall ENDORSE data have been previously published in Gold et al. *Mult Scler.* 2022;28(5):801–16

DMF dimethyl fumarate, EDSS Expanded Disability Status Scale, Gd+ gadolinium enhancing, MS multiple sclerosis, PBO placebo, YA young adults

*Significant difference between Overall YA and Overall ENDORSE population

^aValues are mean (standard deviation) unless otherwise stated

^bCharacteristics at ENDORSE baseline unless otherwise stated

^cDimethyl fumarate

^dAge at randomization

^eOther includes: Egyptian; Greek; Hispanic; Hispanic or Latino; Hispanic/mixed; Latino; Latino/Hispanic; Mixed; Mixed Race–Filipino, Irish, German; Mixed South African; Scottish and Portuguese/South African

^fNumber of years in study from baseline DEFINE/CONFIRM to ENDORSE

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 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 dataset stated above.

Efficacy Assessments

Annualized relapse rate (ARR) (relapse confirmed by an independent Neurologic Evaluation Committee)—defined as new or recurrent neurologic symptoms lasting ≥ 24 h, accompanied by new objective neurologic findings—was assessed for years 0–2 (DEFINE/CONFIRM) and 3–10 (ENDORSE). The proportion of patients relapsed at 10 years (8 years in ENDORSE) was evaluated. Confirmed disability progression (CDP) 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 [22, 23]. In addition, confirmed disability improvement (CDI) at 24 weeks (defined as an EDSS score decrease ≥ 1.0 -point in patients with a baseline score of ≥ 2.0 EDSS; confirmation 24 weeks later required) was assessed. Gadolinium-enhancing (Gd+), T2-hyperintense (T2), and T1-hypointense (T1) lesions were measured by MRI at 2 years in DEFINE/CONFIRM and at 8 years in ENDORSE. Similarly, no evidence of disease activity (NEDA-3), defined as no clinical or MRI worsening (clinical NEDA defined as no relapses or CDW; MRI NEDA defined as no Gd+ lesions or new/enlarging T2 lesions), was measured at 2 years in DEFINE/CONFIRM and at 8 years in ENDORSE. Patient-reported outcomes (PROs) were assessed using the 36-item Short Form Health Survey (SF-36) and EuroQol-5D (EQ-5D).

Patients who received DMF TID in DEFINE/CONFIRM/ENDORSE or GA in CONFIRM were excluded to focus on the approved DMF BID dosage for this analysis.

Statistical Analysis

Safety parameters were summarized using descriptive statistics, and ALC over time was assessed. ALC was characterized using Common Terminology Criteria for Adverse Events: $< 0.5 \times 10^9/L$ (grade 3/4, 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) [12]. 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 number of relapses in the year prior to study entry, baseline EDSS score, and follow-up time. The proportion of patients relapsed at 10 years was based on the Kaplan-Meier product limit method. Cox proportional-hazards model assessed time to first CDP and CDI.

RESULTS

Patients

Of 2079 patients who completed DEFINE/CONFIRM, 1736 entered ENDORSE and received ≥ 1 dose of DMF (ENDORSE intent-to-treat and safety population; Fig. 1) [21]. Overall, 501 patients were continuously treated with DMF BID (DMF/DMF), and 249 received delayed DMF BID treatment (PBO/DMF). The young adult population comprised 125 patients; 86 were continuously treated with DMF BID (DMF/DMF) and 39 received delayed DMF treatment (PBO/DMF) (Fig. 1).

Patient baseline demographics are shown in Table 1. Most young adults completed DMF treatment in DEFINE/CONFIRM ($n = 116$ [93%]). The median (range) total follow-up time from randomization in DEFINE/CONFIRM and ENDORSE for young adults was 6.5 (2.0–10.0)

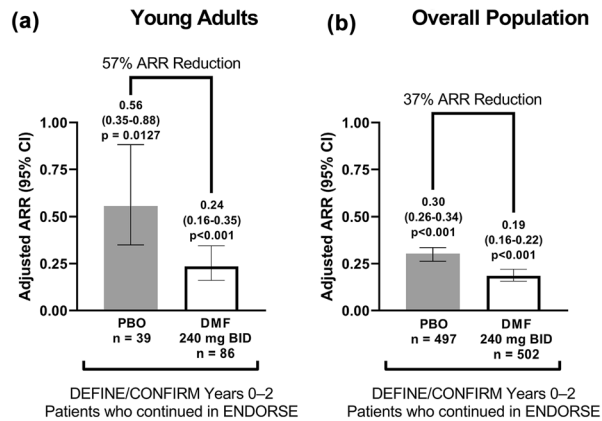


Fig. 2 ARR during treatment with PBO or DMF (years 0–2 in DEFINE/CONFIRM) in **a** young adults and **b** the overall population. ARR annualized relapse rate, BID twice daily, CI confidence interval, DMF dimethyl fumarate, PBO placebo. Adjusted ARR and 95% CI are based on negative binomial regression, adjusting for Expanded Disability Status Scale scores at baseline and relapses in prior 12 months of study start. Relapse was defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting ≥ 24 h accompanied by new objective neurologic findings upon examination by the treating neurologist

years. Thirty-nine young adults had 7 years of follow-up in ENDORSE. Common reasons for study treatment discontinuation in the young adult population were consent withdrawn (18%), investigator decision (6%), AEs (5%), lost to follow-up (3%), MS progression (2%), MS relapse (2%), subject non-compliance (2%), and other reasons (23%).

Clinical Efficacy in the Young Adult and Overall ENDORSE Patient Population

Young adults patients who entered ENDORSE following treatment with 240 mg DMF BID during DEFINE/CONFIRM had a model-based ARR (95% confidence interval [CI]) of 0.24 (0.16–0.35) compared with 0.56 (0.35–0.88) in patients treated with PBO during the same treatment period (Fig. 2a). This was in line with the overall population, where patients entering ENDORSE after treatment with DMF over years 0–2 had a model-based ARR (95% CI) of 0.19

(0.16–0.22) compared with 0.30 (0.26–0.34) in patients treated with PBO (Fig. 2b).

In young adult patients continuously treated with DMF BID (DMF/DMF) in ENDORSE, the ARR (95% CI) adjusted for baseline disease and demographic characteristics remained low, from 0.17 (0.10–0.29) in the first year to 0.07 (0.01–0.47) in years 9–10 (Fig. 3a). ARR (95% CI) remained consistent and low in the overall population, from 0.20 (0.16–0.25) in the first year to 0.11 (0.07–0.17) in years 9–10 (Fig. 3b). The estimated proportion of young adult patients with relapses at 2 years (96 weeks) was 30.2% for DMF/DMF and 59.0% for placebo (PBO/DMF) treatment groups (see Fig. S1 in the electronic supplementary material).

After ~ 8 years of DMF treatment in ENDORSE (year 10), mean (standard deviation [SD]) EDSS scores were low in both the young adult and overall populations: DMF/DMF, 1.9 (1.4); PBO/DMF, 2.4 (1.6) in the young adult subpopulation and DMF/DMF, 2.0 (1.4); PBO/DMF, 1.5 (0.0) in the overall population. Rates of CDP were low over the course of the study; in the young adult subpopulation, the proportion of patients with no 24-week CDP (combined DEFINE/CONFIRM and ENDORSE data) at 96 weeks was 96% and 78% for DMF/DMF and PBO/DMF, respectively. At 336 weeks (~ 7 years), the proportion of young adult patients with no CDP was 81% for DMF/DMF and 72% for PBO/DMF (Fig. 4). In the overall population, over 10 years, the proportion of patients with no CDP was 72% of DMF/DMF and 73% of PBO/DMF patients. In young adult patients, EDSS scores were ≤ 3.5 at year 2 and year 10, respectively, for 92.4% (85/92) and 92.9% (26/28) of DMF/DMF patients and 88.4% (38/43) and 90.9% (10/11) of PBO/DMF patients. In the overall population, 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. The proportion of patients with CDI at 96 weeks was 13% for DMF/DMF and 8% for PBO/DMF and 20% for DMF/DMF and 8% for PBO/DMF at 336 weeks (Fig. S2 in the supplementary material).

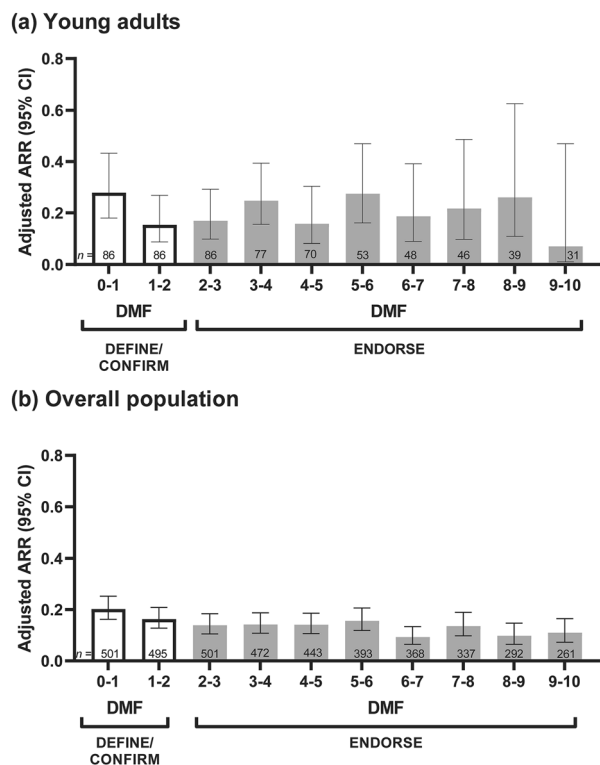


Fig. 3 Adjusted ARR (objective relapses) by yearly interval for the DMF/DMF group in **a** the young adult patient DMF/DMF population and **b** the overall ENDORSE population over 10 years (ENDORSE 8 years). ARR annualized relapse rate, CI confidence interval, DMF dimethyl fumarate. Adjusted ARR and 95% CI are based on negative binomial regression, adjusting for Expanded Disability Status Scale scores at baseline and relapses in prior 12-month of study start. Relapse was defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting ≥ 24 h accompanied by new objective neurologic findings upon examination by the treating neurologist

Radiologic Efficacy in the Young Adult Patient Population

In DEFINE/CONFIRM, mean (SD) number of Gd+ lesions decreased from baseline to week 96 in DMF-treated young adult patients (3.8 [8.0] vs. 0.6 [1.6]), but remained unchanged in PBO-treated patients (1.5 [1.7] vs. 1.4 [1.6]). This is in line with what was observed in the overall population: mean (SD) number of Gd+ lesions decreased from baseline to week 96 in the DMF-treated group (1.9 [5.0] vs. 0.3 [1.3]) and

remained unchanged in the PBO-treated patients (2.2 [5.9] vs. 1.8 [4.9]).

The estimated proportion of patients with NEDA-3 in DEFINE/CONFIRM who entered the ENDORSE study was 54.1% in the young adult DMF-treated patients and 26.3% in the PBO-treated patients at 48 weeks and 43.2% versus 15.8% at 96 weeks following randomization in DEFINE/CONFIRM, respectively. Similarly, the estimated proportion of patients in the overall population with NEDA-3 at 48 weeks was 65.9% in DMF-treated patients and 46.4% in PBO-treated patients and 50.4% and 36.6% at 96 weeks in the DMF and PBO groups, respectively.

Safety and Tolerability

Among young adult patients, AEs experienced by $\geq 2\%$ patients in any treatment group and serious AEs (SAEs) experienced by ≥ 5 patients in any treatment group are summarized in Table 2. The most common AEs in the young adult population during ENDORSE were MS relapse ($n = 53$ [42%]), flushing ($n = 31$ [25%]), and nasopharyngitis ($n = 30$ [24%]). Most AEs were mild ($n = 20$ [23.3%], $n = 7$ [17.9%]) to moderate ($n = 45$ [52.3%], $n = 23$ [59.0%]) in the DMF/DMF and PBO/DMF groups, respectively. The most common SAE was MS relapse ($n = 19$ [15%]). Overall incidence and type of AEs and SAEs among young adults were consistent with those reported in DEFINE and CONFIRM (Table S2 in the supplementary material) and were generally similar across treatment groups.

In ENDORSE, gastrointestinal disorders were reported for 37% of young adult patients and were higher for PBO/DMF (41%) compared with DMF/DMF (35%) (Table 3). These differences were driven by higher rates of incidence in the first year of ENDORSE for the patients switching to DMF from placebo in the PBO/DMF group and are consistent with the timing of gastrointestinal AEs reported in DMF-treated patients in DEFINE and CONFIRM [14, 15]. In DEFINE/CONFIRM, gastrointestinal disorders were reported for 62% DMF/DMF young adult patients compared with 56% PBO/DMF

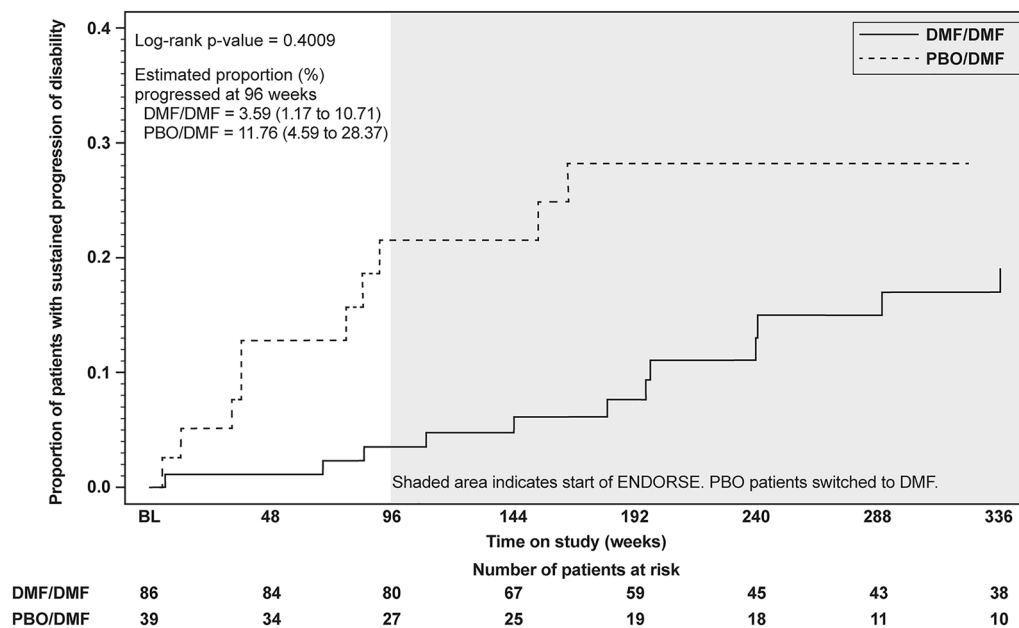


Fig. 4 Kaplan-Meier estimated proportion of patients with 24-week sustained confirmed disability progression^a at 336 weeks (7 years). *BL* baseline, *CI* confidence interval, *DMF* dimethyl fumarate, *PBO* placebo. ^aSustained disability progression defined as ≥ 1.0 -point increase on the Expanded Disability Status Scale (EDSS) from a baseline

EDSS ≥ 1.0 sustained for 24 weeks or a ≥ 1.5 -point increase on the EDSS from a baseline EDSS of 0 sustained for 24 weeks. Image cutoff at 336 weeks due to numbers at risk falling below 10 patients in both groups after this time point

patients. Similar differences were seen for flushing AEs between the DMF/DMF and PBO/DMF groups in ENDORSE (21% and 33%, respectively). Consistent with DEFINE/CONFIRM, microalbuminuria, proteinuria, and hematuria were the most common renal AEs reported (Table 3 and Table S2 in the supplementary material).

Absolute Lymphocyte Count

Post-baseline lymphocyte measurements were available in 81 and 38 young adult patients in the DMF/DMF and PBO/DMF groups, respectively. In the DMF/DMF group, ALC decreased over the first 48 weeks during DEFINE/CONFIRM (mean percent change from baseline ALC, -21.2% at week 48) and remained generally stable for the duration of the study (Fig. 5a). In the ENDORSE follow-up study, the PBO/DMF mean percent change in ALC in young adult patients at 48 weeks after DMF

initiation was -19.1% (week 144 for combined follow-up). An analysis of ALCs in DEFINE/CONFIRM of the young adult patients on DMF showed that 90% of patients had ALC values $> LLN$, whereas 4 (4.4%) had mild lymphopenia (ALC between 0.80 and $0.91 \times 10^9/L$); 3 (3.9%) and 1 (1.3%) of young adult patients developed moderate or severe lymphopenia, respectively (Fig. 5b).

In the overall population of ENDORSE, post-baseline lymphocyte measurements were available in 2222 of 2263 patients. Over the first 48 weeks, ALC decreased: at week 48, mean percentage change from baseline was -27.7% . ALC remained generally stable for the duration of the study and remained $\sim LLN$ ($0.91 \times 10^9/L$) for the majority (59%) of patients. Of patients treated with DMF, 235 (10.6%) developed prolonged moderate lymphopenia and 53 (2.4%) developed prolonged severe lymphopenia, [13].

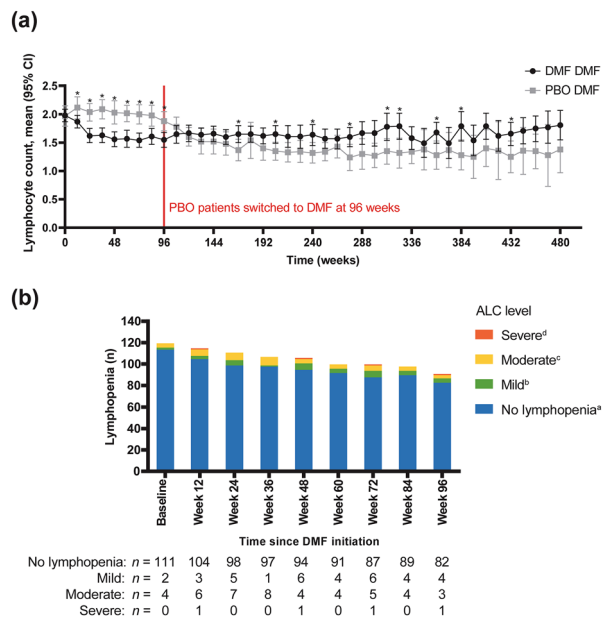


Fig. 5 **a** Lymphocyte mean values over time for young adults continually treated with DMF BID (DMF/DMF) and in young adults whose DMF treatment was delayed (PBO/DMF); **b** severity of lymphopenia over time in young adults treated with DMF. *ALC* absolute lymphocyte count, *BID* twice daily, *CI* confidence interval, *DMF* dimethyl fumarate, *PBO* placebo. **t*-test $p < 0.05$. ^aNo lymphopenia \geq LLN (ALC $\geq 0.91 \times 10^9/L$). ^bMild lymphopenia grade 1, ALC = ≥ 0.8 to $< 0.91 \times 10^9/L$. ^cModerate lymphopenia grade 2, ALC ≥ 0.5 to $< 0.8 \times 10^9/L$. ^dSevere lymphopenia grade 3/4, ALC $< 0.5 \times 10^9/L$.

Patient-reported Outcomes

Among young adults, PROs (SF-36 and EQ-5D) generally remained stable during ENDORSE (Fig. S3 in the supplementary material), which was consistent with the overall ENDORSE population [13].

DISCUSSION

This post hoc integrated analysis of the phase 3 studies DEFINE and CONFIRM and long-term extension study ENDORSE investigated the relationship between MS disease activity and effect of DMF treatment in young adults ages 18–29 years (mean [SD] age 24 [2.8] years) compared with the overall ENDORSE

population (37.9 [9.1] years at randomization). The data support a favorable benefit-risk profile of DMF in young adults, as evidenced by well-characterized safety, sustained efficacy, and stable PROs.

The incidences of AEs and SAEs in young adults were consistent with those observed in the overall adult population in the DEFINE/CONFIRM and real-world datasets. MS relapse, flushing, and nasopharyngitis were most frequently reported, and most AEs were mild to moderate in severity. ALC decreased over the first 48 weeks in young adults treated with DMF, consistent with data from the full adult population of DMF-treated patients, and remained generally stable thereafter. DMF decreases absolute lymphocyte counts but does not affect all subsets uniformly. It particularly decreases the pro-inflammatory T-helper Th1 and Th17 subsets, creating a bias toward more anti-inflammatory Th2 and regulatory subsets [24, 25].

In patients continually treated with DMF BID in DEFINE/CONFIRM and ENDORSE, ARR remained stable and low over 10 years, and most patients in both the overall and young adult patient populations did not experience a relapse. Similarly, in both the overall and young adult populations in DEFINE/CONFIRM and ENDORSE, 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. Similar to the overall ENDORSE population, disability scores among young adults remained stable across the study period, with most (93%) DMF BID-treated patients maintaining walking ability over 7 years. Our CDI findings in young adults, together with the observation of a shorter time since first symptoms/diagnosis compared with the overall population, are consistent with literature supporting the benefit of starting DMT early in younger patients with MS [26]. PROs assessed as part of this integrated analysis were stable with continuous DMF treatment.

There is evidence that disease activity (ARR and number of MRI lesions) is higher in pediatric onset MS [6, 27, 28] and, as it has been shown to decline with age [28], it follows that it would be higher in younger adults with MS than in older adults. Our baseline data are

Table 2 Most common AEs (incidence $\geq 2\%$ in young adult treatment groups) and SAEs (experienced by ≥ 2 patients in any treatment group) in young adults and overall population in ENDORSE [13]

AEs, <i>n</i> (%)	DMF/DMF <i>n</i> = 86	PBO/DMF <i>n</i> = 39	Overall YA safety population <i>N</i> = 125	Overall ENDORSE <i>N</i> = 1736
Any AE	80 (93.0)	36 (92.3)	116 (92.8)	1638 (94.4)
Flushing	18 (20.9)	13 (33.3)	31 (24.8)	335 (19.3)
MS relapse	38 (44.2)	15 (38.5)	53 (42.4)	678 (39.1)
Nasopharyngitis	23 (26.7)	7 (17.9)	30 (24.0)	446 (25.7)
Urinary tract infection	21 (24.4)	5 (12.8)	26 (20.8)	364 (21.0)
Headache	19 (22.1)	6 (15.4)	25 (20.0)	277 (16.0)
Upper respiratory tract infection	11 (12.8)	5 (12.8)	16 (12.8)	280 (16.1)
Diarrhea	12 (14.0)	3 (7.7)	15 (12.0)	230 (13.2)
Microalbuminuria	10 (11.6)	5 (12.8)	15 (12.0)	116 (6.7)
Back pain	8 (9.3)	3 (7.7)	11 (8.8)	251 (14.5)
Proteinuria	9 (10.5)	2 (5.1)	11 (8.8)	157 (9.0)
Pyrexia	8 (9.3)	3 (7.7)	11 (8.8)	94 (5.4)
Nausea	6 (7.0)	4 (10.3)	10 (8.0)	117 (6.7)
Arthralgia	8 (9.3)	2 (5.1)	10 (8.0)	212 (12.2)
Albumin urine present	3 (3.5)	7 (17.9)	10 (8.0)	128 (7.4)
Depression	7 (8.1)	3 (7.7)	10 (8.0)	190 (10.9)
Dizziness	7 (8.1)	2 (5.1)	9 (7.2)	105 (6.0)
Influenza	8 (9.3)	0	8 (6.4)	154 (8.9)
Pharyngitis	5 (5.8)	3 (7.7)	8 (6.4)	94 (5.4)
Pruritus	6 (7.0)	2 (5.1)	8 (6.4)	88 (5.1)
Fatigue	5 (5.8)	3 (7.7)	8 (6.4)	202 (11.6)
Abdominal pain upper	4 (4.7)	3 (7.7)	7 (5.6)	145 (8.4)
Pain in extremity	5 (5.8)	2 (5.1)	7 (5.6)	194 (11.2)
ALT increased	5 (5.8)	2 (5.1)	7 (5.6)	112 (6.5)
Alopecia	6 (7.0)	1 (2.6)	7 (5.6)	33 (1.9)
Rash	6 (7.0)	1 (2.6)	7 (5.6)	85 (4.9)
Hematuria	2 (2.3)	5 (12.8)	7 (5.6)	111 (6.4)
Cough	6 (7.0)	1 (2.6)	7 (5.6)	120 (6.9)
Anxiety	3 (3.5)	4 (10.3)	7 (5.6)	77 (4.4)
Any SAE	24 (27.9)	10 (25.6)	34 (27.2)	363 (20.9)
MS relapse	16 (18.6)	3 (7.7)	19 (15.2)	67 (3.9)
Urinary tract infection	2 (2.3)	0	2 (1.6)	4 (< 1)

Overall ENDORSE data have been previously published in Gold et al. *Mult Scler.* 2022;28(5):801–16

AE adverse event, *ALT* alanine aminotransferase; *DMF* dimethyl fumarate, *MS* multiple sclerosis, *PBO* placebo, *SAE* serious adverse event, *YA* young adults

Table 3 AEs of interest among young adults and overall population in ENDORSE

AEs, <i>n</i> (%)	DMF/ DMF <i>n</i> = 86	PBO/ DMF <i>n</i> = 39	Overall YA population <i>N</i> = 125	Overall ENDORSE <i>N</i> = 1736
Gastrointestinal disorders	30 (34.9)	16 (41.0)	46 (36.8)	748 (43.1)
Vascular disorders				
Flushing	18 (20.9)	13 (33.3)	31 (24.8)	335 (19.3)
Immune system disorders				
Anaphylactic reaction	0	0	0	1 (< 1)
Investigations				
ALT increased	5 (5.8)	2 (5.1)	7 (5.6)	112 (6.5)
AST increased	4 (4.7)	1 (2.6)	5 (4.0)	70 (4.0)
Renal and urinary disorders	24 (27.9)	10 (25.6)	34 (27.2)	443 (25.5)
Microalbuminuria	10 (11.6)	5 (12.8)	15 (12.0)	116 (6.7)
Proteinuria	9 (10.5)	2 (5.1)	11 (8.8)	157 (9.0)
Hematuria	2 (2.3)	5 (12.8)	7 (5.6)	111 (6.4)
Cardiac disorders	5 (5.8)	0	5 (4.0)	98 (5.6)
Tachycardia	3 (3.5)	0	3 (2.4)	22 (1.3)
Serious infections	6 (7.0)	1 (2.6)	7 (5.6)	81 (4.7)
AEs leading to treatment discontinuation	5 (5.8)	3 (7.7)	8 (6.4)	282 (16.2)
GI AEs leading to treatment discontinuation	0	2 (5.1)	2 (1.6)	63 (3.6)

Overall ENDORSE data have been previously published in Gold et al. *Mult Scler.* 2022;28(5):801–16

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *DMF* dimethyl fumarate, *MS* multiple sclerosis, *GI* gastrointestinal, *PBO* placebo, *YA* young adults

reflective of this finding in that younger adults had more relapses than the overall population in the 12 months prior to study entry, as well as a trend toward a higher number of Gd+ lesions. However, despite a seemingly greater baseline disease activity, the treatment effect of DMF in younger adults in terms of reductions in relapse rates, MRI lesion activity, and disability progression was comparable to that in the overall study population.

As expected in a long-term extension study, discontinuation rates were higher than in the DEFINE/CONFIRM 2-year studies. Reasons for discontinuations from long-term studies are

varied and could be a result of patient's pregnancy, moving, sites closing, countries dropping out of the study once the drug gains regulatory approval, or pregnancy.

Our findings are supported by other studies in the literature evaluating the effects of DMTs in young adults with MS. A post hoc analysis of phase 3 studies in the fingolimod program reported that ARR were higher in younger patients (all $p < 0.05$) and significantly reduced with fingolimod versus placebo or interferon beta-1a (IFNβ-1a), with the youngest patients showing the highest reductions in ARR [29]. Furthermore, a retrospective analysis of 2477

patients with relapsing-remitting MS showed that relapse rates were age dependent and that patients aged < 40 years tended to benefit the most from DMTs [30]. In a meta-analysis of randomized, blinded MS clinical trials involving > 28,000 patients with MS [31], the efficacy of DMTs on MS disability was reported to depend greatly on age, with younger patients showing the most benefit. In addition, the results suggested that delaying DMT at an early stage of MS could lead to a decrease in the cumulative efficacy of DMT treatment when patients are older [31]. In pediatric patients with MS aged 10–17 years, DMF has been shown to be more effective than IFN β -1a in that more patients were free of new or newly enlarging T2 lesions following 96 weeks of treatment with DMF compared with IFN β -1a (16% vs. 5%, respectively) [32]. These studies provide further evidence of the beneficial effects of early and consistent treatment with DMF.

Limitations of these data include a relatively small sample size of the young adult population, especially among the PBO/DMF cohort ($n = 39$) in ENDORSE; however, we included pooled data with total number of young adults of 125 patients. As this was an exploratory post hoc analysis, these findings should be interpreted with caution. Like most MS studies, enrolling diverse patients and including more ethnicities would be desirable for future design.

CONCLUSION

Overall, these findings suggest a favorable benefit-risk profile for DMF in the treatment of relapsing-remitting MS in young adults. In particular, the reductions in relapse rates and number of Gd+ lesions following DMF treatment were comparable to those seen in the overall study population, despite evidence of higher disease activity in young adults versus the overall population at baseline.

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Compliance with Ethics Guidelines. The study was approved by local or central ethics committees and conducted in accordance with International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent. For a full list of the central ethics committees for ENDORSE, please see Table S3 in the supplementary material.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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