Efficacy and Safety of Delayed-release Dimethyl Fumarate for Relapsing-remitting Multiple Sclerosis in Prior Interferon Users: An Integrated Analysis of DEFINE and CONFIRM

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ABSTRACT

Purpose: In Phase III studies (DEFINE [Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS]/CONFIRM [Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis]), delayed-release dimethyl fumarate (DMF) demonstrated significant efficacy and a favorable benefit-risk profile in patients with relapsing-remitting multiple sclerosis (RRMS). Post hoc analyses of integrated data from DEFINE/CONFIRM were conducted to evaluate the effect of DMF in patients previously treated with interferon (IFN) beta.

Methods: Patients (age 18–55 years; Expanded Disability Status Scale score, 0–5.0) were randomized to receive DMF 240 mg BID or TID, placebo, or glatiramer acetate (CONFIRM only) for up to 2 years. Previous IFN users received at least 1 IFN treatment >3 months before randomization. Data for DMF 240 mg BID (approved dosing regimen) are reported.

Findings: In the integrated intention-to-treat population, 172 and 169 patients receiving DMF or placebo, respectively, had received ≥1 prior IFN. In this subgroup, significant reductions with DMF versus placebo were observed for the annualized relapse rate (rate ratio, 0.55 [95% CI, 0.40–0.77]), new/newly enlarging T2-hyperintense lesions (lesion mean ratio, 0.16 [95% CI, 0.09–0.29]), odds of having more gadolinium-enhancing lesions (odds ratio, 0.17 [95% CI, 0.07–0.44]), and new T1-hypointense lesions (lesion mean ratio, 0.25 [95% CI, 0.14–0.45]). Median Expanded Disability Status Scale scores remained stable during the study period. Adverse events associated with DMF included flushing and gastrointestinal events.

Implications: In this post hoc analysis in patients with previous IFN treatment, DMF demonstrated significant efficacy over 2 years versus placebo and an adverse event profile consistent with the overall population of DEFINE/CONFIRM. ClinicalTrials.gov identifiers: DEFINE, NCT00420212; and CONFIRM, NCT00451451. (*Clin Ther*. 2017;39:1671–1679) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: clinical, delayed-release dimethyl fumarate, interferon beta, neuroradiological, relapsing-remitting multiple sclerosis, safety.

INTRODUCTION

Interferon (IFN) beta has historically been a first-line treatment of choice for relapsing-remitting multiple sclerosis (RRMS). However, some patients opt to

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discontinue IFN treatment for reasons that include perceived lack of efficacy, injection site reaction, and safety and tolerability concerns, thus necessitating a switch to an alternative disease-modifying therapy (DMT).[1,2] Evaluation of the efficacy of other DMTs in patients previously treated with IFN will help inform treatment decisions.

Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated significant efficacy and a favorable benefit-risk profile in patients with RRMS in 2 randomized, double-blind, placebo-controlled, Phase III clinical trials: DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS)[3] and CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis).[4] Forty percent of patients in the intention-to-treat (ITT) population of DEFINE and 28% of patients in the ITT population of CONFIRM had previously been treated with an approved MS DMT, including IFN beta-1a (27% and 21%, respectively) and IFN beta-1b (14% and 11%, respectively), as well as glatiramer acetate (GA) and natalizumab.[3,4] Included among the reasons for patient discontinuation of previous therapy in DEFINE and CONFIRM were efficacy, tolerability, and patient or neurologist preference. In a prespecified subgroup analysis of integrated data from DEFINE and CONFIRM, DMF demonstrated efficacy on clinical and neuroradiological end points in the subset of patients with previous MS treatment.[5]

To examine the efficacy and safety of DMF in RRMS patients with a history of IFN treatment, post hoc analyses of data from DEFINE, CONFIRM, and integrated data from DEFINE and CONFIRM were conducted. IFN efficacy can be reduced in patients who develop neutralizing antibodies.[6] Switching therapies represents a management strategy of MS; hence, evaluating the efficacy of DMF and other DMTs in patients switching from IFN is of great relevance for clinicians and health care providers. The analysis population in the present report included patients who received treatment with ≥ 1 IFN before study entry.

PATIENTS AND METHODS

Patients and Study Design

The designs of DEFINE and CONFIRM have been reported previously.[3,4] Briefly, eligibility criteria included age 18 to 55 years; diagnosis of RRMS (McDonald Diagnostic Criteria)[7]; Expanded Disability Status Scale (EDSS)[8] score 0 to 5.0; and ≥ 1 relapse in the 12 months before randomization, with a previous brain magnetic resonance imaging (MRI) scan demonstrating lesion(s) consistent with MS or ≥ 1 gadolinium-enhancing (Gd^+) lesion on a brain MRI scan within 6 weeks before randomization. Patients previously treated with ≥ 1 approved MS therapy, including IFN beta (>3 months before enrollment), GA (>3 months before enrollment [DEFINE only]), and natalizumab (>6 months before enrollment), were eligible to enroll. Key exclusion criteria included progressive forms of MS, other significant illness or prespecified abnormal laboratory parameters, and MS relapse or corticosteroid use within 50 days before randomization.

In DEFINE, patients were randomized 1:1:1 to receive oral DMF 240 mg BID or TID or placebo for up to 96 weeks. In CONFIRM, patients were randomized 1:1:1:1 to receive oral DMF 240 mg BID or TID, placebo, or subcutaneous GA (reference comparator) 20 mg once daily for up to 96 weeks. Study visits were scheduled every 4 weeks.

DEFINE and CONFIRM were approved by central and local ethics committees and were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline and the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Statistical Analysis

The integrated analysis of DEFINE and CONFIRM, including the analysis of patients previously treated with DMT, was prespecified before the unblinding of CONFIRM and was to be conducted only if the patient population and treatment effects were similar between the studies.[5] The analysis reported here includes patients with ≥ 1 previous IFN; results are reported for placebo, DMF 240 mg BID (approved dose and dosing schedule, hereafter referred to as DMF), and GA.

The annualized relapse rate (ARR) was examined in the ITT population, defined as patients who underwent randomization and received at least 1 dose of study drug. Adjusted ARRs and 95% CIs were based on a negative binomial regression model adjusted for baseline EDSS score (≤ 2.0 vs >2.0), baseline age (<40 vs ≥ 40 years), region, and study (DEFINE vs CONFIRM).

The cumulative probability of disability progression (defined as ≥1.0-point increase in EDSS score in patients with a baseline score ≥1.0 or ≥1.5-point increase in patients with a baseline score of 0, with the increased score sustained for ≥12 weeks) was estimated by using the Kaplan-Meier product limit method and analyzed by using a Cox proportional hazards model with study as a stratifying factor and adjusted for the following covariates: baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40 years), and region. Median EDSS scores at baseline and week 96 were computed for the placebo and DMF groups (integrated data from DEFINE and CONFIRM). Median change from baseline EDSS score was computed based on patients in the ITT population with data available at both baseline and week 96.

MRI end points were examined in a subset of patients in the ITT population at sites with full MRI capabilities (MRI cohort). MRIs were performed by blinded MRI technicians using a standardized acquisition, and scans were analyzed by a central MRI reading center (NeuroRx Research, Montreal, Quebec, Canada) for blinded evaluation. MRI scans with full head coverage were performed by using proton density- and T2-weighted 2-dimensional multislice turbo/fast spin-echo; precontrast T1-weighted 3-dimensional spoiled gradient-recalled echo; 2-dimensional T2-weighted fast fluid attenuated inversion recovery; and postcontrast 3-dimensional spoiled gradient-recalled echo T1-weighted sequences.

For number of new/newly enlarging T2-hyperintense lesions and number of new T1-hypointense lesions, lesion mean ratio, percentage reduction, 95% CI, and *P* value for comparisons between the placebo and active groups were based on a negative binomial regression model adjusted for region, baseline volume of T2 or T1 lesions, and study (DEFINE vs CONFIRM). For Gd^+ lesion activity, odds ratio, percentage reduction, 95% CI, and *P* value for comparisons between the placebo and active groups were based on ordinal logistic regression, adjusted for region, baseline number of Gd^+ lesions, and study (DEFINE vs CONFIRM). The number of Gd^+ lesions was categorized as 0, 1, 2, 3, and 4, representing ordering in 0, 1, 2, 3 to 4, and ≥5 counts, respectively.

Safety data were analyzed with the use of descriptive statistics for patients who received ≥1 dose of study medication, excluding data obtained after patients switched to alternative MS medications.

RESULTS

Patients

Group numbers in the overall study population and in the subgroup of patients with ≥1 previous IFN are summarized in Table I. Demographic and baseline disease characteristics of patients with previous IFN treatment (integrated study population) were generally comparable across treatment arms (Table II).

Annualized Relapse Rate

In patients with ≥1 previous IFN, the frequency of relapse was reduced significantly at week 96 by DMF compared with placebo (Figure). In DEFINE, the adjusted ARR (95% CI) was 0.24 (0.16–0.36) in

Table I. Group numbers in the overall study population and in the subgroup of patients with ≥1 previous interferon (IFN) in the DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS) and CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis) studies and the integrated study population.

	Total Population		Population With ≥1 Previous IFN	
Variable	ITT	MRI Cohort	ITT	MRI Cohort
DEFINE				
Placebo	408	180	77	32
DMF*	410	176	86	32
Total	818	356	163	64
CONFIRM				
Placebo	363	167	92	41
DMF*	359	169	86	40
GA	350	175	87	44
Total	1072	511	265	125
Integrated				
Placebo	771	347	169	73
DMF*	769	345	172	72
Total	1540	692	341	145

DMF = delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF); GA = glatiramer acetate; ITT = intention-to-treat; MRI = magnetic resonance imaging.
*240 mg BID.

Table II. Demographic characteristics and baseline multiple sclerosis (MS) disease characteristics of patients with ≥1 previous interferon (IFN) (integrated study population).

Characteristic*	Population With ≥1 Previous IFN	
	Placebo (n = 169)	DMF† (n = 172)
Age, y	36.8 (9.2)	38.8 (8.6)
Female, no. (%)	121 (72)	112 (65)
Race, no. (%)		
White	146 (86)	141 (82)
Black/African American	7 (4)	4 (2)
Asian	2 (1)	2 (1)
Other	7 (4)	13 (8)
Missing	7 (4)	12 (7)
Time since first MS symptoms, y	9.3 (6.7)	10.1 (6.3)
Time since MS diagnosis, y	7.0 (5.6)	7.4 (5.2)
Relapses in prior year	1.2 (0.8)	1.3 (0.7)
EDSS score‡	2.6 (1.3)	2.4 (1.3)
MRI cohort, n	73	72
T2-hyperintense lesion volume, cm^3§	10.4 (11.0)	12.9 (13.6)
No. of Gd^+ lesions‖	3.5 (9.9)	2.0 (4.7)
Absent, %	49	56
Present, %	51	44
T1-hypointense lesion volume,‖ cm^3	2.3 (3.4)	3.9 (5.6)

DMF = delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF); EDSS = Expanded Disability Status Scale; Gd^+ = gadolinium-enhancing; MRI = magnetic resonance imaging.
*Values are given as mean (SD) unless otherwise indicated.
†240 mg BID.
‡Placebo, n=168, DMF, n=171.
§Placebo, n=73, DMF, n=72.
‖Placebo, n = 73; DMF, n = 71.

the DMF group compared with 0.47 (0.34–0.64) in the placebo group, representing a relative reduction of 49% ($P = 0.0038$). In CONFIRM, the adjusted ARR (95% CI) was 0.28 (0.19–0.42) in the DMF group compared with 0.47 (0.33–0.67) in the placebo group, representing a relative reduction of 40% ($P = 0.0519$). In the integrated analysis, the adjusted ARR (95% CI) was 0.25 (0.19–0.32) in the DMF group compared with 0.44 (0.35–0.56) in the placebo group, representing a relative reduction of 45% ($P = 0.0005$). In CONFIRM, the frequency of relapse was not reduced significantly by GA compared with placebo: adjusted ARR (95% CI) was 0.38 (0.26–0.55) in the GA group, representing a relative reduction of 21% versus placebo ($P = 0.3673$).

Disability Progression

Overall, the estimated proportion of patients with disability progression within all arms of the ≥1 previous IFN subgroup (including placebo) was low. There were no statistically significant differences in the estimated probability of disability progression in DEFINE, CONFIRM, or the integrated analysis of DEFINE and CONFIRM (all $P > 0.05$).

Among patients with ≥1 previous IFN who had data available at baseline and week 96, the median (minimum, maximum) EDSS score at baseline was 2.5 (0, 5.0) and 2.0 (0, 6.5) in the placebo (n = 168) and DMF (n = 171) groups, respectively, and at week 96 was 2.5 (0, 6.5) and 2.0 (0, 6.0) in the placebo (n = 104) and DMF (n = 122) groups.

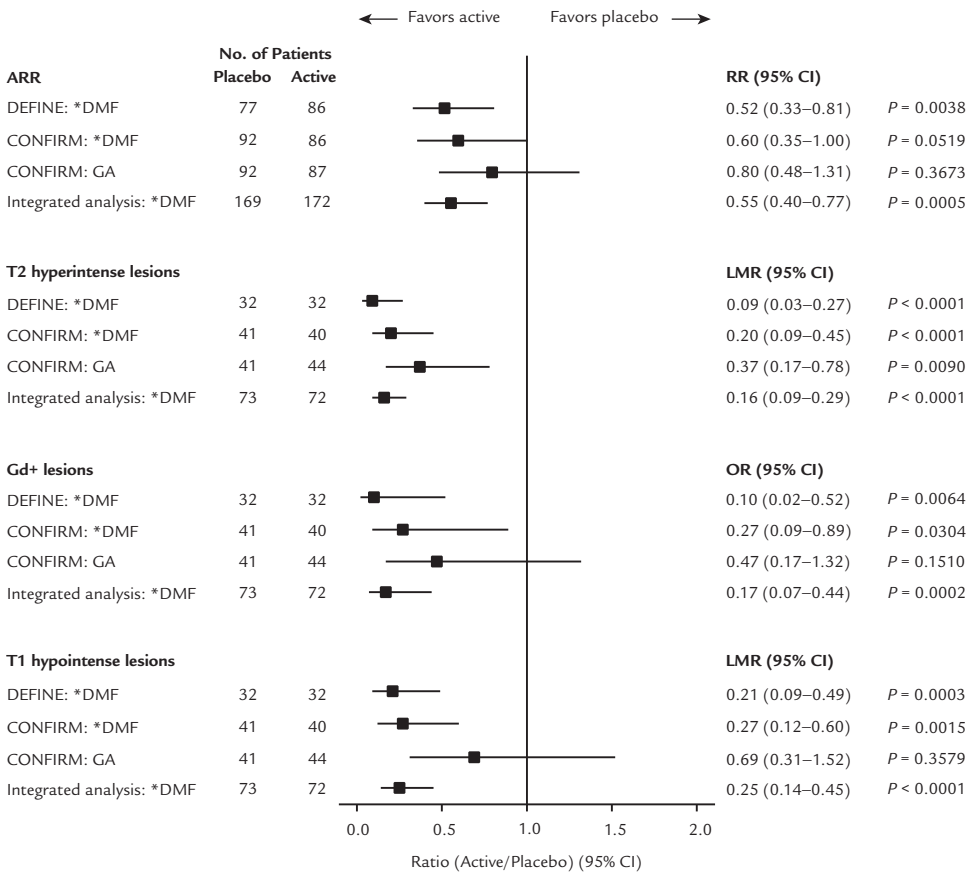

Figure. Annualized relapsed rate (ARR), new/newly enlarging T2-hyperintense lesions, odds of having new gadolinium-enhancing (Gd+) lesions, and T1-hypointense lesions at week 96 in patients with ≥1 previous interferon. *P* values are for comparison versus placebo. CONFIRM = Comparator and an Oral Fumarate in Relapsing-Remitting MS; DEFINE = Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; DMF = delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF); GA = glatiramer acetate; LMR = lesion mean ratio; OR = odds ratio; RR = rate ratio.

Median (minimum, maximum) change in EDSS score from baseline to week 96 was 0 (−3.5, 3.5) in the placebo group and 0 (−2.5, 3.5) in the DMF group.

MRI Endpoints DC

In patients with ≥1 previous IFN, the adjusted mean (95% CI) number of new/newly enlarging T2-hyperintense lesions at week 96 was reduced significantly by DMF compared with placebo in DEFINE (2.77 [1.34–5.75] vs 30.10 [15.30–59.20]; 91% reduction; $P < 0.0001$), CONFIRM (4.30 [2.44–7.57] vs 21.40 [12.00–38.10]; 80% reduction; $P < 0.0001$), and the integrated analysis (3.65 [2.38–5.59] vs 22.50 [15.00–33.90]; 84% reduction; $P < 0.0001$) (Figure). In CONFIRM, there was a statistically significant reduction in the adjusted mean number of new/newly enlarging T2-hyperintense lesions at week 96 with GA compared with placebo (7.84 [4.33–14.20] vs 21.40 [12.00–38.10]; 63% reduction; $P = 0.0090$).

The odds of having more Gd+ lesions at week 96 were reduced significantly by DMF compared with placebo in DEFINE (mean [SD] number of new Gd+ lesions: 0.10 [0.44] vs 3.40 [6.49]; 90% reduction; $P = 0.0064$), CONFIRM (0.20 [0.48] vs 2.90 [8.55]; 73% reduction; $P = 0.0304$), and the integrated analysis (0.20 [0.46] vs 3.20 [7.58]; 83% reduction; $P = 0.0002$) (Figure). In CONFIRM, the odds of

having more Gd+ lesions were not reduced significantly by GA compared with placebo: mean (SD) number of new Gd+ lesions in the GA group was 0.70 (1.40), representing a reduction of 53% versus placebo ($P = 0.1510$).

The adjusted mean (95% CI) number of new T1-hypointense lesions at week 96 was reduced significantly by DMF compared with placebo in DEFINE (1.97 [1.06–3.66] vs 9.32 [5.46–15.90]; 79% reduction; $P = 0.0003$), CONFIRM (2.00 [1.10–3.64] vs 7.51 [4.14–13.60]; 73% reduction; $P = 0.0015$), and the integrated analysis (2.01 [1.32–3.06] vs 7.90 [5.43–11.50]; 75% reduction; $P < 0.0001$) (Figure). In CONFIRM, the adjusted mean (95% CI) number of new T1-hypointense lesions was not reduced significantly by GA (5.19 [2.79–9.64]) compared with placebo (31% reduction; $P = 0.3579$).

Safety

The overall incidence of adverse events (AEs) was 94%, 98%, and 86% in the placebo, DMF, and GA groups, respectively (Table III). Frequently reported AEs (incidence ≥10% in any treatment group) with an incidence ≥3% higher in the DMF BID group versus the placebo group were flushing (40% vs 5%), diarrhea (16% vs 11%), upper respiratory tract infection (14% vs 11%), arthralgia (12% vs 7%), upper abdominal pain (13% vs 5%), rash and pruritus (each, 10% vs 4%).

The overall incidence of serious AEs was 18%, 20%, and 10% in the placebo, DMF, and GA groups, respectively (Table III). The only 2 serious AEs reported by ≥2 patients in the placebo, DMF BID, or GA groups were MS relapse, with an incidence of 12%, 10%, and 7%, respectively, and gastroenteritis, with an incidence of 0%, 1%, and 0%, respectively. There were no deaths.

The overall incidence of AEs leading to discontinuation of study treatment was 6%, 15%, and 15% in the placebo, DMF, and GA groups, respectively (Table III). AEs leading to discontinuation in ≥2 patients in the placebo, DMF BID, or GA groups included flushing (0%, 5%, and 0%, respectively), MS relapse (4%, 1%, and 1%, respectively), nausea (0%, 1%, and 2%, respectively), diarrhea (0%, 1%, and 0%, respectively), and pruritus (0%, 1%, and 0%, respectively). In addition, injection site erythema, asthenia, erythema, injection site pain, injection site pruritus, injection site swelling, swelling face, and tachycardia were reported in ≥2 patients in the GA group and no patients in the placebo or DMF groups.

DISCUSSION

Limited data, particularly prospective data, are available on the efficacy of other DMTs in patients previously treated with IFN.[9,10] In this integrated post hoc analysis of data from DEFINE and CONFIRM, we found that DMF significantly reduced ARR by 45% ($P = 0.0005$), number of new/newly enlarging T2-hyperintense lesions by 84% ($P < 0.0001$), odds of having more Gd+ lesions by 83% ($P = 0.0002$), and number of new T1-hypointense lesions by 75% ($P < 0.0001$) over 2 years compared with placebo in patients with RRMS previously treated with ≥1 previous IFN (integrated analysis). EDSS scores remained stable during the study period; there were no statistically significant differences across treatment arms in the estimated probability of disability progression in DEFINE, CONFIRM, or the integrated analysis of DEFINE and CONFIRM.

The effects of DMF in patients with previous IFN treatment are broadly consistent with those in the overall study populations of DEFINE and CONFIRM.[3,4] In an analysis of integrated data from DEFINE and CONFIRM, DMF 240 mg BID significantly reduced ARR by 49% ($P < 0.0001$), number of new/newly enlarging T2-hyperintense lesions by 78% ($P < 0.0001$), Gd+ lesion activity by 83% ($P < 0.0001$), and number of new T1-hypointense lesions by 65% ($P < 0.0001$) over 2 years compared with placebo.[5]

Generally, statistically significant benefits were not observed with the reference comparator, GA, with the exception of the new/newly enlarging T2-hyperintense lesions measure. The small sample size in the GA group (drawn solely from CONFIRM) likely contributed to the lack of significant effects on the other outcome measures. However, in previous studies, the effect of GA in patients with previous IFN treatment was modest.[11,12]

In DEFINE and CONFIRM, AEs associated with DMF treatment included flushing and gastrointestinal events.[3,4] These events were mostly mild or moderate in severity, manageable with symptomatic treatment, and transient, and they generally did not lead to treatment discontinuation.[13] The AE profile of DMF in patients with previous IFN treatment was broadly consistent with that in the overall study population, and was

Table III. Summary of adverse events (AEs) in patients with ≥1 previous interferon (IFN) (integrated study population).

Event*	Placebo (n = 169)	DMF† (n = 172)	GA‡ (n = 87)
Any AE	159 (94)	168 (98)	75 (86)
Most common AEs§			
MS relapse	77 (46)	63 (37)	29 (33)
Nasopharyngitis	40 (24)	40 (23)	14 (16)
Flushing	8 (5)	69 (40)	1 (1)
Headache	35 (21)	27 (16)	15 (17)
Urinary tract infection	29 (17)	30 (17)	12 (14)
Fatigue	26 (15)	29 (17)	12 (14)
Diarrhea	18 (11)	27 (16)	5 (6)
Upper respiratory tract infection	18 (11)	24 (14)	6 (7)
Back pain	22 (13)	24 (14)	9 (10)
Nausea	17 (10)	19 (11)	5 (6)
Arthralgia	11 (7)	21 (12)	6 (7)
Proteinuria	18 (11)	14 (8)	7 (8)
Depression	17 (10)	14 (8)	7 (8)
Influenza	14 (8)	10 (6)	4 (5)
Upper abdominal pain	8 (5)	22 (13)	1 (1)
Pruritus	7 (4)	18 (10)	3 (3)
Rash	6 (4)	17 (10)	2 (2)
Any SAE	31 (18)	35 (20)	9 (10)
Most common SAEs‖			
MS relapse	21 (12)	18 (10)	6 (7)
Gastroenteritis	0	2 (1)	0
AE leading to discontinuation	10 (6)	25 (15)	13 (15)
Most common AEs leading to discontinuation‖			
Flushing	0	8 (5)	0
MS relapse	7 (4)	2 (1)	1 (1)
Nausea	0	2 (1)	2 (2)
Diarrhea	0	2 (1)	0
Pruritus	0	2 (1)	0
Injection site erythema	0	0	3 (3)
Asthenia	0	0	2 (2)
Erythema	0	0	2 (2)
Injection site pain	0	0	2 (2)
Injection site pruritus	0	0	2 (2)
Injection site swelling	0	0	2 (2)
Swelling face	0	0	2 (2)
Tachycardia	0	0	2 (2)

DMF = delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF); GA = glatiramer acetate; MS = multiple sclerosis; SAE = serious adverse event.
*Values are given as no. (%).
†240 mg BID.
‡CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis) study only.
§Incidence ≥10% in the placebo, DMF, or GA groups.
‖Reported by ≥2 patients in the placebo, DMF, or GA groups.

characterized by an increased incidence (compared with placebo) of flushing, upper respiratory tract infection, arthralgia, gastrointestinal events (including diarrhea and upper abdominal pain), rash and pruritus.

Limitations of the present analysis include the relatively small sample size and the fact that DEFINE and CONFIRM were not specifically designed to evaluate DMF in patients with previous IFN treatment. As the present study was a post hoc analysis, the results should be interpreted with an appropriate degree of caution. Further research to evaluate the effects of DMF in previously treated patients with MS is warranted.

CONCLUSIONS

The findings of this post hoc analysis suggest that DMF may be an efficacious treatment in patients with RRMS who have discontinued IFN treatment, with a favorable benefit-risk profile.

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Julie Adkins from Complete Medical Communications wrote the first draft of the manuscript based on input from authors; Karyn Myers from Excel Scientific Communications incorporated feedback from authors; and Elizabeth Cassell from Excel Scientific Solutions copyedited and styled the manuscript per journal requirements. Drs. Giovannoni, Fox, Gold, and Phillips were responsible for study conception and design; and Drs. Fernández, Giovannoni, Fox, Gold, and Phillips were responsible for acquisition of data. All authors were responsible for analysis and interpretation of data and drafting and review of the manuscript. The authors had full editorial control of the paper and provided their final approval of all content.

CONFLICTS OF INTEREST

Biogen provided funding for medical writing support in the development of the paper, and Biogen reviewed and provided feedback on the paper to the authors.

Dr. Fernández has received honoraria as a consultant in advisory boards and as chairman or lecturer in meetings; and has participated in clinical trials and other research projects promoted by Allergan, Almirall, Bayer HealthCare, Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva. Dr. Giovannoni has received honoraria from AbbVie, Bayer HealthCare, Biogen, Canbex, FivePrime, Genzyme, Glaxo SmithKline, GW Pharma, Merck Serono, Novartis, Protein Discovery Laboratories, Roche, Synthon, Teva Neuroscience, UCB, and Vertex; research grant support from Biogen, Ironwood, Merck Serono, Merz, and Novartis; and compensation from Elsevier as co-chief editor of *Multiple Sclerosis and Related Disorders*. Dr. Fox has received consultant fees from Actelion, Biogen, MedDay, Novartis, Questcor, Teva, and Xenoport; served on advisory committees for Actelion, Biogen, and Novartis; and received research grant funding from Novartis. Dr. Gold has received honoraria from Bayer HealthCare, Biogen, Merck Serono, Novartis, and Teva Neuroscience; research support from Bayer HealthCare, Biogen, Merck Serono, Novartis, and Teva Neuroscience; and compensation from Sage for serving as editor of *Therapeutic Advances in Neurological Disorders*. Dr. Phillips has received consulting fees from Acorda, Biogen, Genzyme, Merck Serono, and Sanofi-Aventis; and research support from Roche. Dr Okwuokenye, is an employee of and holds stock/stock options in Biogen. Drs Potts and Marantz performed the majority of the work while employees of Biogen, Cambridge, MA. Dr. Marantz's current affiliation is with Alexion Pharmaceuticals, New Haven, CT. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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