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Safety Profile of Delayed-Release Dimethyl Fumarate in Relapsing–Remitting MS: Long-term Interim Results from the ENDORSE Extension Study

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INTRODUCTION

Delayed-release dimethyl fumarate (DMF) is approved in the United States and Australia for the treatment of relapsing forms of multiple sclerosis (MS) and relapsing MS, respectively, and in the European Union and Canada for the treatment of relapsing–remitting MS (RRMS).

Treatment with delayed-release DMF has been shown in two pivotal Phase 3 trials (DEFINE and CONFIRM) to result in significant reductions in clinical and magnetic resonance imaging (MRI) activity, and to have an acceptable safety profile in patients with RRMS.[1–3]

ENDORSE is a 5-year extension study of DEFINE and CONFIRM that is being conducted to evaluate the long-term safety and efficacy of delayed-release DMF in patients with RRMS.

As of June 12, 2013, a total of 2,513 MS patients (representing 6,133.1 patient-years) have received delayed-release DMF in Phase 2 and Phase 3 studies, including patients with at least 1 year (n=1,870), 2 years (n=1,586), 3 years (n=1,066), 4 years (n=824), and 5 or more years (n=292) of experience on delayed-release DMF.

OBJECTIVE

- To report safety findings (as of June 2013 data cut) from ENDORSE, investigating the longer-term effects of delayed-release DMF in patients with RRMS

METHODS

Study Design

- ENDORSE is a multicenter, parallel-group, dose-blind study with up to 5 years of follow-up
- Eligible patients who completed the 2-year parent studies (DEFINE and CONFIRM) were enrolled:
  - Patients who received 240 mg of delayed-release DMF twice daily (BID) or three times daily (TID) for up to 2 years in the parent study remained on the same dosage in ENDORSE
  - Patients who received placebo (PBO; both parent studies) or glatiramer acetate (GA; CONFIRM) were randomized 1:1 to receive 240 mg of delayed-release DMF BID or TID
- Updated safety analyses based on ENDORSE data only (June 2013 data cut) are presented according to treatment received in the parent and extension studies

Safety Assessments

- Adverse events (AEs) and concomitant medications were monitored and recorded throughout the study
- Regular laboratory assessments including blood chemistry, urinalysis, and hematology were performed:
  - Blood chemistry and urinalysis at baseline, then every 4 weeks until Week 24, and every 12 weeks thereafter
  - Hematology laboratory parameters at baseline and every 12 weeks thereafter
- Safety parameters were tabulated according to treatment received (BID/BID, TID/TID, PBO/BID, PBO/TID, GA/BID, and GA/TID) and summarized using descriptive statistics

RESULTS

Patients

- A total of 1,736 patients comprised the intent-to-treat (ITT) population in ENDORSE; baseline demographics of the ITT population at the start of the studies were generally well-balanced across treatment groups (Table 1)

Table 1: Baseline demographics at start of ENDORSE (ITT population)

	Continued DMF[a]		New to DMF[a]			
Characteristic	BID/BID (n=501)	TID/TID (n=502)[b]	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=118)[b]
Age, mean (SD) years	39.7 (9.1)	40.0 (9.1)	39.9 (8.8)	40.5 (9.4)	38.2 (8.5)	39.5 (9.5)
Age <40 years, n (%)	237 (47)	233 (46)	119 (48)	114 (46)	68 (58)	56 (47)
Female, n (%)	352 (70)	354 (71)	178 (71)	166 (67)	86 (73)	76 (64)
White, n (%)	403 (80)	413 (82)	202 (81)	198 (80)	98 (83)	103 (87)
Weight, mean (SD) kg	70.6 (17.8)	71.8 (17.0)	70.8 (16.6)	73.8 (16.9)	73.4 (21.5)	72.0 (17.9)

[a]DMF, delayed-release DMF.
[b]Safety population grouped according to treatment received. One patient randomized to DMF TID took GA thoughout the CONFIRM study. This patient was counted in the TID/TID group of the ITT population and in the GA/TID group of the safety population in ENDORSE.
SD, standard deviation.

- As of June 2013 data cut, total time followed in the ENDORSE study amounted to 3,841.8 patient-years (Table 2)
- A total of 445 patients (435 continuers) had been exposed to delayed-release DMF BID and 427 patients (416 continuers) had been exposed to delayed-release DMF TID cumulatively for at least 4 years in DEFINE/CONFIRM and ENDORSE

Safety Experience in ENDORSE

- The overall incidence of AEs, serious AEs (SAEs), and discontinuations due to AEs were similar among:
  - The two treatment groups of patients who continued delayed-release DMF from the parent studies (Table 3)
  - The four treatment groups new to delayed-release DMF (previously treated with placebo or GA) (Table 3)

Table 2: Time on study in ENDORSE (safety population)

	Continued DMF[a]		New to DMF[a]			
Characteristic	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Total number of patient-years of follow-up	1187.4	1170.8	531.7	508.1	231.0	212.8
Time on study, mean (SD) months	30.9 (9.7)	30.5 (10.4)	27.9 (12.2)	26.7 (12.5)	25.5 (10.7)	23.3 (12.4)
Patients on study for at least, n (%)						
6 months	490 (98)	484 (97)	225 (90)	219 (88)	108 (92)	103 (87)
1 year	472 (94)	465 (93)	208 (84)	205 (83)	101 (86)	90 (76)
2 years	434 (87)	424 (85)	190 (76)	187 (75)	85 (72)	75 (63)
3 years	144 (29)	154 (31)	68 (27)	55 (22)	17 (14)	16 (13)
4 years	20 (4)	19 (4)	9 (4)	10 (4)	0	1 (<1)

[a]DMF, delayed-release DMF.

Table 3: Safety overview in ENDORSE (safety population)

	Continued DMF[a]		New to DMF[a]			
Events, n (%)	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Any AE	447 (89)	453 (90)	232 (93)	224 (90)	102 (86)	100 (84)
Serious AEs	88 (18)	97 (19)	55 (22)	36 (15)	15 (13)	21 (18)
Discontinued treatment due to AE	19 (4)	30 (6)	40 (16)	39 (16)	16 (14)	27 (23)
Occurring within 6 months	7 (1)	14 (3)	32 (13)	36 (15)	11 (9)	21 (18)
Infections	307 (61)	298 (59)	132 (53)	131 (53)	56 (47)	53 (45)
Serious infections	14 (3)	7 (1)	6 (2)	7 (3)	2 (2)	3 (3)
Malignancy	6 (1)	5 (<1)	5 (2)	0	0	3 (3)
Deaths[b]	2 (<1)	1 (<1)	1 (<1)	0	0	0

[a]DMF, delayed-release DMF.
[b]No death was assessed by investigators as being related to study drug.

- The most common individual AEs are summarized in Table 4
  - MS relapse and nasopharyngitis were most common in the BID/BID and TID/TID groups
  - Flushing and gastrointestinal (GI)–related events were more common among patients previously treated with placebo or GA and new to delayed-release DMF treatment

Table 4: Common adverse events occurring in ≥10% of patients in any treatment group (safety population)

	Continued DMF[a]		New to DMF[a]			
Events, n (%)	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Any AE	447 (89)	453 (90)	232 (93)	224 (90)	102 (86)	100 (84)
MS relapse	133 (27)	152 (30)	66 (27)	59 (24)	24 (20)	29 (24)
Nasopharyngitis	114 (23)	109 (22)	40 (16)	41 (17)	16 (14)	16 (13)
Flushing	47 (9)	61 (12)	73 (29)	57 (23)	25 (21)	24 (20)
Urinary tract infection	76 (15)	64 (13)	28 (11)	30 (12)	13 (11)	9 (8)
Headache	58 (12)	53 (11)	27 (11)	25 (10)	9 (8)	9 (8)
Upper respiratory tract infection	55 (11)	54 (11)	28 (11)	28 (11)	7 (6)	8 (7)
Diarrhea	38 (8)	33 (7)	37 (15)	33 (13)	11 (9)	11 (9)
Back pain	46 (9)	50 (10)	24 (10)	22 (9)	9 (8)	3 (3)
Upper abdominal pain	14 (3)	24 (5)	27 (11)	27 (11)	10 (8)	12 (10)

[a]DMF, delayed-release DMF.

- Patients new to delayed-release DMF experienced flushing and GI symptoms at incidences generally consistent with those seen in patients treated with delayed-release DMF in the parent studies
  - In the parent studies, the incidence of flushing and GI events was highest during the first month and decreased substantially thereafter
- The incidence of patients with AEs leading to treatment discontinuation was 4–6% in patients who continued delayed-release DMF from DEFINE and CONFIRM and 14–23% in patients new to delayed-release DMF in ENDORSE (Table 5)

Table 5: Adverse events leading to treatment discontinuation occurring in ≥1% of patients in any group (safety population)

	Continued DMF[a]		New to DMF[a]			
Events, n (%)	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Discontinued due to any AE	19 (4)	30 (6)	40 (16)	39 (16)	16 (14)	27 (23)
Flushing	1 (<1)	1 (<1)	9 (4)	4 (2)	2 (2)	1 (<1)
MS relapse	4 (<1)	5 (<1)	2 (<1)	0	2 (2)	1 (<1)
Upper abdominal pain	0	0	8 (3)	4 (2)	0	3 (3)
Diarrhea	0	1 (<1)	4 (2)	5 (2)	4 (3)	1 (<1)
Nausea	1 (<1)	0	2 (<1)	6 (2)	2 (2)	3 (3)
Abdominal pain	0	0	4 (2)	2 (<1)	2 (2)	5 (4)
Vomiting	0	0	0	3 (1)	4 (3)	4 (3)
Pruritus	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (2)	0
Urticaria	0	0	1 (<1)	2 (<1)	2 (2)	1 (<1)
Dyspepsia	0	0	3 (1)	1 (<1)	1 (<1)	0
Hot flush	0	1 (<1)	0	2 (<1)	0	2 (2)
GI disorder	0	0	1 (<1)	3 (1)	0	0
Dyspnea	0	0	3 (1)	1 (<1)	0	0
Vertigo	0	0	0	0	2 (2)	0
Increased hepatic enzyme	0	0	1 (<1)	0	0	2 (2)
Increased gamma-glutamyltransferase	0	1 (<1)	0	2 (<1)	2 (2)	0

[a]DMF, delayed-release DMF.

- The incidence of individual AEs leading to treatment discontinuation was low (≤1–4%)
  - Of those patients new to delayed-release DMF in ENDORSE, AEs leading to treatment discontinuation were generally related to flushing and GI-tolerability events; the majority of discontinuations occurred during the first 6 months of treatment (Table 3)
- The most commonly reported SAE was MS relapse, while other individual SAEs occurred in no more than four patients in any treatment group (Table 6)

Table 6: Serious adverse events occurring in ≥3 patients in any treatment group (safety population)

	Continued DMF[a]		New to DMF[a]			
Events, n (%)	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Any SAE	88 (18)	97 (19)	55 (22)	36 (15)	15 (13)	21 (18)
MS relapse	44 (9)	52 (10)	23 (9)	17 (7)	6 (5)	10 (8)
Urinary tract infection	4 (<1)	0	1 (<1)	3 (1)	1 (<1)	0
Breast cancer	3 (<1)	1 (<1)	0	0	0	2 (2)
Gastritis	2 (<1)	0	0	3 (1)	0	0
Fall	3 (<1)	1 (<1)	0	0	1 (<1)	0
Uterine leiomyoma	0	0	3 (1)	0	0	0

Safety population is based on received treatment.
[a]DMF, delayed-release DMF.

- The incidence of serious infections was low (≤3% in any treatment group; Table 3)
  - Only serious AEs of urinary tract infections (9 patients), appendicitis (4 patients), and cellulitis (3 patients) were reported in more than 1 patient
- There were no confirmed opportunistic infections
- The overall incidence of malignancies remained low (1%) for patients who continued receiving delayed-release DMF (Table 7)
  - There is no evidence of an increased risk of malignancy among patients treated with delayed-release DMF
- There were no new findings in hematologic outcomes compared to the parent DEFINE and CONFIRM studies
  - Patients new to delayed-release DMF had decreases in mean white blood cell (WBC) and lymphocyte counts consistent with those observed in patients treated with delayed-release DMF in the parent studies
  - In patients continuing delayed-release DMF, mean WBC and lymphocyte counts remained stable, and no further overall decrease in mean baseline values was observed compared to DEFINE and CONFIRM
  - The incidence of WBC counts <3.0 × 10^9/L was 6% to 7% in the continued delayed-release DMF groups and 7% to 10% in the new to delayed-release DMF groups
  - The incidence of lymphocyte counts <0.5 × 10^9/L was 6% to 8% in the continued delayed-release DMF groups and 5% to 9% in the new to delayed-release DMF groups

Table 7: Malignancies reported in ENDORSE (safety population)

	Continued DMF[a]		New to DMF[a]			
Events, n (%)	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Malignancies	6 (1)	5 (<1)	5 (2)	0	0	3 (3)
Breast cancer	3 (<1)	1 (<1)	0	0	0	2 (2)
Melanoma	0	2 (<1)	0	0	0	0
Cervical carcinoma	1 (<1)	0	0	0	0	0
Lung carcinoma	1 (<1)	0	0	0	0	0
Renal cell carcinoma	1 (<1)	0	1 (<1)[b]	0	0	0
Salivary gland cancer	0	1 (<1)	0	0	0	0
Thyroid cancer	0	1 (<1)	0	0	0	0
Breast cancer in situ	0	0	1 (<1)	0	0	0
Endometrial cancer	0	0	1 (<1)[b]	0	0	0
Glioma	0	0	1 (<1)	0	0	0
Mesothelioma	0	0	1 (<1)	0	0	0
Squamous cell carcinoma	0	0	1 (<1)	0	0	0
Rectal cancer	0	0	0	0	0	1 (<1)

[a]DMF, delayed-release DMF.
[b]Reported in the same patient.

- Hepatic AEs occurred in ≤3% of patients in any treatment group
  - Few patients (≤2%) continuing delayed-release DMF had ALT or AST levels ≥3× upper limit of normal (ULN)
  - No case fulfilled Hy's law criteria for drug-induced liver injury (transaminase elevations ≥3× ULN associated with bilirubin >2× ULN)
- For patients continuing delayed-release DMF treatment, renal or urinary events were reported in 19% and 18% of patients in the BID/BID and TID/TID patient groups, respectively
  - In the parent studies, 19% and 23% of patients receiving delayed-release DMF BID and TID, respectively, and 20% of placebo-treated patients experienced renal or urinary events
  - The incidence of renal events was similar among patients who switched from PBO to delayed-release DMF in ENDORSE (17% and 19% for PBO/BID and PBO/TID) and for patients who switched from GA to delayed-release DMF (10% for both GA/BID and GA/TID)
  - The most common renal AEs occurring in at least 3% of patients in all treatment groups were proteinuria, microalbuminuria, and hematuria

CONCLUSIONS

- The long-term safety analysis from ENDORSE continues to demonstrate an acceptable safety profile for delayed-release DMF in RRMS patients
- There were no new or worsening safety signals identified among patients who continued treatment with delayed-release DMF from DEFINE and CONFIRM
  - The incidence of serious infections and malignancies remained low, there were no confirmed opportunistic infections, and WBC and lymphocyte counts were stable
- The safety profile for patients newly exposed to delayed-release DMF in ENDORSE is consistent with that observed in DEFINE and CONFIRM
- Together with clinical and neuroradiologic efficacy data,[5,6] these findings support the potential for delayed-release DMF to become a valuable treatment option for patients with relapsing MS

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