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The Use of Delayed-release Dimethyl Fumarate in Routine Medical Practice in the Treatment of Multiple Sclerosis (ESTEEM): Six-Month Interim Analysis

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INTRODUCTION

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated strong efficacy and a favorable benefit-risk profile in Phase 3 clinical studies of patients with relapsing-remitting multiple sclerosis (RRMS).[1,2]
- ESTEEM is an ongoing, multinational, 5-year prospective study evaluating the long-term safety and effectiveness of DMF in 5000 patients (NCT02047097).

OBJECTIVES

- The objective of ESTEEM is to characterize the benefit-risk profile of DMF in patients with MS treated under routine clinical care in a long-term observational study. In this first interim analysis, we report results on the primary objective of the study, which is to determine the incidence, type, and pattern of serious adverse events (SAEs) and adverse events (AEs) leading to treatment discontinuation in patients with MS treated with DMF.

METHODS

Study Design

- Eligibility criteria include:
  - Diagnosis of MS
  - Newly prescribed DMF under routine clinical care; patients are followed even if they do not initiate treatment
  - Must be naive to DMF, fumeric acid esters, and compounded fumarates at the time of enrollment but may have received other MS therapies
  - Age ≥12 years
    - Patients 12 to <18 years of age will be excluded in locales where the enrollment of pediatric patients is considered interventional or is otherwise prohibited by local regulations
  - Must not be enrolled in a clinical trial or other study, except the DMF Pregnancy Registry or other studies that do not conflict with the observational nature of the study.
- Follow-up:
  - Routine visits for up to 5 years
  - Patient-reported outcomes (PROs) are completed on paper or electronically during routine visits or within 1 week before/after the routine visit.
- Patients are being recruited from ~380 global sites. The first 1000 patients with a minimum of 6 months' follow-up (as of July 22, 2015) are included in this analysis; however, data on a total of 5000 patients followed for up to 5 years will ultimately be accrued.
- The primary endpoints will be evaluated primarily by assessment of the incidence and incidence rate of treatment-emergent SAEs and of AEs leading to treatment discontinuation.
- Secondary endpoints, not reported here, will assess:
  - Effectiveness of DMF on MS disease activity (e.g., relapse-related endpoints and Expanded Disability Status Scale–based disability progression)
  - Patient health-related quality of life (QOL) will be evaluated by assessment of change in PROs over time: Multiple Sclerosis Impact Scale, QOL data in 5 dimensions (EuroQol-5 Dimensions 5-level version), patients' rating of their overall health using a visual analog scale (EuroQol visual analog scale), the Modified Fatigue Impact Scale 5-item version, and the Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis
  - Health care resource consumption also will be evaluated.

Statistical Analysis

- Statistical analyses will generally be descriptive and exploratory in nature; no formal statistical hypothesis testing is planned.
- Statistical analyses will be based on all patients who enroll in the study (defined as having an available date of informed consent) and receive ≥1 dose of DMF. Patients who have a major protocol deviation resulting in their removal from the study also will be excluded from the analysis.

RESULTS

Patients

- As of July 22, 2015, 1000 patients enrolled and accrued a minimum of 6 months' follow-up time for those remaining on study. Of the initial 1000 patients, 897 qualified for the interim analysis (Figure); 680 (75.8%) were female. Mean and median age at enrollment was 42 years (Table 1).
- The majority of patients (n=658; 73.4%) received prior RRMS treatments.

Figure. Patient disposition

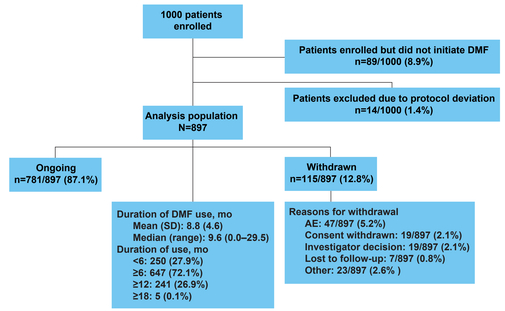

Table 1. Baseline demographics and disease characteristics

Characteristic	N=897
Mean (SD) age at enrollment, y	**42.1 (11.6)**
<40	388 (43.3)
≥40	508 (56.7)
Female, n (%)	**680 (75.8)**
Race, n (%)	
American Indian or Alaska Native	3 (0.3)
Asian	3 (0.3)
Black/African American	41 (4.6)
Other	11 (1.2)
White	831 (92.6)
Not reported due to confidentiality regulations	8 (0.9)
Mean (SD) age at MS diagnosis,[a] y	**36.3 (10.6)**
Mean (SD) total no. of relapses in prior year	**0.7 (0.8)**
Any prior DMT, n (%)	**658 (73.4)**
Prior MS treatments, n (%)	
Glatiramer acetate	241 (26.9)
Intramuscular IFN beta-1a	232 (25.9)
Subcutaneous IFN beta-1a	206 (23.0)
IFN beta-1b	160 (17.8)
Natalizumab	87 (9.7)
Fingolimod	70 (7.8)
Teriflunomide	29 (3.2)

IFN = interferon
[a]Data on age at MS diagnosis were only available for 884 of the 897 patients

Overall Safety Summary

- A total of 28 (3.1%) patients reported an SAE, of which 8 patients reported an infection and 5 patients reported gastrointestinal disorders (Table 2).
- No opportunistic infections were reported; 1 death (unrelated to DMF treatment) occurred.

Table 2. Most frequently occurring SAEs in ≥2 patients

Category,[a] n (%)	N=897
Any SAE	**28 (3.1)**
Gastrointestinal disorders	5 (0.6)
Hepatobiliary disorders	2 (0.2)
Infections and infestations[b]	8 (0.9)
Pneumonia	2 (0.2)
Metabolism and nutrition disorders	3 (0.3)
Dehydration	3 (0.3)
Nervous system disorders	3 (0.3)
Psychiatric disorders	2 (0.2)
Renal and urinary disorders	2 (0.2)
Uncoded	2 (0.2)

[a]AEs coded using Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Percentages calculated based on total number of patients (N=897). A patient with >1 event for a SOC or PT is counted only once for that SOC or PT
[b]Other SAEs in infections and infestations were 1 case each of appendicitis, cellulitis, parasitic infection, pyelonephritis, septic shock, urosepsis, and viral infection

- A total of 151 (16.8%) patients reported an AE leading to treatment discontinuation; gastrointestinal disorders represented the most frequent AE leading to discontinuation of DMF treatment (Table 3). Patients who discontinued treatment may be initiated back on DMF, if so specified by their health care provider.
- Two cases of shingles (herpes zoster) were reported. One was enrolled in ESTEEM in April 2014 and developed shingles in July 2014. The other case enrolled in June 2014 and developed shingles in May 2015. In both cases, DMF was discontinued for 3 weeks and then restarted.

Table 3. Most common AEs leading to DMF discontinuation with an incidence of ≥1% in any treatment group

Category,[a] n (%)	N=897
Any AE leading to treatment discontinuation	**151 (16.8)**
Gastrointestinal disorders	80 (8.9)
Nausea	22 (2.5)
Diarrhea	21 (2.3)
Vomiting	16 (1.8)
Abdominal pain–upper	12 (1.3)
Abdominal pain	12 (1.3)
Nervous system disorders[b]	17 (1.9)
Skin and subcutaneous tissue disorders[c]	16 (1.8)
Vascular disorders[d]	22 (2.5)
Flushing	20 (2.2)

[a]AEs coded using MedDRA SOC and PT. Percentages calculated based on total number of patients (N=897). A patient with >1 event for a SOC or PT is counted only once for that SOC or PT
[b]Most common AEs in nervous system disorders were dizziness and headache
[c]Most common AEs in skin and subcutaneous tissue disorders were urticaria and rash
[d]The other 2 vascular events leading to DMF discontinuation were categorized as hot flushes

- A total of 49 (5.5%) patients reported an AE leading to study withdrawal; gastrointestinal disorders represented the most frequent AE leading to study withdrawal (Table 4).

Table 4. Most common AEs leading to study withdrawal in ≥2 patients

Category,[a] n (%)	N=897
Any AE leading to study withdrawal	**49 (5.5)**
Cardiac disorders	2 (0.2)
Gastrointestinal disorders	28 (3.1)
Diarrhea	10 (1.1)
Vomiting	10 (1.1)
Nausea	5 (0.6)
Abdominal pain–upper	3 (0.3)
Abdominal pain	3 (0.3)
Gastrointestinal disorder	2 (0.2)
General disorders and administration site conditions	2 (0.2)
Hepatobiliary disorders	2 (0.2)
Nervous system disorders	5 (0.6)
Skin and subcutaneous tissue disorders	5 (0.6)
Rash	2 (0.2)
Urticaria	2 (0.2)
Vascular disorders[b]	5 (0.6)
Flushing	4 (0.4)
Uncoded	4 (0.4)

[a]AEs coded using MedDRA SOC and PT. Percentages calculated based on total number of patients (N=897). A patient with >1 event for a SOC or PT is counted only once for that SOC or PT
[b]The other vascular event leading to study withdrawal was categorized as hot flush

CONCLUSIONS

- In this first interim analysis of ESTEEM, 28 (3.1%) patients reported SAEs, with infections and gastrointestinal disorders as the most common.
- Similarly, 16.8% of patients reported an AE leading to treatment discontinuation, with gastrointestinal disorders as the most common.
- Data on absolute lymphocyte counts are being collected and will be analyzed once there is a sufficient number of patients with >6 months' follow-up.
- No new safety signals were observed in this interim analysis. The overall benefit-risk profile of DMF remains favorable.

References

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Disclosures

NJE, CP, and SL: employees of and hold stock/stock options in Biogen; KB: grant/research support from Biogen and Teva; speaker bureau for Teva; RM: grant/research support from Biogen; JW: advisory boards for Genzyme, Merck, Novartis, Roche, and Teva; KG: consulting fees from EMD Serono; advisory board for Genzyme; speaker bureau/advisory board for Biogen.

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