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HPASS INFORMATION

Title	A Multicenter, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Tecfidera™ (Dimethyl Fumarate) When Used in Routine Medical Practice in the Treatment of Multiple Sclerosis (ESTEEM)
Version identifier of the final study report	1.0
Date of last version of the final study report	21 August 2023
EU PAS register number	EUPAS6782
Active substance	L04AX07 Dimethyl fumarate (DMF)
Medicinal product	Tecfidera 120 mg and 240 mg, gastroresistant hard capsules
Product reference	EU/1/13/837
Procedure number	EMEA/H/C/2601
Marketing authorisation holder(s)	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp The Netherlands
Joint PASS	No
Research question and objectives	The purpose of this study was to better characterize the long-term benefit-risk profile of DMF (Tecfidera™) in patients with multiple sclerosis (MS) who were prescribed DMF under routine clinical care.The primary objective of the study was to determine the incidence, type, and pattern of serious adverse events, including but not limited to serious infections (including opportunistic infections), hepatic events, malignancies,

	and renal events, and of adverse events leading to DMF treatment discontinuation, in patients with MS treated with DMF.Secondary study objectives were the following: To determine DMF prescription and utilization patterns in routine clinical practice in patients with MS To assess the effectiveness of DMF on MS disease activity and disability progression; andTo assess the effect of DMF on health-related quality of life, healthcare resource consumption, and work productivity [redacted]
Countries of study	Argentina, Australia, Austria, Belarus, Bosnia, Bulgaria, Canada, Costa Rica, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Herzegovina, Hungary, India, Ireland, Israel, Italy, Latvia, Macedonia, Mexico Moldova, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, United States (including Puerto Rico)
Author	Study Medical Director: [redacted], [redacted], [redacted], Safety and Benefit-Risk Management: [redacted], MD Medical Writer: [redacted], PhD

MARKETING AUTHORISATION HOLDER(S)

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1. ABSTRACT

Title

A Multicenter, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Tecfidera™ (Dimethyl Fumarate) When Used in Routine Medical Practice in the Treatment of Multiple Sclerosis (ESTEEM)

Keywords

Dimethyl Fumarate, Multiple Sclerosis, Observational, Serious Adverse Events, Health-related quality of life

Rationale and background

Multiple sclerosis (MS) is an inflammatory autoimmune disease affecting the central nervous system (CNS) and is characterized by increased permeability of the blood-brain barrier. This allows autoreactive immune cells (macrophages and lymphocytes) to infiltrate into the CNS. The infiltrated autoreactive immune cells trigger a cascade of inflammation, which leads to chronic demyelination and neurodegeneration. Dimethyl fumarate (DMF) is an oral disease-modifying treatment with demonstrated neuroprotective and immunomodulatory effects for relapsing-remitting MS (RRMS). DMF has been approved by the United States (US) Food and Drug Administration (2013) and the EMA (2014) for the management of relapsing forms of MS. Currently, DMF is approved in > 70 countries.

This study was conducted as part of the planned pharmacovigilance activities for DMF. The safety of DMF has been evaluated extensively in both nonclinical and clinical studies and has been shown to be well tolerated and have an acceptable safety profile. During the development of DMF, events of interest were identified, including (but not limited to) serious and opportunistic infections, malignancies, serious hepatic events, and serious renal events. To date, DMF has not been associated with an increased risk for these events compared with placebo. This study further monitored the occurrence of these events and characterized the safety profile of DMF during long-term use in routine clinical practice. This study also included patient populations that were not studied during the clinical development of DMF (e.g., patients over the age of 55 years).

Phase 3 clinical studies have shown positive urinary ketones in 63% of DMF-treated patients. The presence of urinary ketones was not thought to have any clinical meaningful implication and may be due to assay interference by a chemical interaction between a DMF metabolite and urine ketone testing strip. [redacted]

Research question and objectives

The purpose of this study was to better characterize the long-term benefit-risk profile of DMF in patients with MS who were prescribed DMF under routine clinical care.

Objectives

The primary objective of the study was to determine the incidence, type, and pattern of serious adverse events (SAEs), including but not limited to infections (including opportunistic infections), hepatic events, malignancies, and renal events, and adverse events (AEs) leading to DMF treatment discontinuation in patients with MS treated with DMF.

Note: All opportunistic infections and malignancies were considered serious and were reported as SAEs. Laboratory abnormalities leading to DMF treatment discontinuation were reported as AEs.

Secondary objectives of the study in this population were as follows:

- To determine DMF prescription and utilization patterns in routine clinical practice in patients with MS.
- To assess the effectiveness of DMF on MS disease activity and disability progression in routine clinical practice as determined by the Expanded Disability Status Scale (EDSS) score and MS relapse information.
- To assess the effect of DMF on health-related quality of life (HRQoL), healthcare resource consumption, and work productivity.

[redacted]

Study design

This was a prospective, global, observational study designed to provide long-term safety data in patients with MS who had been newly prescribed DMF in routine clinical practice. Enrolled patients who had been newly prescribed DMF were followed for up to 5 years ± 3 months from the date of their first dose of DMF, independent of the number of doses administered. Patients with an unknown DMF dosing start date, and those who did not start DMF but continued participating in the study were followed for up to 5 years ± 3 months from the date of the verbal and/or written informed consent. Data were collected by the Prescribing Physician from patients at enrolment (Baseline) and during routine clinical practice visits, which occurred approximately every 6 months. Patient-reported outcomes (PROs) were completed by patients during the routine clinical practice visit, or, if outside of the Prescribing Physician's office, within 1 week (before or after) of the routine visit.

[redacted]

Primary endpoint:

Safety was evaluated primarily by assessment of the incidence and incidence rate of treatment-emergent SAEs and AEs leading to DMF treatment discontinuation.

Secondary endpoints:

- DMF prescription and utilization patterns were evaluated by assessment of prescribed dosing frequency, duration of DMF use, and primary reason for discontinuation of DMF treatment.
- Effectiveness of DMF on MS disease activity and disability progression were evaluated by assessment of relapse-related endpoints (e.g., annualized relapse rate [ARR], time to first relapse, proportion of patients with relapse, and distribution of the number of relapses) and by assessment of EDSS-based disability progression-related endpoints (e.g., proportion of patients with progression and time to first progression), respectively.
- Changes in HRQoL measures were evaluated over time. Healthcare resource consumption was evaluated by assessment of endpoints such as number of hospitalizations, emergency room visits, and neurologist visits. Work productivity was evaluated by assessment of ability to work and time needed away from work due to MS.

[redacted]

Setting

Approximately 450 sites in multiple regions, including the US, the European Union (EU), and Rest of World (RoW), participated in the study. [redacted]

Subjects and study size, including dropouts

Of approximately 5600 planned enrolment patients, 5495 patients were enrolled, and 5124 patients were included in the Full Analysis Set (FAS).

Variables and data sources

The following data were collected at enrolment (Baseline; to coincide with a routine clinical visit): demographics, medical history, MS disease history, results of latest brain magnetic resonance imaging (MRI) scan, prior and concurrent (at enrolment [Baseline]) medication use, pregnancy status, SAEs, CBC, other recommended laboratory tests in local label, PRO information, and DMF prescription and utilization information. Laboratory and PRO data were collected if consistent with local regulations. EDSS information was recorded when obtained (at enrolment [Baseline]) as part of routine clinical practice. Subsequently, the following data were collected during routine clinical practice visits approximately every 6 months: SAEs, AEs (including laboratory abnormalities) leading to DMF treatment discontinuation, complete blood count and other recommended laboratory tests in local label, concomitant medication use, EDSS information (when collected as routine clinical practice), PRO information, MS relapse information, DMF prescription and utilization information, and pregnancy status.

[redacted]

Data source

Data from patients with MS who were newly prescribed DMF under routine clinical care were collected during routine clinical practice visits.

Results

Results addressing the primary objective

For the 5124 patients who were enrolled in the study and included in the FAS, the median (range) age at Baseline was 39.0 (18, 83) years, and 73.8% were female. Race and ethnicity were not reported for most patients due to confidentiality regulations. Overall, patients were followed-up for a median (range) of 52.6 (0.03, 77.99) months and had a median (range) DMF treatment duration of 28.5 (0.03 77.50) months.

A total of 1959 (38.2%) of the patients in the FAS completed the study and stayed in the study for at least 57 months. Among the 3165 (61.8%) patients who did not complete the study or participated in the study for < 57 months, 2584 discontinued the study prematurely. The most common primary reasons for not completing the study were "other reason" for 834 (32.3%) patients, lost to follow-up for 602 (23.3%) patients, and withdrawal of consent for 520 (20.1%) patients.

Among the 5124 patients in the FAS, 2613 (51.0%) patients permanently discontinued DMF treatment during the study. The most common primary reasons for treatment discontinuation were AEs for 1138 (43.6%) patients, "other reason" for 754 (28.9%) patients, and efficacy reasons for 566 (21.7%) patients.

Of the 5495 patients enrolled in the study, a total of 27 deaths were reported (24 of these deaths occurred in the FAS population), of which 19 were assessed as unrelated to treatment by the Investigator. One death (due to lung neoplasm malignant) was assessed by the Investigator to be related to DMF treatment; however this patient had [redacted]. For the remaining 7 deaths, no Investigator causality assessments between the deaths and DMF treatment were available.

Of the 5124 patients in the FAS, 377 (7.4%) patients reported a total of 612 SAEs. Overall, 1.1% of patients had SAEs that were assessed as treatment related by the Investigator. By preferred term (PT), the most commonly reported (> 0.1% of patients) SAEs were fall (0.4%), abortion spontaneous (0.3%), pneumonia (0.3%), maternal exposure during pregnancy (0.2%), MS relapse (0.2%), urinary tract infection (0.2%), and breast cancer (0.2%). The overall incidence rate of SAEs (total number of events divided by the total follow-up time at risk for the events, per 100,000 patient-years) in the FAS was 4554 per 100,000 person-years.

Of the 5124 patients in the FAS, 1237 (24.1%) patients discontinued DMF treatment due to AEs; of these, 1083 (21.1% of the FAS population) patients reported AEs leading to discontinuation assessed as related to DMF treatment by the Investigator. By PT, the

most commonly reported AEs leading to DMF treatment discontinuation (≥ 2% of the patients) were lymphopenia (3.8%), flushing (3.6%), diarrhoea (2.6%), and nausea (2.5%). The overall incidence rate of AEs leading to DMF treatment discontinuation (total number of events divided by the total follow-up time at risk for the events, per 100,000 patient-years) was 14,348 per 100,000 person-years.

Two patients reported an SAE with the PT of lymphopenia in this study; both were considered treatment-related by the Investigator. Overall, 3.8% of patients discontinued DMF due to AEs related to lymphopenia, 1.5% due to lymphocyte count decreased, and < 1% due to leukopenia, white blood cell decreased, and CD8 lymphocytes decreased.

A total of 308 (9.8%) of the patients who had at least 1 reported lymphocyte count during the study had lymphocyte counts < 800×10^9/L for ≥ 6 months; of these 8 (2.6%) patients reported SAEs in the system organ class (SOC) of Infections and infestations. Of the 308 patients who had lymphocyte counts < 800×10^9/L for ≥ 6 months with at least 1 reported lymphocyte count during the study, 26 (8.4%) patients reported 37 SAEs, and 93 (30.2%) patients experienced 122 AEs leading to DMF treatment discontinuation. A total of 40 (1.3%) patients had lymphocyte counts < 500×10^9/L for ≥ 6 months; of these 16 (40.0%) patients had 23 AEs leading to DMF treatment discontinuation. No SAEs were reported in patients who had lymphocyte counts < 500×10^9/L for ≥ 6 months in the SOC of Infections and infestations.

No adverse events of special interest (AESIs) of progressive multifocal leukoencephalopathy (PML) were reported in this study.

Of the 5124 patients in the FAS, 102 (2%) patients experienced SAEs in the SOC of Infections and infestations, and 42 (0.8%) patients experienced an AE leading to DMF treatment discontinuation in the SOC of Infections and infestations. The overall incidence rate of SAEs (total number of events divided by the total follow-up time at risk for the events, per 100,000 patient-years) in the SOC of Infections and infestations was 915 (95% confidence interval [CI]: 767-1092) per 100,000 person-years.

Of the 5124 patients in the FAS, 58 (1.1%) patients experienced SAEs in the SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps), and 19 (0.4%) patients in the FAS experienced AEs leading to DMF treatment discontinuation in the SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps). The overall incidence rate of SAEs (total number of events divided by the total follow-up time at risk for the events, per 100,000 patient-years) in the SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps) was 352 (95% CI: 276, 449) per 100,000 person-years.

Results addressing the secondary objectives

Overall, most patients had DMF prescriptions of 240 mg over the study period. The mean (range) exposure to DMF during study was 31.0 (0.03, 77.5) months.

Overall, 95.2% of patients had at least 1 visit to health care providers (HCPs) due to MS at Baseline. The median number of visits to HCPs at Baseline per patient due to MS was 2.0. At Month 60 of the study, most patients (94.9% of patients with healthcare

consumption data at Month 60) visited HCPs due to MS, and the median number of visits to HCPs per patient due to MS at Month 60 was 2.0.

Of the 958 patients with healthcare consumption data at Month 60, a total of 7 (0.7%) patients had admission to any healthcare facilities due to MS, of whom 6 were admitted to home/residential hospice or MS centre.

After adjusting for gender, Baseline age (< 40 versus ≥ 40 years), and number of relapses in the 1 year prior to study entry, the adjusted ARR at Year 0 to 5 and at Year 0 to EOS were both 0.11 (95% CI: 0.10, 0.12).

Among the 3025 patients with both Baseline and any postbaseline EDSS score, a total of 422 (8.2%) patients had sustained disability progression and 639 (12.5%) patients had an improvement in the disability status as per definition 1; a total of 507 (9.9%) patients had sustained disability progression and 650 (12.7%) patients had an improvement in disability status per definition 2. A total of 1091 (21.3%) patients experienced a relapse during the study. Overall, the probability of patients without relapse was 68.2% at Month 60.

The median Multiple Sclerosis Impact Scale-29 Items Questionnaire (MSIS-29) psychological impact score decreased from Baseline (18.0) to Month 60 (16.0), suggesting minor improvement in HRQoL related to psychological functioning.

No meaningful changes from Baseline to Month 60 were observed in the median Multiple Sclerosis Impact Scale-29 Items Questionnaire (MSIS-29), EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L), and EuroQoL Visual Analogue Scale (EQ-VAS), suggesting that despite minor differences in the scores attributed to each dimension of the PROs, no overall changes in the health status for clinical and economic evaluation were reported. Similar results at Baseline and Month 60 were also reported for Modified Fatigue Impact Scale-5 Items Questionnaire (MFIS-5); the median MFIS-5 score change from Baseline to Month 60 (n = 818 [16.0%]) was 0, suggesting no overall change in the physical, cognitive, and psychological impact of fatigue on a patient within the last 4 weeks. The overall scores attributed to all components of the Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis, Version 2.0 (WPAI-MS) PRO were also comparable between Baseline and Month 60; no change in median score was observed for absenteeism, presenteeism, and work or activity impairment.

Discussion

The objective of 109MS401 was to characterize the long-term benefit-risk profile of DMF in patients with MS who were prescribed DMF under routine clinical care. The results demonstrate a positive benefit-risk profile of long-term exposure to DMF (mean [range] exposure to DMF was 31.0 [0.03 to 77.5] months) with up to 6.5 years of follow-up. The incidence of SAEs and AEs leading to DMF treatment discontinuation in patients who were prescribed DMF was consistent with previous long-terms studies of DMF. Exposure to DMF was not associated with a higher incidence rate of serious infections or malignancies compared to the MS population. Additionally, subgroup

analyses generally demonstrated similar rates of SAEs and AEs leading to DMF treatment discontinuation compared to the overall DMF exposed population.

Despite some variations in the percentage of patients reporting SAEs and AEs leading to DMF treatment discontinuation in the categories of special interest, the observed safety profile was comparable between the subgroups analysed and the FAS population.

Long-term effectiveness of DMF has been demonstrated through a relatively small number of relapses observed in patients during the follow-up and low ARR throughout the study compared to previous reports for the MS population. There was a low chance of confirmed disability progression over 5 years, with most patients being either stable or having improved disability.

Results of this postauthorisation safety study (PASS) inform real-world treatment with DMF for patients with MS and are aligned with those of previous clinical trials of DMF and safety reported in real-world observational studies in the MS population.

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