PASS INFORMATION

PROTOCOL 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:	Version 3 (European Union)
DATE:	15 August 2014
EU PAS REGISTER NUMBER:	ENCEPP/SDPP/6782
ACTIVE SUBSTANCE:	N07XX09 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:	Biogen Idec MA Inc., Biogen Idec Research Limited, and Biogen Idec Australia Pty Ltd
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES	The purpose of this study is to better characterize the long-term benefit-risk profile of DMF in patients with multiple sclerosis (MS) who are prescribed DMF under routine clinical care. The primary objective of the study is 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 treatment discontinuation, in patients with MS treated with DMF. Secondary study objectives are to (1) determine DMF prescription and utilization patterns in routine clinical practice in patients with MS; (2) assess the effectiveness of DMF on MS disease activity and disability progression; and (3) assess the effect of DMF on health-related quality of life, healthcare resource consumption, and work productivity.
COUNTRIES OF THE STUDY:	Global study including sites in the United States, the European Union, and Rest of World.
AUTHOR:	[redacted], PhD [redacted] Biogen Idec MA Inc. Tel.: [redacted]

Supersedes previous version 2 dated 17 September 2013.

MARKETING AUTHORISATION HOLDER INFORMATION

MARKETING AUTHORISATION HOLDER (MAH):	Biogen Idec MA Inc. 14 Cambridge Center Cambridge, MA 02142, USA Biogen Idec Research Limited Innovation House 70 Norden Road Maidenhead Berkshire SL6 4AY United Kingdom Biogen Idec Australia Pty Ltd Avaya Building Suite 1, Level 5 123 Epping Road NORTH RYDE, NSW 2113 Australia
MAH CONTACT PERSON:	[redacted], MD, PhD [redacted] Biogen Idec Research Limited Tel.: [redacted]

SIGNATURE PAGE

Protocol 109MS401 was approved by:

[redacted] 15 August 2014

[redacted], MD, PhD Date

[redacted]

Biogen Idec Research Limited

SIGNATURE PAGE

Protocol 109MS401 was approved by:

[redacted]

17-Aug-2014

[redacted], MD

Date

[redacted]

Biogen Idec MA Inc.

SIGNATURE PAGE

Protocol 109MS401 was approved by:

[redacted] 15 AUG 2014

[redacted], MB, MRCPI, M Med Sci Date

[redacted]

[redacted]

Biogen Idec MA Inc.

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
CBC	complete blood count
CC	Coordinating Center
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CRF	case report form
CRO	Contract Research Organization
DMF	dimethyl fumarate
EDSS	Expanded Disability Status Scale
EQ-5D-5L	EuroQol-5 Dimensions (5 Level)
EQ VAS	EuroQol Visual Analogue Scale
EU	European Union
GI	Gastrointestinal
HCUP	Healthcare Cost and Utilization Project
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
MFIS-5	Modified Fatigue Impact Scale-5
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale-29 Items
Nrf2	nuclear factor (erythroid-derived 2)-related factor 2
NSAID	non-steroidal anti-inflammatory drug
OTC	over the counter
PRO	patient-reported outcome
QPPV	qualified person for pharmacovigilance
ROW	Rest of World
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SEER	Surveillance, Epidemiology and End Results
TID	3 times daily
ULN	upper limit of normal
US	United States
WPAI-MS	Work Productivity and Activity Impairment questionnaire: Multiple Sclerosis, Version 2.0

3. RESPONSIBLE PARTIES

Qualified person for pharmacovigilance (QPPV):

[redacted], MD, PhD

[redacted]

Biogen Idec Research Limited

Tel.: [redacted]

Main author:

[redacted], PhD

[redacted]

Biogen Idec MA Inc.

Tel.: [redacted]

Contract research organization:

Quintiles

Real World & Late Phase Research

201 Broadway, Cambridge, MA, USA 01945

Tel: [redacted]

Fax: [redacted]

Email: [redacted]

4. ABSTRACT

Table 1: Abstract for Protocol 109MS401

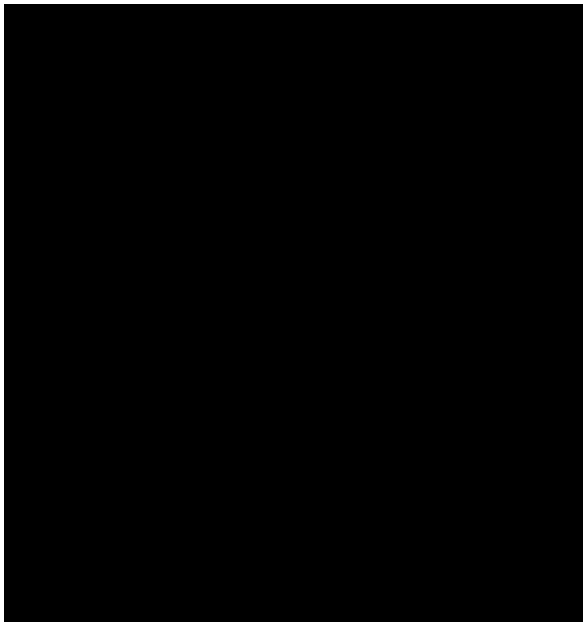
Protocol Title:	A Multicenter, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Tecfidera™ (Dimethyl Fumarate) When Used in Routine Medical Practice in the Treatment of Multiple Sclerosis (ESTEEM)
Version Number:	3 (EU)
Date of Protocol:	15 August 2014
Name and Affiliation of Main Author:	[redacted], PhD [redacted] Biogen Idec MA Inc.
Rationale and Background:	This study is being conducted as part of the planned pharmacovigilance activities for dimethyl fumarate (DMF). The safety of DMF has been evaluated extensively in both nonclinical and clinical studies. Overall, DMF has been shown to have an acceptable safety profile. During the development of DMF, events of interest were identified, including (but not limited to) serious and opportunistic infections (based on its putative immunomodulatory mechanism of action and its potential for reducing lymphocyte counts in humans), malignancies (based on its mechanism of action and results of the rodent carcinogenicity studies), serious hepatic events (based on its potential for elevating liver transaminases), and serious renal events (based on nonclinical data identifying the kidney as a target organ of toxicity). To date, DMF has not been associated with an increased risk for these events compared with placebo. This study will further monitor for the occurrence of these types of events, and will provide data to characterize the safety profile of DMF during long-term use in routine clinical practice. This study also will provide data on populations not studied during the clinical development of DMF (e.g., patients over the age of 55 years). [redacted]

	[redacted]
Research Question and Objectives:	The purpose of this study is to better characterize the long-term benefit-risk profile of DMF in patients with multiple sclerosis (MS) who are prescribed DMF under routine clinical care. *Objectives* The primary objective of the study is 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 of AEs leading to treatment discontinuation in patients with MS treated with DMF. *Note: All opportunistic infections and malignancies are considered serious and are to be reported as SAEs. Laboratory abnormalities that lead to treatment discontinuation are to be reported as AEs.* Secondary objectives of this study in this population are 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, healthcare resource consumption, and work productivity. [redacted]
Study Design:	This will be a prospective, observational study in patients with MS who have been prescribed DMF in a clinical practice setting as part of routine care. Primary endpoint: • Safety will be evaluated primarily by assessment of the incidence and incidence rate of treatment-emergent SAEs and AEs leading to treatment discontinuation. Secondary endpoints: • DMF prescription and utilization patterns will be evaluated by assessment of prescribed dosing frequency, duration of DMF use, and primary reason for discontinuation of DMF. • Effectiveness of DMF on MS disease activity and disability progression will be evaluated by assessment of relapse-related endpoints (e.g., annualized relapse rate, 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 health-related quality of life measures will be evaluated over time. Healthcare resource consumption will be evaluated by assessment of endpoints such as number of hospitalizations, emergency room visits, and neurologist visits. Work productivity will be evaluated by assessment of ability to work and time

	needed away from work due to MS. Safety and effectiveness evaluations will include comparisons to external databases. Health-related quality of life, healthcare resource consumption, and work productivity evaluations will be based on changes from baseline. No internal control cohort will be included in the study. [redacted]
Population:	This study will be conducted in patients aged 18 and older, with MS who have been newly prescribed DMF under routine clinical care. Patients must be naïve to DMF, Fumaderm®, and compounded fumarates at the time of enrollment, but need not be naïve to other MS treatments. Patients must not be currently enrolled in any other clinical trial or study except the DMF Pregnancy Registry or other studies that, according to the study Medical Director, do not conflict with this observational study (e.g., health economic studies). Enrollment of approximately 5000 patients with MS who have been newly prescribed DMF is planned. Approximately 450 sites in multiple regions, including the US, the European Union (EU), and Rest of World (ROW), will participate. Enrollment will be managed to ensure adequate representation in each region. Patients will be followed for up to 5 years. Follow-up is planned regardless of whether patients do not initiate or discontinue treatment with DMF. [redacted]
Variables:	The following will be collected at enrollment (to coincide with a routine clinical visit): demographics, medical history, MS disease history (including relapse history and latest EDSS score prior to enrollment), results of latest brain magnetic resonance imaging scan (MRI), prior and concurrent (at enrollment)

	medication use, and pregnancy status. Laboratory and patient reported outcomes (PRO) data will be collected *if consistent with local regulation*s. EDSS information (including Functional System Scores and Ambulation, scores) will be recorded *when obtained (at enrollment) as part of routine clinical practice*. Subsequently, the following will be collected during routine clinical practice visits anticipated to occur approximately every 6 months: SAEs, AEs (including laboratory abnormalities) leading to treatment discontinuation, concomitant medication use, MS relapse information, DMF prescription and utilization information, and pregnancy status. Laboratory and PRO data will be collected *if consistent with local regulation*s. EDSS information will be recorded *when obtained as part of routine clinical practice*. [redacted]
Data Sources:	In the prospective cohort study, data from patients with MS who have been newly prescribed DMF under routine clinical care will be collected during routine clinical practice visits. Background comparator rates will be ascertained using external databases.
Study Size:	A sample size of approximately 5000 MS patients who have been newly prescribed DMF will be enrolled in the study and followed for up to 5 years. Enrollment will close after 5000 enrolled MS patients have been treated with DMF (defined as having taken at least 1 dose of DMF). The sample size and study duration were chosen to ensure a reasonable likelihood of observing rare events over a 5-year period and calculating informative confidence intervals (CIs) for SAE incidence and incidence rate point estimates. Based on withdrawal rates observed in DMF clinical trials and prior Biogen Idec observational studies, it is expected that

	approximately 16,000 to 18,000 person-years of follow-up will accrue. Enrollment may be increased if the withdrawal rate is substantially greater than expected. With this sample size, the probability of observing an event with an incidence of 0.06% (60/100,000 persons, or 1/1667 persons) will be 95%, the probability of observing an event with an incidence of 0.05% (50/100,000 persons, or 1/2000 persons) will be 92%, and the probability of observing an event with an incidence of 0.03% (32/100,000 persons, or 1/3125 persons) will be 80%. 
Data Analysis:	Statistical analyses will be based on all patients who enroll in the study and take at least 1 dose of DMF. Statistical analyses will generally be descriptive and exploratory in nature. No formal statistical hypothesis testing is planned. Ninety-five percent CIs for incidence and incidence rate point estimates will be calculated using the binomial distribution and the Poisson distribution, respectively. Analyses of clinical laboratory parameters may include summaries of actual values over time, change from baseline over time, percent change from baseline over time, shift tables, and/or summaries of worst post-baseline values. Annualized relapse rate will be analyzed using a negative binomial model, adjusted for appropriate prognostic factors, and

	time-to-event endpoints will be analyzed using Kaplan-Meier estimates. Summary statistics will be presented for health-related quality of life, healthcare resource consumption, and work productivity outcomes over time. [redacted]
Milestones:	Start of data collection: Q4 2013 End of data collection: Q4 2022 Study progress reports: Study progress reports will be submitted after completion of each interim report (see below). Interim reports: Safety data will be analyzed after 1000 patients have completed 6 months of follow up, then at least annually. Other study objectives may be assessed on a similar schedule. Final report of study results: Q4 2023

5. AMENDMENTS AND UPDATES

None.

Table 2: Substantial Amendments and Updates to Protocol 109MS401 after the Start of Data Collection

Number	Date	Section of Study Protocol	Amendment or Update	Reason

6. MILESTONES

Table 3: Milestones for Protocol 109MS401

Milestone	Planned Date
Start of data collection	Q4 2013 Dependent on timing of reimbursement approval.
End of data collection	Q4 2022 Dependent on market uptake of drug and recruitment into the study.
Study progress reports	Study progress reports will be submitted after completion of each interim report (see below).
Interim reports	The first interim study report will be based on safety data collected after 1000 patients have completed 6 months of follow up; the report is anticipated to be completed 12 months after that time. Subsequent interim reports will be completed at least annually. Other study objectives may be assessed on a similar schedule. Dates are dependent on market uptake and recruitment into the study.
Registration in EU PAS register	ENCEPP/SDPP/6782
Final report of study results	Q4 2023 Dependent on market uptake of drug and recruitment into the study.

7. RATIONALE AND BACKGROUND

7.1. Profile of Previous Experience

7.1.1. Preclinical Experience With DMF

A thorough battery of nonclinical safety studies was carried out to support the development of dimethyl fumarate (DMF) for the treatment of multiple sclerosis (MS). Central nervous system, respiratory, and cardiovascular safety pharmacology studies (conducted with a formulation containing DMF) demonstrated no drug-related adverse effects on those systems, which is consistent with human data. In repeat-dose toxicology studies of DMF in rodents (mouse and rat) and non-rodents (dog and monkey), the forestomach, liver, testes, and kidney were identified as DMF target organs.

The findings in the forestomach, liver, and testes were evaluated and concluded to be of limited concern to human risk as described below

- In studies in mice and rats, DMF-related reversible histologic changes in the forestomach included hyperplasia, hyperkeratosis, inflammation, and/or ulceration. These rodent-specific findings were considered to be of limited concern to human risk because no human correlate to the forestomach exists and no gastrointestinal (GI) tract changes were observed after long-term exposure in non-rodent mammals (dogs, monkeys). Additionally, the clinical formulation of DMF limits the release of materials from a capsule in low pH, thereby lowering the risk to humans.
- DMF-related changes in the liver (partially reversible minimal hepatic necrosis and reversible minimal bile duct hyperplasia) were considered to be of low risk for humans, as they were observed only during a 6-month study in the rat, were not associated with any changes in clinical chemistry, and were not observed in any other study or species.
- DMF-related changes to the testes (degeneration of the seminiferous epithelium in the dog and rat, spermatid giant cells and hypospermia in the epididymis in the dog, and interstitial [Leydig] cell hyperplasia and adenoma in the rat) were considered to be of low risk to humans because the changes in the dog were reversible and were observed at 3 to 6 times the recommended human dose (based on area under the concentration-time curve), and the endocrine mechanisms that resulted in Leydig cell hyperplasia and adenoma in the rat are not relevant to humans.

DMF-related changes in the kidney were observed in the mouse, rat, dog, and monkey. While the spectrum of renal changes depended on dose, duration of dosing, and species, regeneration of the tubular epithelium was observed in all nonclinical species at exposures similar to the human therapeutic exposure. The DMF-related tubular effects, although modest in nonclinical species, were taken into consideration for human risk assessment, and a correlate biomarker, urinary albumin, was identified in the rat. The

Phase 3 clinical studies (109MS301 and 109MS302) of DMF included sensitive biomarkers for tubular injury (microalbumin and β2-microglobulin), in addition to the standard serum chemistry and urinalysis, and demonstrated that DMF-treated subjects did not have a higher risk of renal or urinary events (Section 7.1.2).

Renal tumors were observed at a low incidence in both male and female mice and rats in 2-year carcinogenicity studies. Laboratory rodents are known to have a species-specific, age-related nephropathy, and DMF was found to exacerbate this age-related nephropathy. Neither DMF nor its primary active metabolite, monomethyl fumarate (MMF), was found to be genotoxic, and it is likely that exacerbation of the rodent-specific, age-related nephropathy is a contributory event in the development of renal tumors. As reviewed by [Hard 2009], compounds that promote renal tumors in the rat by exacerbation of age-related nephropathy should be excluded from assessment of human risk. Given the contributory effect of a rodent-specific nephropathy to the production of renal tumors in rodents, and the absence of DMF-related tubular effects in DMF-treated subjects with MS (Section 7.1.2), the relevance of rodent renal tumors to human risk is considered to be low.

7.1.2. Clinical Experience With DMF

The clinical development program for DMF in MS included 6 clinical studies that were conducted in subjects with relapsing-remitting MS. A total of 2468 MS subjects received at least 1 dose of DMF in Phase 2 and 3 placebo-controlled efficacy and safety studies and/or their uncontrolled extension studies. Of these, 2340 subjects received DMF at or above the approved commercial dose (240 mg twice daily [BID] or 3 times daily [TID]); 1469 subjects were exposed for ≥1 year and 1095 subjects were exposed for ≥2 years.

Overall, the safety data from the clinical development program showed that DMF was well tolerated and has an acceptable safety profile. In placebo-controlled studies, the most common adverse events (AEs) reported at an increased incidence (≥2%) in subjects treated with 240 mg BID were flushing or hot flush and GI events (diarrhea, nausea, abdominal pain upper, abdominal pain, vomiting, and dyspepsia), which are events known to occur frequently with other fumarates. Other AEs that occurred at an incidence at least 2% higher with DMF than placebo included skin events (pruritus, rash, erythema), albumin urine present, aspartate aminotransferase (AST) increased, and lymphopenia. The AE profile was similar for subjects who received 240 mg TID.

In placebo-controlled studies, decreases in mean white blood cell and lymphocyte counts were observed over the first year of treatment (approximately 10% and 30%, respectively) with both doses of DMF. Mean white blood cell and lymphocyte counts then plateaued and remained stable, even during longer periods of observation of approximately 3.5 years. An analysis of the data did not show a clear correlation between infections, serious infections, and lymphocyte counts. No increased risk of infection, serious infection, or opportunistic infection was observed in subjects treated with DMF.

DMF was also associated with a small increase in the incidence of elevations of liver transaminases compared to placebo. In the controlled studies, this increase was primarily

due to differences that occurred within the first 6 months of treatment. The majority of subjects with elevations had alanine aminotransferase (ALT) or AST levels <3 times the upper limit of normal (ULN). No patients had elevations of ALT or AST ≥3 × ULN associated with an elevation in total bilirubin of >2 × ULN. There were no cases of hepatic failure due to DMF. During extended treatment with DMF, ALT and AST levels remained stable through 3.5 years of observation. Based on these data, there appears to be a transient increase in liver transaminases with DMF relative to placebo that does not appear to be associated with any increase in clinically significant liver pathology.

Although the kidney was identified as a target organ of DMF toxicity in nonclinical studies (Section 7.1.1), subjects treated with DMF in the clinical studies did not appear to have a higher risk of renal or urinary events. Small increases in proteinuria were observed, but the increases did not appear to be clinically significant. On laboratory evaluation, there were no clinically relevant changes in blood urea nitrogen, creatinine, electrolytes, calcium, phosphorus, parathyroid hormone, or 1,25-dihydroxyvitamin D. In the Phase 3 studies (109MS301 and 109MS302), there were no differences between placebo and DMF BID in the incidence of proteinuria on 2 consecutive urinalyses (defined as trace or greater) or on findings of 3+ or 4+ protein, both of which are potential indicators of significant proteinuria and renal dysfunction. In addition, there was no evidence of changes in β2-microglobulin and microalbumin, 2 more sensitive and specific markers of renal tubular dysfunction, over time even during longer periods of observation of approximately 3.5 years.

As discussed, renal tumors were observed at a low incidence in 2-year carcinogenicity studies in rodents, but this finding was considered to be of low relevance to humans (Section 7.1.1). In the controlled studies, there was no increased incidence of malignancies in subjects who received DMF compared with placebo. The types of malignancies observed and their incidence was within expected background rates.

7.2. Study Rationale

This study is being conducted as part of the planned pharmacovigilance activities for DMF. As discussed in Section 7.1.1 and 7.1.2, the safety of DMF has been evaluated extensively in both nonclinical and clinical studies. Overall, DMF has been shown to have an acceptable safety profile. During the development of DMF, events of interest were identified, including (but not limited to) serious and opportunistic infections (based on the putative immunomodulatory mechanism of action of DMF and its potential for reducing lymphocyte counts in humans), malignancies (based on its mechanism of action, as well as results of the 2-year carcinogenicity studies in rodents), serious hepatic events (based on its potential for elevating liver transaminases), and serious renal events (based on nonclinical data identifying the kidney as a target organ of toxicity). To date, DMF has not been associated with an increased risk for these events compared with placebo. This study will further monitor for the occurrence of these types of events, and will provide data to characterize the safety profile of DMF during long-term use in routine clinical practice. This study also will provide data on populations not studied during the clinical development of DMF (e.g., patients over the age of 55 years).

8. RESEARCH QUESTION AND OBJECTIVES

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

8.1. Primary Objective

The primary objective of the study is 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 of AEs leading to treatment discontinuation in patients with MS treated with DMF.

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

8.2. Secondary Objectives

Secondary objectives of this study in this study population are 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, healthcare resource consumption, and work productivity.

9. RESEARCH METHODS

9.1. Study Design

This is a prospective, global, observational study primarily designed to provide long-term safety data in patients with MS who have been prescribed DMF in a clinical practice setting as part of routine care.

DMF will not be supplied for this study. The study will collect data in an observational manner from patients aged 18 and older, who are prescribed DMF by physicians, according to the approved label in the respective country.

Enrollment of approximately 5000 patients with MS who have been newly prescribed DMF is planned. Approximately 450 sites in multiple regions, including the US, the European Union (EU), and Rest of World (ROW), will participate. Enrollment will be managed to ensure adequate representation in each region.

Safety and effectiveness evaluations will include comparisons to external databases. Health-related quality of life, healthcare resource consumption, and work productivity evaluations will be based on changes from baseline. No internal control cohort will be included in the study (see Section 9.2.2).

[redacted]

9.1.1. Primary Endpoint

Safety will be evaluated primarily by assessment of the incidence and incidence rate of treatment-emergent SAEs and of AEs leading to treatment discontinuation (see Section 9.7.3).

9.1.2. Secondary Endpoints

Secondary endpoints will address non-safety related study objectives, as follows:

- DMF prescription and utilization patterns will be evaluated by assessment of prescribed dosing frequency, duration of DMF use, and primary reason for discontinuation of DMF (see Section 9.7.4).
- Effectiveness of DMF on MS disease activity and disability progression will be evaluated by assessment of relapse-related endpoints (e.g., annualized

relapse rate, 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 (see Section 9.7.5).

- Changes in health-related quality of life measures will be evaluated over time. Healthcare resource consumption will be evaluated by assessment of endpoints such as number of hospitalizations, emergency room visits, and neurologist visits. Work productivity will be evaluated by assessment of ability to work and time needed away from work due to MS (see Section 9.7.6).

[redacted]

9.2. Setting

9.2.1. Prospective Cohort Study in Patients With MS

9.2.1.1. Selection Criteria

Patients aged 18 and older with MS who have been newly prescribed DMF under routine clinical care are eligible to participate in the study. Efforts will be made to recruit a variety of physicians who are representative of DMF prescribers. Eligible patients must be naïve to DMF, Fumaderm®, and compounded fumarates at the time of enrollment, but need not be naïve to other MS treatments, and must not be currently enrolled in any other clinical trial or study except for the DMF Pregnancy Registry or other studies that, according to the study Medical Director, do not conflict with this observational study (e.g., health economic studies).

Patients with previous exposure to DMF, Fumaderm®, and compounded fumarates are excluded so as not to introduce bias; these patients may be more or less likely to experience AEs and may fail to report AEs that occurred before study enrollment. Patients participating in other clinical studies are excluded so as not to unduly confound causality assessments when a concomitant experimental agent's safety profile has yet to be established and/or the physician is blinded to the patient's treatment assignment.

[redacted]

9.2.1.2. Overall Study Duration and Follow-Up

The study consists of enrollment and a follow-up period. Patient participation in the study will be for up to 5 years from enrollment. Follow-up is planned regardless of whether patients who have been prescribed DMF do not initiate treatment or discontinue treatment with DMF.

Enrollment

The decision to enroll a patient in this study must not be made until after the Prescribing Physician and patient decide to begin DMF treatment and DMF has been prescribed. Patients agreeing to participate in the study will read and sign the consent and confidentiality statements. Enrollment data will be collected by the physician at the routine clinical visit at which DMF treatment is first prescribed (see Section 9.3.1 for details). During enrollment, the physician will also inform female patients of childbearing potential about the DMF Pregnancy Registry (in countries where the registry is conducted).

Patients enrolled in the study will be assigned unique patient ID numbers that will be used to track the patients throughout the study. Any patient identification numbers that are assigned will not be reused even if a patient does not start DMF treatment.

An individual study patient may only be included once in the study. Patients who prematurely withdraw from the study for any reason will not be eligible to re-enroll.

Follow-Up

After enrollment, the Prescribing Physician will collect patient information during routine clinical visits as described in Section 9.3.2. For the purposes of this study, routine clinical visits are defined as any visit scheduled per local standard of care. The collected information for each patient will be sent to the Contract Research Organization (CRO) managing the study (see Section 3) through their Coordinating Center (CC) approximately every 6 months for up to 5 years after enrollment. If the CC does not receive completed data from the physician on a patient for whom 6-month follow-up is expected, the CC will contact the site to remind them to complete the required data.

PROs, which include all health economic assessments, may be completed by patients during the routine clinic practice visit, or, if outside of the physician's office, within 1 week (before or after) the routine visit. Patients will receive reminders from the CC or the Prescribing Physician to complete the assessments 1 week prior to each visit, if consistent with local regulations.

All information will be sent to the CC by electronic or paper means. The information received by the CC will be stored in a secure database.

[redacted]

9.2.1.3. Discontinuation or Withdrawal of Patients from the Study

9.2.1.3.1. Discontinuation of DMF and Continued Participation in the Study

Patients who discontinue treatment with DMF will have the option to continue participating in the study. The Prescribing Physician will record the primary reason for

DMF discontinuation, including AEs (including laboratory abnormalities) leading to discontinuation. If the primary reason for discontinuation of DMF was a laboratory finding, the patient's complete history of relevant laboratory values collected during the study (starting with the most recent values prior to initiating DMF [see Section 9.3.1]) is also to be recorded. Information will be collected at routine clinical visits following the standard protocol as described in Section 9.3.2 through 30 days after the last dose. At routine visits thereafter, the standard protocol will also be followed, except SAE data collected will be limited to reports of malignancies. In the event that a patient does not have a routine visit within 6 months after his/her last dose of DMF, the physician will contact the patient by telephone to obtain the information, with the exception of laboratory data and EDSS score.

It should be noted that patients who discontinue treatment with DMF but continue to be followed in the study should have the option of restarting DMF treatment at any time within the 5-year follow-up period. Once a patient has restarted DMF, the information collected should follow the standard protocol.

9.2.1.3.2. Noninitiation of DMF and Continued Participation in the Study

Patients who are prescribed DMF but do not initiate treatment (i.e., do not take at least 1 dose of DMF) after enrollment in the study will have the option to continue participating in the study. Information will be collected at routine clinical visits following the standard protocol as described in Section 9.3.2, except for SAE and pregnancy data. Serious adverse event and pregnancy data will be collected from the first dose of DMF.

It should be noted that patients who do not initiate treatment with DMF but continue to be followed in the study should have the option of starting DMF treatment as part of routine clinical practice at any time within the 5-year follow-up period. Once a patient has started DMF, the information collected should follow the standard protocol.

9.2.1.3.3. Premature Withdrawal From the Study

Patients may withdraw consent to participate in the study at any time. If withdrawal occurs during a routine clinical visit, the Prescribing Physician will collect information one last time following the standard protocol as described in Section 9.3.2, if permitted by the patient. If a patient withdraws from the study outside of the physician's office, information will be collected one last time by telephone according to the standard protocol, with the exception of laboratory data and EDSS score, if permitted by the patient.

For patients who discontinue DMF and continue to participate in the study but subsequently withdraw, similar information will be collected one last time at the time of withdrawal, but SAE data collection will be limited as described in Section 9.2.1.3.1.

For patients who do not initiate treatment with DMF and continue to participate in the study but subsequently withdraw, similar information will be collected one last time at the time of withdrawal except SAE and pregnancy data as described in Section 9.2.1.3.2.

9.2.1.3.4. Lost to Follow-Up

If a patient has not been in contact with the Prescribing Physician for 12 months following his or her last routine visit, the site will contact the patient by telephone to assess the patient's interest in continuing study participation. If the site is unable to make contact with the patient, a follow-up attempt must be made. A site may consider a patient lost to follow-up after 3 failed documented contact attempts, one of which must be a certified letter. If a patient's status is determined to be lost to follow-up, this must be recorded on the End of Study CRF. If the physician ascertains a patient has died, the death should be recorded and reported as described in Section 11.2.4.1.

9.2.1.3.5. Patient Transfers

In the event that a patient wishes to transfer to a different physician to receive MS care, Biogen Idec will attempt to find another study site at which the patient can continue to participate in the study. If the patient continues care with a physician who is not participating in the DMF observational study, Biogen Idec may include the new site in the observational study program, if feasible.

[redacted]

9.2.1.4. Study Stopping Rules

Biogen Idec may terminate this study at any time, after informing participating physicians. Physicians will be notified by Biogen Idec or designee if the study is placed on hold, completed, or closed.

9.2.2. External Control Populations

In this study, background comparator rates for events of interest (Section 8.1) and any new potential safety signals identified will be ascertained using external databases. Examples of such external databases include the following: Clinical Practice Research Datalink (CPRD), GLOBOCAN, Healthcare Cost and Utilization Project (HCUP), InVision Data Mart Multiplan (U.S. Healthcare Claims), and Surveillance, Epidemiology and End Results (SEER). The use of external databases should be a sufficient substitute for an internal control cohort for the following reasons:

- The primary objective of this observational study is to characterize the long-term safety profile of DMF; no specific hypothesis is being tested.

- Most SAEs will be associated with hospitalization. As such, background comparator rates for SAEs calculated using health insurance claims or electronic medical record databases (e.g., CPRD) are considered to be a reasonable approximation of the background incidence rates of relevant events. For example, myocardial infarction [Austin 2002; Choma 2009; Chung 2010; Kiyota 2004; Levy 1999; Petersen 2009] and serious infection [Patkar 2009; Schneeweiss 2007] outcomes have been previously validated in claims databases.
- It is anticipated that malignancy background rates will be obtained from SEER and GLOBOCAN. These registries will provide more accurate malignancy background rates due to their large size and standardized collection and classification of cases. Malignancy background rates obtained from these registries are an appropriate comparison for an MS population since patients with MS do not appear to be at increased risk for most malignancies compared to the general population [Bahmanyar 2009; Fois 2010; Handel and Ramagopalan 2010; Koch-Henriksen 1999; Midgard 1996; Møller 1991; Nielsen 2006; Sumelahti 2004]. There have been a few studies that have suggested an increased risk of developing site-specific cancers such as breast [Nielsen 2006], brain [Bahmanyar 2009], and urinary [Bahmanyar 2009]. SEER and GLOBOCAN rates will be supplemented by MS-specific rates obtained from the peer-reviewed literature when appropriate.
- MS cohorts derived from external databases are more likely to share similar demographic and clinical characteristics with DMF-treated MS patients than would a concurrently enrolled active comparator cohort. A concurrently enrolled active comparator cohort might be subject to significant channeling biases (i.e., a form of allocation bias where drugs for the same indication are differentially prescribed based on real or perceived prognostic differences for efficacy or safety) [Petri and Urquhart 1991]. Which segment of the MS population will initiate DMF treatment and whether or not there will be any channeling bias that influences a physician's choice to prescribe DMF versus another first-line treatment cannot be predicted prior to commercial availability. Amongst the new oral MS agents, physicians may channel patients with significant cardiac or pulmonary history to an agent other than fingolimod given its cardiovascular risks and observed decreases on pulmonary function tests. If so, this may bias rates of cardiovascular and pulmonary events in fingolimod patients in comparisons to other agents. Likewise, for patients switching from another MS therapy, it is unclear where DMF will fit into the treatment algorithm. Any real or perceived differences in efficacy and safety between the available MS treatments will likely influence treatment decisions. For example, if DMF is viewed as having a strong benefit-risk profile, physicians may preferentially prescribe it to patients switching from second and third line agents such as natalizumab or mitoxantrone. This would bias the DMF cohort with patients with more aggressive disease who may be at greater risk for AEs due to the morbidity

associated with advanced MS and its treatments. Thus, it is plausible that a concurrently recruited active comparator cohort will differ from the DMF cohort on multiple important risk factors for SAEs of interest (e.g., immunosuppressant and immunodulator use related to risk of serious infections or malignancies). Utilizing external databases will provide access to a larger pool of patients with MS and will allow flexibility in constructing comparator cohorts that reflect current MS treatment standards as they evolve over the course of the study. This will increase the likelihood of successfully using statistical techniques such as propensity score matching to calculate background rates from a comparable cohort of patients with MS who are using other first-line treatments.

- Based on the known safety profile of DMF, no special non-routine safety assessments are anticipated (e.g., annual ophthalmology examination) and thus no ascertainment bias is anticipated. The standard of care outlined in the proposed DMF prescribing information is similar to the standard of care for most other first-line MS therapies. Furthermore, the frequency of physician visits or medical procedures is not expected to differ between DMF-treated patients and similar patients with MS treated with other first-line agents. Therefore, DMF-treated patients should not be any more or less likely to receive a particular diagnosis due to recommended safety assessments.

9.3. Variables

9.3.1. Information Collected at Enrollment

Patients must be consented before any information is collected. The Prescribing Physician will collect (unless otherwise noted) and record the following information for enrollment at a routine clinical visit. See also the Schedule of Events (Section 16.1).

- demographic data
- medical history: assessment of clinically significant medical and surgical history and concomitant diseases, and known cardiovascular risk factors (e.g., smoking, alcohol consumption, patient and family history of high cholesterol, high blood pressure, cardiac disease, peripheral artery disease, arrhythmia, cerebrovascular disease, and diabetes mellitus)
- MS disease history (including type of MS, relapse history [see Section 9.3.2 for relapse definition], and the latest EDSS score based on last neurologic examination conducted prior to enrollment) and results of the latest brain MRI scan, which may include lesion count
- prior use and duration of therapies for MS (if any)
- prior use and duration of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents (if any)
- prior use and duration of hepatotoxic and nephrotoxic agents (e.g., paracetamol, nonsteroidal anti-inflammatory drugs, antibiotics, anticonvulsants, protease inhibitors, diuretics, and lithium) (if any)

- complete blood count (CBC) with differential, *if consistent with local regulations*††
- other laboratory tests recommended in local label (e.g., liver and renal function tests, urinalysis) *if consistent with local regulations* ††
- concomitant use (i.e., at enrollment) of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies (if any)
- concomitant use (i.e., at enrollment) of hepatotoxic and nephrotoxic agents (e.g., paracetamol, nonsteroidal anti-inflammatory drugs, antibiotics, anticonvulsants, protease inhibitors, diuretics, and lithium) (if any)
- recording of EDSS information (including Functional System Scores and Ambulation scores), based on neurological examination at enrollment, *when collected as part of routine clinical practice* (i.e., not specifically performed for the study) †††
- DMF prescription information, including prescribed dosing frequency and start date (if started on the day of enrollment; otherwise record start date at the next visit)
- patient assessment of the following outcome measures, *if consistent with local regulations*: ††††
    - physical and psychological impact of MS using the Multiple Sclerosis Impact Scale-29 Items (MSIS-29) questionnaire
    - impression of functional health and well-being using the EQ-5D-5L questionnaire and EQ Visual Analogue Scale (EQ VAS)
    - patient's assessment of the perceived effect of MS-related fatigue on daily activities using the Modified Fatigue Impact Scale (MFIS)-5 questionnaire
    - work productivity and activity impairment using the Work Productivity and Activity Impairment questionnaire: Multiple Sclerosis, Version 2.0 (WPAI-MS)
    - Healthcare resource consumption questionnaire (e.g., MS-related neurologist visits, visits to other health care professionals for MS-related and other reasons)
- pregnancy status (patient-reported, female patients)

††***Note***: In the US, physicians will be asked to record the results of the most recent CBC. If the results of a CBC conducted within 6 months of baseline are not available to be recorded, physicians will be encouraged to conduct blood draws for CBC at the time of enrollment and to record the results. To be consistent with local regulations, physicians in the EU and ROW will be asked to record the most recent CBC, liver function, renal function, and urinalysis results *if collected as part of routine clinical practice* (i.e., not specifically performed for the study). Additionally, for patients who discontinue DMF due to an abnormal laboratory test result, physicians will be asked to record all relevant

laboratory test results collected during the course of the study *as part of routine clinical practice*.

†††***Note***: In order to assure high reliability of assessments, it is essential to have standardized examinations and consistent definitions for the EDSS. Neurostatus certification is highly recommended for all participating physicians. Physicians will be asked to provide their certification information. If they are not certified, they will be provided a copy of the interactive Neurostatus Training DVD-ROM edited by L Kappos and S Wu, Basel – Switzerland and offered a free-of-charge online certification training (www.neurostatus.net).

††††***Note***: PROs will be available to patients online or on paper to allow completion of the questionnaires outside of the physician's office. However, the questionnaires are to be completed within 1 week (before or after) the scheduled visit. Questionnaires may be completed by a proxy (e.g., family member).

9.3.2. Information Collected During the Follow-Up Period

The following information will be collected (unless otherwise noted) by the Prescribing Physician at each routine clinical practice visit, and also recorded. Visits are anticipated to occur approximately every 6 months. See also the Schedule of Events (Section 16.1).

- SAEs, including but not limited to infections (including opportunistic infections), hepatic events, malignancies, and renal events (note: all opportunistic infections and malignancies are to be reported as SAEs);
- AEs (including laboratory abnormalities) leading to treatment discontinuation;
- concomitant use of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies (if any)
- concomitant use of hepatotoxic and nephrotoxic agents (e.g., paracetamol, nonsteroidal anti-inflammatory drugs, antibiotics, anticonvulsants, protease inhibitors, diuretics, and lithium) (if any)
- complete blood count (CBC) with differential, *if consistent with local regulations*††
- results of other clinical laboratory test results recommended in the local label (e.g., liver and renal function tests, urinalysis) *if consistent with local regulations*††
- recording of EDSS information (including Functional System Scores and Ambulation scores), based on neurological examination, *when collected as part of routine clinical practice* (i.e., not specifically performed for the study) †††
- recording of MS relapse information (see below for the definition of relapse)
- DMF prescription and utilization information, including prescribed dosing frequency, duration of DMF use, and primary reason for discontinuation of DMF

- patient assessment of the following outcome measures, *if consistent with local regulations*: MSIS-29, EQ-5D and EQ VAS, MFIS-5, WPAI-MS, and healthcare resource consumption (as described above)††††
- pregnancy status (patient-reported, female patients) †††††

††***Note***: At sites in the US, physicians will be asked to conduct blood draws for CBC (not more frequently than every 12 months unless indicated per local standard of care) and to record the results. To be consistent with local regulations, physicians in the EU and ROW will be asked to record CBC, liver function, renal function, and urinalysis results *if collected as part of routine clinical practice* (i.e., not specifically performed for the study). Additionally, if a patient discontinues DMF due to an abnormal laboratory test result, physicians will be asked to record all relevant laboratory test results collected during the study (starting with the most recent values prior to initiating DMF) *as part of routine clinical practice.*

†††***Note***: In order to assure high reliability of assessments, it is essential to have standardized examinations and consistent definitions for the EDSS. Neurostatus certification is highly recommended for all participating physicians. Physicians will be asked to provide their certification information. If they are not certified, they will be provided a copy of the interactive Neurostatus Training DVD-ROM edited by L Kappos and S Wu, Basel – Switzerland and offered a free-of-charge online certification training (www.neurostatus.net).

††††***Note***: PROs will be available to patients online or on paper to allow completion of the questionnaires outside of the physician's office. However, the questionnaires are to be completed within 1 week (before or after) the scheduled visit. Questionnaires maybe completed by a proxy (e.g., family member).

†††††***Note***: Pregnancy status will not be collected for female patients who are enrolled in the study but have not initiated treatment with DMF.

Definition of Relapse

For the purposes of this study, relapses are defined as new or recurrent neurologic symptoms not associated with fever, lasting at least 24 hours. New or recurrent neurologic symptoms that evolve gradually over months are to be considered disease progression, not an acute relapse. New or recurrent neurologic symptoms that occur fewer than 30 days following the onset of a relapse as defined above are to be considered part of the same relapse.

[redacted]

9.4. Data Sources

In the prospective cohort study, individual patient data will be collected at routine clinic visits (see Sections 9.2.1.2 and 9.3).

Background comparator rates for AEs of interest and any new potential safety signals identified will be ascertained using external databases (see Section 9.2.2).

9.5. Study Size

A sample size of approximately 5000 MS patients who have been newly prescribed DMF will be enrolled in the study and followed for up to 5 years. Follow-up is planned regardless of whether patients do not initiate or discontinue treatment with DMF. Enrollment will close after 5000 enrolled MS patients have been treated with DMF (defined as having taken at least 1 dose of DMF). The sample size and study duration were chosen to ensure a reasonable likelihood of observing rare events over a 5-year period and calculating informative confidence intervals (CIs) for SAE incidence and incidence rate point estimates.

Based on withdrawal rates observed in DMF clinical trials and prior Biogen Idec observational studies, it is expected that approximately 16,000 to 18,000 person-years of follow-up will accrue. Enrollment may be increased if the withdrawal rate is substantially greater than expected.

With this sample size, the probability of observing an event with an incidence of 0.06% (60/100,000 persons, or 1/1667 persons) will be 95%, the probability of observing an event with an incidence of 0.05% (50/100,000 persons, or 1/2000 persons) will be 92%, and the probability of observing an event with an incidence of 0.03% (32/100,000 persons, or 1/3125 persons) will be 80%.

In addition, the study's estimated power to detect potential clinically relevant increases in the risk of malignancies, serious infections, serious hepatic events, and serious renal events in a given year, as compared to expected background rates, is shown in Table 4. These power calculations assume a sample size of 5000 patients and an exact binomial test with a nominal, 2-sided significance level of 0.05.

Table 4: Estimate of Power for Detecting Potential Clinically Relevant Increases in the Risk of Events of Interest Compared With Expected Background Rates

Outcome	Expected	Risk Ratio	Power (%)
Malignancies[1, 2]	449.9/100,000 persons/year	2.0	97
Serious infections[3]	2000/100,000 persons	1.5	99
Serious hepatic events[3, 4]	130/100,000 persons	2.5	82
Serious renal events[3]	260/100,000 persons	2.0	86

[1] Source data: SEER; Fast Stats: an interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats. Accessed on 20 January 2012.

[2] Excludes basal and squamous cell carcinomas of the skin, except when these occur on the skin of the genital organs, and in situ cancers, except urinary bladder.

[3] Source data: incidence in placebo arms of Studies 109MS301 and 109MS302

[4] No placebo subjects in Studies 109MS301 and 109MS302 experienced a serious hepatic event; for the purpose of power calculations, 1 placebo subject was imputed.

Table 5 shows the SAE incidence and incidence rate point estimates and 95% CIs for various scenarios of observed number of cases. The SAE incidence was calculated based on the assumption of 5000 patients in the analysis population. The SAE incidence rate was calculated based on the assumption of observing 17,000 person-years of follow-up. The 95% CIs were calculated based on the binomial distribution for SAE incidence and based on the Poisson distribution for SAE incidence rates.

Table 5: SAE Incidence and Incidence Rate: Point Estimates and 95% Confidence Intervals Based on Number of Observed Cases

Number of Observed Cases (in 5000 patients with 17,000 person-years of follow-up)	SAE Incidence		SAE Incidence Rate (per 100,000 person-years)	
	Point Estimate	2-sided 95% CI	Point Estimate	2-sided 95% CI
1	0.02%	(0.001%, 0.111%)	5.9	(1.5, 32.8)
2	0.04%	(0.005%, 0.144%)	11.8	(3.6, 42.5)
3	0.06%	(0.012%, 0.175%)	17.7	(6.4, 51.6)
4	0.08%	(0.022%, 0.205%)	23.5	(4.5, 60.2)
5	0.1%	(0.032%, 0.233%)	29.4	(9.6, 68.6)
10	0.2%	(0.096%, 0.367%)	58.8	(28.2, 108.2)
20	0.4%	(0.244%, 0.617%)	117.6	(71.9, 181.7)

[redacted]

[redacted]

9.6. Data Management

Data collection will be performed using electronic or paper Case Report Forms (CRFs). Data will be entered into a central database managed by a CRO.

9.7. Data Analysis

Statistical analyses will generally be descriptive and exploratory in nature. No formal statistical hypothesis testing is planned.

9.7.1. Analysis Population

Statistical analyses will be based on all patients who enroll in the study (defined as having an available date of informed consent) and take at least 1 dose of DMF.

9.7.2. Demography and Baseline Disease Characteristics

Demographic and baseline disease characteristics will be summarized by descriptive summary statistics for continuous variables and frequency distribution for categorical variables.

9.7.3. Safety

The incidence and incidence rate of all reported treatment-emergent SAEs and AEs leading to treatment discontinuation will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. (Note: laboratory abnormalities leading to discontinuation are to be reported as AEs.) An event is considered to be treatment-emergent if it has an onset date on or after the first dose of DMF or if it was present prior to the start of DMF and subsequently worsened. Incidence is defined as the proportion of patients with a given event out of the number of patients in the analysis population. Incidence rate is defined as the number of patients with a given event adjusted for duration of follow-up for the particular event (e.g., incidence rate per 100,000 patient years). Ninety-five percent CIs for incidence and incidence rate point estimates will be calculated using the binomial distribution and the Poisson distribution, respectively.

Potential safety signals may be identified in this observational study after clinical review of SAE reports or comparisons of incidence/incidence rates to external background rates. These comparisons will be based on examination of point estimates and 95% CIs. Examples of applicable external databases include the CPRD, GLOBOCAN, HCUP, InVision Data Mart Multiplan (U.S. Healthcare Claims), and SEER. Also, other Biogen Idec-sponsored observational studies may be utilized. When possible, comparisons will be made to MS-specific background rates in addition to general population background

rates. The background rates will serve as references when examining the rates in the study population. However, no formal inferential statistical comparisons to the background rates are planned.

Analyses of clinical laboratory parameters will be limited to frequency descriptions of the number of patients with abnormal laboratory results. History of laboratory abnormalities (e.g., lymphocyte count <3 times the lower limit of normal) may be used to stratify patients when assessing the rates of selected SAEs.

Analyses of SAEs, AEs leading to treatment discontinuation, and clinical laboratory parameters may also be undertaken for patient subgroups defined by appropriate demographic and/or baseline prognostic factors, and/or concomitant medication exposure (e.g., concomitant MS therapies and potentially nephrotoxic medications). Analyses may also be stratified by treatment duration or study duration epochs.

9.7.4. DMF Prescription and Utilization

Duration of DMF use and prescribed dosing frequency will be summarized both descriptively and categorically, as appropriate. Primary reasons for discontinuation of DMF will be tabulated.

9.7.5. Effectiveness

The effectiveness of DMF on MS disease activity and disability progression will be based on assessment of relapse-related endpoints and EDSS-based progression-related endpoints, respectively. Effectiveness evaluations will include comparisons to external databases.

MS disease activity will be assessed by evaluating the frequency of relapses over time. These analyses may include the following parameters:

- annualized relapse rate
- time to first relapse
- proportion of patients with relapse
- distribution of the total number of relapses

Disability progression will be assessed by evaluating EDSS evolution over time. These analyses may include the following parameters:

- proportion of patients with progression (defined as at least a 1.0 point increase from a baseline EDSS ≥1.0 or at least a 1.5 point increase from a baseline EDSS = 0)
- time to first progression
- proportion of patients with sustained progression for at least 6 months
- time to sustained progression for at least 6 months
- proportion of patients with post-baseline EDSS values greater than certain thresholds (e.g., ≥4.0, >6.5) at any time and sustained for at least 6 months

- proportion of patients whose disability status worsened, stabilized, or improved over time, including an analysis based on values sustained for at least 6 months. Improvement may be defined as a decrease of at least 1.0 point from baseline, a stable condition as a change of ≤0.5 point from baseline, and worsening as an increase of at least 1.0 point from baseline.

Annualized relapse rate will be analyzed using a negative binomial model, adjusted for appropriate prognostic factors, and time-to-event endpoints will be analyzed using Kaplan-Meier estimates. Analyses of relapse related and progression related endpoints may also be undertaken for patient subgroups defined by appropriate demographic and/or baseline prognostic factors (e.g., EDSS score).

9.7.6. Patient-Reported and Health Economic Outcomes

Summary statistics over time, as well as changes from baseline over time, will be presented for the following outcome measures:

- MSIS-29 physical and psychological MS impact scores
- EQ-5D-5L index score, as well as 5 individual component scores
- EQ VAS (0-100 scale)
- MFIS-5 total score
- WPAI-MS impairment percentages
- Healthcare resource consumption (including number of hospitalizations [MS-related, non-MS related, relapse-related, resulting in steroid use], MS-related emergency room visits, MS-related neurologist visits, visits to other health care professionals for MS-related and other reasons) will be summarized over time with frequency distribution and/or descriptive statistics.

[redacted]

9.7.8. Interim Analyses

Safety data will first be analyzed after 1000 patients have completed 6 months of follow up, then at least annually. Other study objectives may be assessed on a similar schedule.

9.8. Quality Control

9.8.1. Study Site Initiation

The Prescribing Physician must not enroll any patients in this observational study prior to completion of a study initiation visit, conducted by Biogen Idec or designee. This initiation visit will include a detailed review of the protocol and study procedures.

9.8.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen Idec or the regulatory authorities may wish to perform on-site audits. The physician will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

9.8.3. Monitoring of the Study

Biogen Idec or designee representatives may conduct onsite visits at the study facilities for the purpose of monitoring various aspects of the study. The physician must agree to Sponsor-authorized personnel having direct access to the patient (or associated) files for the purpose of verifying entries made in the CRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the physicians or study staff. The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

9.8.4. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the physician is requested to notify Biogen Idec in writing. In addition, the physician is requested to notify Biogen Idec of any changes in the archival arrangements (e.g., archival at an off-site facility or transfer of ownership if the physician leaves the site).

9.9. Limitations of the Research Methods

Disease-specific background rates are important in populations like MS where the prevalence of confounding factors is likely different from the general population (e.g. immunosuppressant use). Background rates will be obtained from external databases due to reasons previously described in Section 9.2.2, such as potential channeling biases.

However, the potential limitations of external databases, namely the differential ascertainment of select variables, should be acknowledged.

There is the potential for differential ascertainment of non-MS medication and over the counter (OTC) medications use. In this study, medication use will be documented by the Prescribing Physician. It is assumed that almost all Prescribing Physicians will be the patient's treating neurologist; therefore, capture of MS treatments should be fairly complete. Capture of other medications will depend on the patient's ability to accurately report concomitant medications to their neurologist. Medical claims databases capture prescription drug treatments when claims are submitted for reimbursement; they do not capture medications such as OTC medications which are not submitted for reimbursement. For the purposes of safety signaling, any bias attributable to unmeasured OTC medication use should not threaten the validity of safety signal analyses. The one exception may be OTC non-steroidal anti-inflammatory drugs (NSAID) and paracetamol use when evaluating renal and hepatic events, respectively. The potential for differential use of these agents should be considered when evaluating renal and hepatic event rates across data sources.

There is also the potential for differential ascertainment of medical events. The ascertainment of serious medical events will likely be similar in the proposed data sources. Also, ascertainment of malignancies and opportunistic infections should be similar, regardless of seriousness. A medical claim or patient record should be generated anytime a patient is diagnosed with a malignancy. Similarly, most patients with a clinically significant opportunistic infection will seek medical care; therefore, external databases should also provide reasonable background rates for these events. A differential ascertainment of these events between MS patients in the observational study and external databases is unlikely, so comparing these rates across the data sources should be appropriate. However, the availability of clinical details in external databases will likely be limited to information gleaned from medical terminology codes contained in a medical claim or electronic patient record.

The ascertainment of non-serious medical events may be more limited in external databases, particularly medical claims databases. Patients may not seek care for non-serious events (e.g. nasopharyngitis), therefore, these events would not be captured in external databases. The availability and validity of background rates for non-serious AEs leading to discontinuation will need to be evaluated on a case-by-case basis as they are reported. However, it may be appropriate to use data from the DMF clinical development program to calculate background rates for some non-serious events leading to discontinuation. For example, non-serious flushing and GI tolerability issues were routinely captured in the DMF clinical development program. The differences between the clinical trial population and the post-market population would need to be taken into account when making such comparisons.

The ascertainment of potential confounders, such as diabetes and hypertension, from a patient's medical history is subject to the limitations described above. For example, untreated diabetes or hypertension may not be well captured if the patient is not seeking medical care for these conditions. In addition, information on vital signs and lifestyle

risk factors such as nicotine use are generally not available in most external databases. The limitations of these databases to identify confounders are widely acknowledged; however, medical and pharmacy records/claims are routinely used for confounding adjustment in pharmacoepidemiologic studies. The potential impact of residual confounding resulting from unmeasured comorbidities or medication use will be evaluated and noted for each comparison made with external databases, but it should not threaten the validity of these comparisons for purposes of signal detection.

Overall, any comparison of data from the observational study to external databases will be discussed in the context of its limitations.

9.10. Other Aspects

9.10.1. Study Funding

Biogen Idec is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, physician, and Biogen Idec.

9.10.2. Publications

Details on any restrictions on the publication of study data by Prescribing Physicians are included in the clinical study agreement for this study.

10. PROTECTION OF HUMAN SUBJECTS

Biogen Idec and participating physicians must comply with this protocol and applicable International Conference on Harmonisation and Good Pharmacovigilance Practices guidelines, and conduct the study according to local regulations. The patient's privacy; physical, mental, and social integrity; and the confidentiality of his or her personal information will be strictly respected in accordance with the World Medical Association Declaration of Helsinki.

10.1. Ethics Committee

Participating physicians must obtain ethics committee approval of the protocol, informed consent form (ICF), and other required study documents prior to starting the study. The CRO (Section 3) will submit documents on behalf of the study sites in countries other than the US.

If the physician makes any changes to the ICF, Biogen Idec must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen Idec. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen Idec.

It is the responsibility of the physicians to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen Idec must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen Idec.

10.2. Subject Information and Consent

Prior to any data collection under this protocol, written informed consent with the approved ICF must be obtained from the patient or patient's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all patients participating in a clinical study conducted by Biogen Idec. [redacted]

Information about the DMF observational study and that study participation is voluntary for the patient must be explained to the patient. The patient must be given sufficient time to consider whether to participate in the study. A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent

must be documented in the patient's medical record prior to any data collection under this protocol.

Each consent form should contain an authorization allowing the physician and Biogen Idec to use and disclose protected health information (i.e., patient-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

10.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and Regulatory Authorities if required by local law. Protocol modifications that affect patient safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen Idec may, at any time, amend this protocol to eliminate an apparent immediate hazard to a patient. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the patient consent form may require similar modifications (see Sections 10.1 and 10.2).

10.4. Subject Data Protection

Prior to any data collection under this protocol, patients must also provide all authorizations required by local law (e.g., protected health information authorization in the US).

The patient will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. Biogen Idec and designee(s), ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

10.5. Internal Safety Review

Safety and Benefit-Risk Management (SABR) and other applicable personnel at Biogen Idec will review all SAEs on a regular basis.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Additionally, AEs are defined to include laboratory abnormalities leading to treatment discontinuation.

11.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death
- in the view of the Prescribing Physician, places the patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

While MS relapses resulting in hospitalization are considered SAEs, they will not be reported as SAEs in the study unless, in the opinion of the physician, a relapse is complicated by other SAEs.

All opportunistic infections and malignancies should be considered serious and reported as SAEs.

An SAE may also be any other medically important event that, in the opinion of the Prescribing Physician, may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

11.2. Monitoring and Recording Events

11.2.1. Adverse Events

Nonserious AEs, except for those AEs that lead to discontinuation of DMF (including laboratory abnormalities that lead to discontinuation), will not be collected as part of this study and should follow spontaneous postmarketing rules as per local regulations.

Note: if a patient discontinues DMF due to a laboratory abnormality, all relevant laboratory test results collected during the study (starting with the most recent values prior to initiating DMF) are also to be reported.

11.2.2. Serious Adverse Events

Any SAE experienced by the patient between the time of the first dose of DMF and study completion or premature study withdrawal, or within 30 days of discontinuation of DMF is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to DMF. For patients who discontinue treatment but continue to participate in the study, any malignancy occurring more than 30 days after the last dose of DMF will be treated as an SAE and reported on an SAE form. For reporting timelines and procedures, see Section 11.2.4.

11.2.3. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 11.1.2.
- The relationship of the event to DMF as defined in Section 11.3.1.

11.2.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen Idec SABR or designee within 24 hours of becoming aware of the SAE. It is the Prescribing Physician's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time of the first dose of DMF and study completion or premature study withdrawal, or within 30 days of discontinuation of DMF must be reported to Biogen Idec SABR or designee within 24 hours of the study site becoming aware of the event. For patients who prematurely discontinue treatment with DMF but continue to participate in the study, any malignancy occurring more than 30 days after the last dose of DMF will be treated as an SAE and must be reported to Biogen Idec SABR or designee within 24 hours of the study site staff becoming aware of the event.

A report ***must be submitted*** to Biogen Idec SABR or designee regardless of the following:

- the severity of the event
- the relationship of the event to DMF

To report initial or follow-up information on an SAE, fax or email a completed SAE form to the following:

Refer to the Investigator Site File for fax numbers and email information

11.2.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the Adverse Event CRF. Additionally, the date and cause of death should be reported on the Record of Death CRF. If applicable, death should also be recorded as the reason for treatment discontinuation and/or study withdrawal. All causes of death must be reported as SAEs. The Prescribing Physician should make every effort to obtain and send death certificates and autopsy reports to Biogen Idec SABR or designee.

11.3. Safety Classifications

11.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to DMF:

Relationship of Event to Commercial Drug	
Not related	An adverse event will be considered "not related" to the use of DMF if there is not a possibility that the event has been caused by DMF. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.
Related	An adverse event will be considered "related" to the use of DMF if there is a possibility that the event may have been caused by DMF. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.

11.3.2. Expectedness of Events

Expectedness of all AEs will be determined by Biogen Idec SABR according to the approved local label.

11.4. Procedures for Handling Special Situations

11.4.1. Overdose

An overdose is any dose of DMF given to a patient or taken by a patient that exceeds the dose described in the local label. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to Biogen Idec SABR or designee within 24 hours. An overdose should be reported even if it does not result in an AE.

11.4.2. Reporting Pregnancy and Coordination With the Pregnancy Registry

The Prescribing Physician should refer to the approved local label for guidance if female patients become pregnant or are considering becoming pregnant during the study.

At each routine visit, female patients of childbearing potential will be asked about their pregnancy status and possible pregnancies/spontaneous abortions since the last visit or contact. Spontaneous abortions are considered to be SAEs and must be reported as such (Section 11.2.4).

A DMF Pregnancy Registry is being conducted independently of this study, and pregnant women who have received DMF since the first day of their last menstrual period prior to conception or at any time during pregnancy (regardless of participation in any studies) will be offered participation in the Registry, in countries where the Registry is conducted. Pregnant women may be dually enrolled in this study and the DMF Pregnancy Registry. If a pregnant female patient received DMF since the first day of her last menstrual period prior to conception or at any time during pregnancy, and if the patient is willing to

participate, the Prescribing Physician should contact Biogen Idec SABR or designee within 24 hours of the site becoming aware of the pregnancy to initiate the enrollment process (refer to the DMF Registry Brochure for contact details). Note: the patient's consent to participate will be obtained under the DMF Pregnancy Registry protocol (109MS402).

If a pregnant female patient declines participation in the Pregnancy Registry, pregnancy information will be collected under this protocol. The Prescribing Physician should report the pregnancy to Biogen Idec SABR or designee (via fax or email [see Investigator Site File for fax numbers and email information], using the Pregnancy Form) within 24 hours of the site becoming aware of the pregnancy, and should follow the outcome of the pregnancy and provide the outcome to Biogen Idec SABR or designee.

If the partner of a male patient receiving DMF becomes pregnant at any time during the study, the Prescribing Physician should follow the pregnancy outcome and report any congenital anomaly or birth defect as an SAE to Biogen Idec or designee. Pregnant female partners will not be referred to the DMF Pregnancy Registry.

11.5. Prescribing Physician Responsibilities

The Prescribing Physician's responsibilities include the following:

- Monitor and record all SAEs, regardless of the relationship to DMF.
- Determine the relationship of each SAE to DMF.
- Determine the onset and resolution dates of each SAE.
- Record all pregnancies (including pregnancies in partners of male patients receiving DMF) and refer all pregnant women taking DMF to the Pregnancy Registry, in countries where the Registry is conducted.
- Complete an SAE form for each SAE and fax it to Biogen Idec SABR or designee within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen Idec SABR or designee within 24 hours of the study site staff becoming aware of new information.
- Ensure all SAE reports are supported by documentation in the patients' medical records.
- Report SAEs to local ethics committees, as required by local law.
- Monitor and record all AEs leading to discontinuation of DMF.

11.6. Biogen Idec Responsibilities

Biogen Idec's responsibilities include the following:

- Before study site activation and patient enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definition of

AEs and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- Determine the expectedness of all SAEs.
- Biogen Idec is to notify all appropriate regulatory authorities, central ethics committees, and Prescribing Physicians of SAEs, as required by local law, within required time frames.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The first interim study report will be based on safety data collected after 1000 patients have completed 6 months of follow up; the report is anticipated to be completed within 12 months of that time. Subsequent interim reports will be completed at least annually. A final study report will be sent to Health Authorities within 12 months of the end of data collection.

12.1. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

12.2. Registration of Study and Disclosure of Study Results

Biogen Idec will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

13. REFERENCES

Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. Am Heart J. 2002;144(2):290-6.

Bahmanyar S, Montgomery SM, Hillert J, et al. Cancer risk among patients with multiple sclerosis and their parents. Neurology. 2009;72(13):1170-7.

Choma NN, Griffin MR, Huang RL, et al. An algorithm to identify incident myocardial infarction using Medicaid data. Pharmacoepidemiol Drug Saf. 2009;18(11):1064-71.

Chung CP, Murray KT, Stein CM, et al. A computer case definition for sudden cardiac death. Pharmacoepidemiol Drug Saf. 2010;19(6):563-72.

Fois AF, Wotton CJ, Yeates D, et al. Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's disease: record linkage studies. J Neurol Neurosurg Psychiatry. 2010;81(2):215-21.

Handel AE, Ramagopalan SV. Multiple sclerosis and risk of cancer: a meta-analysis. J Neurol Neurosurg Psychiatry. 2010;81(12):1413-4.

Hard G, Johnson K, Cohen S. A comparison of rat chronic progressive nephropathy with human renal disease-implications for human risk assessment. Crit Rev Toxicol. 2009;39(4):332-46.

Kiyota Y, Schneeweiss S, Glynn RJ, et al. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J. 2004;148(1):99-104.

Koch-Henriksen N. The Danish Multiple Sclerosis Registry: a 50-year follow-up. Mult Scler. 1999;5(4):293-6.

Levy AR, Tamblyn RM, Fitchett D, et al. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Can J Cardiol. 1999;15(11):1277-82.

Midgard R, Glattre E, Grønning M, et al. Multiple sclerosis and cancer in Norway. A retrospective cohort study. Acta Neurol Scand. 1996;93(6):411-5.

Møller H, Kneller RW, Boice JD, et al. Cancer incidence following hospitalization for multiple sclerosis in Denmark. Acta Neurol Scand. 1991;84(3):214-20.

Nielsen NM, Rostgaard K, Rasmussen S, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. Int J Cancer. 2006;118(4):979-84.

Patkar NM, Curtis JR, Teng GG, et al. Administrative codes combined with medical records based criteria accurately identified bacterial infections among rheumatoid arthritis patients. J Clin Epidemiol. 2009;62(3):321-7, 7.e1-7.

Petersen LC, Elm T, Ezban M, et al. Plasma elimination kinetics for factor VII are independent of its activation to factor VIIa and complex formation with plasma inhibitors. Thromb Haemost. 2009;101(5):818-26.

Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. Stat Med. 1991;10(4):577-81.

Schneeweiss S, Robicsek A, Scranton R, et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol. 2007;60(4):397-409.

Sumelahti ML, Pukkala E, Hakama M. Cancer incidence in multiple sclerosis: a 35-year follow-up. Neuroepidemiology. 2004;23(5):224-7.

14. ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Table 6: List of Stand-Alone Documents for Protocol 109MS401

Number	Document Reference Number	Date	Title
None			

15. ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14-January-2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	18,20
1.1.2 End of data collection[2]	☒	☐	☐	18,20
1.1.3 Study progress report(s)	☒	☐	☐	18,20
1.1.4 Interim progress report(s)	☒	☐	☐	18,20,52
1.1.5 Registration in the EU PAS register	☒	☐	☐	1,20
1.1.6 Final report of study results.	☒	☐	☐	18,20,52

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	2,12,13,23,24
2.1.2 The objective(s) of the study?	☒	☐	☐	2,13,25
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	2,12,13,25
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	25,30,36

Comments:

This is an observational study conducted as part of routine pharmacovigilance. The study is descriptive in nature and is not testing any a priori hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14,26
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14,25
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	17,38-40

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15,26,27
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☐	☒	☐	
4.2.2 Age and sex?	☒	☐	☐	15,26,27
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	27
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	15,27

Comments:

There will be no restrictions on enrollment in terms of sex, country of origin, study time period, or co-morbidity as the goal of the study is to recruit a sample reflective of DMF use among MS patients in routine clinical practice. Enrollment will be monitored to ensure the study sample is not overly skewed with respect to key demographic features (e.g. sex). Recruitment and follow-up will span multiple years, thus we do not anticipate seasonality effects due to date of enrollment.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	33,34
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	42
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

DMF exposure will be recorded based on physician prescribing and patient-reported initiation and discontinuation. Any relationship between DMF exposure and study outcomes will be explored in terms of treatment duration which will be described in the statistical analysis plan and final clinical study report. Safety outcomes (except for malignancies) are only collected while patients are exposed to DMF and, if DMF is discontinued, 6 months after last DMF dose.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	14,26,32-35,36
6.2 Does the protocol discuss the validity of	☒	☐	☐	30-32, 41-43

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)				

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	32-36,41-43
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

There are no known effect modifiers with respect to the safety (i.e. serious adverse events) or effectiveness of DMF. Collected confounders will be explored as potential effect modifiers if descriptive analyses suggest a potential relationship.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	32-36
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	32-36
8.1.3 Covariates?	☒	☐	☐	32-36
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	32-36
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	32-36
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	32-36
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	38
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification	☐	☒	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
System)				
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

MedDRA will be used to classify medical events in the prospective cohort and administrative medical codes (e.g. ICD-9, READ) will be used to describe events in the external databases. Drug exposure in the prospective cohort and external databases will be described using Biogen Idec standards (e.g. WHO Drug Dictionary) when possible, and in the native standard when not possible. No direct linkage between study cohorts will be made.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	16, 17,36-38

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	38-40
10.3 Are descriptive analyses included?	☒	☐	☐	17,18, 38-40
10.4 Are stratified analyses included?	☒	☐	☐	38-40
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	38-40
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Formal measures of excess risk (e.g. relative risk, number needed to harm) will not be calculated for this study. Potential safety signals will be assessed by examination of point estimates and 95% confidence intervals. A detailed description of the statistical analyses used to analyze study data will be provided in the statistical analysis plan, which will be included in the clinical study report.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management	☐	☒	☐	

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
of missing data?				
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	41
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Data management for this study will be performed by a vendor selected by Biogen Idec, and in a manner consistent with internal Biogen Idec quality standards. Details will be provided in the final clinical study report.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	30-32
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	41-43
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	41-43

Comments:

Study feasibility is not discussed in the protocol, but Biogen Idec has successfully completed two studies of similar scope and size in MS.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	44
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	45

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	19

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	52
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	43,52

Name of the main author of the protocol: [redacted], PhD

Date: [redacted]

Signatu[redacted]

[redacted], PhD

16. ANNEX 3: ADDITIONAL INFORMATION

16.1. Schedule of Events

Table 7: DMF Study 109MS401: Study Activities

Enrollment through Study Completion, Chart 1 of 2

Assessments	Enrollment (Baseline)	Data Collected at Routine Clinical Visits[1]
Informed consent	X	
Demographic data	X	
Medical history[2]	X	
MS disease history (including type of MS, relapse history, and last EDSS score prior to enrollment)	X	
Results of latest brain MRI scan[3]	X	
Prior use and duration of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies	X	
Prior use and duration of hepatotoxic and nephrotoxic agents (e.g., paracetamol, nonsteroidal anti-inflammatory drugs, antibiotics, anticonvulsants, protease inhibitors, diuretics, and lithium)	X	
SAEs[4,9]		X
CBC with differential[5]	X	X
Other laboratory tests recommended in local label[5]	X	X
Concomitant use of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies	X	X
Concomitant use of hepatotoxic and nephrotoxic agents (e.g., paracetamol, nonsteroidal anti-inflammatory drugs, antibiotics, anticonvulsants, protease inhibitors, diuretics, and lithium)	X	X

Assessments	Enrollment (Baseline)	Data Collected at Routine Clinical Visits[1]
EDSS information (Functional System Scores and Ambulation scores), based on neurological examination [6]	X	X
MS relapse information		X
DMF prescription information: start date, prescribed dosing frequency and duration of use[7]	X	X
MSIS-29, EQ-5D and EQ VAS, WPAI-MS, MFIS-5, and healthcare resource consumption questionnaire[8]	X	X
Pregnancy status (patient-reported, female patients) [9]	X	X

[1] Study information should be collected at any routine clinical visits scheduled per local standard of care.
[2] Includes an assessment of cardiovascular risk factors.
[3] May include lesion count.
[4] MS relapses resulting in hospitalization will not be reported as SAEs in this study unless, in the opinion of the physician, a relapse is complicated by other SAEs. All opportunistic infections and malignancies should be considered serious and reported as SAEs.
[5] US sites will be asked to conduct blood draws for CBC (not more frequently than every 12 months unless indicated per local standard of care) and to report the results. Physicians in the European Union and Rest of World will be asked to record CBC, liver function, renal function, and urinalysis results, *if collected as part of routine clinical practice*. Additionally, in all regions, if a patient discontinues DMF due to a laboratory abnormality (see Table 7, Continued, below), physicians will be asked to record all relevant laboratory test results collected during the course of the study as part of routine clinical practice.
[6] When collected as part of routine clinical practice.
[7] If treatment with DMF is not started on the day of enrollment, the start date should be recorded at the next routine visit.
[8] PROs may be assessed at a routine visit or online outside of the physician's office, *if consistent with local regulations*. If completed online, PROs should be completed within 1 week (before or after) the scheduled visit.
[9] SAEs and pregnancy status will not be collected in patients who are enrolled in the study but do not initiate treatment with DMF. SAE and pregnancy status will be collected from the first dose of DMF.

Abbreviations: CBC = complete blood count; EDSS = Expanded Disability Status Scale; EQ VAS = EQ Visual Analogue Scale; MFIS-5 = Modified Fatigue Impact Scale-5; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale-29 Items; PROs = patient-reported outcomes; SAE = serious adverse event; US = United States; WPAI-MS = Work Productivity and Activity Impairment questionnaire: Multiple Sclerosis.

Table 7: DMF Study 109MS401: Study Activities (Continued)

Discontinuation of Treatment and/or Premature Study Withdrawal Visit, Chart 2 of 2

Assessments	DMF Discontinuation With Continued Study Participation		Premature Study Withdrawal Visit[1]
	First Routine Visit After Last Dose[2]	Subsequent Routine Visits After Last Dose	
Date of and primary reason for discontinuation of DMF, and last prescribed dose	X		X
AEs (including laboratory abnormalities) leading to treatment discontinuation	X		
SAEs[3,4]	X		X[8]
Reports of malignancies only		X[4]	
CBC with differential [5]	X	X	X
Other laboratory tests recommended in local label[5]	X	X	X
Concomitant use of immunomodulatory, immunosuppressive (including corticosteroids), and anti-neoplastic agents, and other approved MS therapies	X	X	X
Concomitant use of hepatotoxic and nephrotoxic agents (e.g., paracetamol, nonsteroidal anti-inflammatory drugs, antibiotics, anticonvulsants, protease inhibitors, diuretics, and lithium)	X	X	X
EDSS score (including Function System Scores and Ambulation Scores), based on neurological examination[6]	X	X	X
MS relapse information	X	X	X
MSIS-29, EQ-5D and EQ VAS, WPAI-MS, MFIS-5, and healthcare resource consumption questionnaire[7]	X	X	X
Pregnancy status (patient-reported, female patients)	X	X	X[8]

[1] If withdrawal from the study occurs during a routine visit, information collected one last time from the patient will follow the standard protocol, if the patient allows. If withdrawal occurs outside of the physician's office, the physician will contact the patient by telephone to obtain information one last time from the patient, with the exception of laboratory results and EDSS score, if the patient allows.

[2] If a patient does not have a routine visit within 6 months after the last dose of DMF, the physician will contact the patient by telephone to obtain information, with the exception of laboratory results and EDSS score.

[3] MS relapses resulting in hospitalization will not be reported as SAEs in this study unless, in the opinion of the physician, a relapse is complicated by other SAEs. All opportunistic infections and malignancies should be considered serious and reported as SAEs.

[4] All SAEs that occur within 30 days after the last dose will be collected. Thereafter, AE data collection will be limited to reports of malignancies.

[5] US sites will be asked to conduct blood draws for CBC (not more frequently than every 12 months unless indicated per local standard of care) and to report the results. Physicians in the European Union and Rest of World will be asked to record CBC, liver function, renal function, and urinalysis results *if collected as part of routine clinical practice*. Additionally, if a patient discontinues DMF due to a laboratory abnormality, physicians will be asked to record all relevant laboratory test results collected during the course of the study as part of routine clinical practice.

[6] When collected as part of routine clinical practice.

[7] PROs may be assessed by patients during routine visits or online outside of the physician's office, *if consistent with local regulations*. If completed online, PROs should be completed within 1 week (before or after) the scheduled visit.

[8] SAEs and pregnancy status will not be collected in patients who do not initiate treatment with DMF and withdraw from the study.

Abbreviations: AE = adverse event; CBC = complete blood count; EDSS = Expanded Disability Status Scale; EQ VAS = EQ Visual Analogue Scale; MFIS-5 = Modified Fatigue Impact Scale-5; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale-29 Items; PROs = patient-reported outcomes; SAE = serious adverse event; US = United States; WPAI-MS = Work Productivity and Activity Impairment questionnaire: Multiple Sclerosis.