Post Authorization Utilization Study Protocol

Title	**Claims database study of utilization patterns of dimethyl fumarate in Germany**
Protocol ID:	109MS409
Protocol version	FINAL 1.0
Date of last version of protocol	06 OCT 2014
EU PAS register number	Study to be registered prior to start of data analysis
Active substance	Dimethyl fumarate (DMF) ATC classification: N07XX09
Medicinal product	Dimethyl fumarate (Tecfidera®), 120 mg and 240 mg gastro-resistant hard capsule,
Product reference	EU/1/13/837/001 (120 mg) EU/1/13/837/002 (240 mg)
Procedure reference	EMEA/H/C/2601
Marketing authorization holder:	Biogen Idec MA Inc. Biogen Idec Research Limited
Joint PASS	No
Research question and objectives	**Primary objective:** - To estimate the proportion of DMF use that is prescribed "on-label" versus "off-label". **Secondary Objectives** - To describe the demographic characteristics and medical history of DMF users. - To describe prescription drug history and concomitant medication use of DMF users. - To describe the duration of therapy in patients newly initiating DMF treatment. - To describe the medical specialties of DMF prescribers.
Country of study	Germany
Main Author:	[redacted], PhD, Biogen Idec [redacted], Biogen Idec MA Inc. Tel.: [redacted]

CONFIDENTIAL

The information and data included in this protocol contain trade secrets and privileged or confidential information which is the property of the Sponsor. No person is authorized to make it public without written permission of the Sponsor. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential. This material may be disclosed to and used by your staff and associates as it may be necessary to conduct the clinical study.

Marketing authorization holder

Marketing authorization holder:	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
MAH contact person	[redacted], MD, PhD [redacted] Biogen Idec Research Limited Tel.: [redacted]

1 Signature Pages

1.1 Signature Page

Protocol 109MS409 was approved by:

_____ _____

[redacted], MD, PhD Date

[redacted]

Biogen Idec Research Limited

1.2 Signature Page

Protocol 109MS409 was approved by:

_____ _____

[redacted], MD Date

[redacted]

[redacted]

Biogen Idec MA Inc.

1.3 Signature Page

Protocol 109MS409 was approved by:

_____ _____

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

[redacted]

[redacted]

Biogen Idec MA Inc.

2 Table of Contents

Section page

List of Tables

List of Figures

3 List of Abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
CCS	Clinical Classification Software
CRO	Contract Research Organization
DMF	Dimethyl fumarate
EBM	Einheitlicher Bewertungsmaßstab [unified valuation schedule]
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GCP	Good Clinical Practice: a set of government and corporate mandated guidelines that guides the conduct of clinical trials on a drug substance or medical device to ensure compliance with appropriate ethical and quality standards
GFL	Gesundheitsforen Leipzig
ICD	International Classification of Diseases
IQR	Interquartile range
MA	Market Authorization
MAH	Market Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities: a standard terminology recommended by ICH, used to describe, catalogue, analyse, and report all adverse events
MMF	Monomethyl fumarate
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
PAS	Post-Authorization Study
PBRER	Periodic Benefit Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QPPV	Qualified person for pharmacovigilance
SAP	Statistical Analysis Plan
SD	Standard Deviation

SGB	Sozialgesetzbuch [Social Code]
SOP	Standard operating procedure
WHO	World Health Organization

4 Responsible parties

Research Manager	[redacted], PhD [redacted], Biogen Idec [redacted], USA e-mail: [redacted] T [redacted] F [redacted]
Qualified Person for Pharmacovigilance (QPPV)	[redacted], MD, PhD [redacted] Biogen Idec Research Limited Tel.: [redacted]
Contracted Research Organizations (CRO)	[redacted] Dr. [redacted] [redacted] Germany T [redacted] F [redacted] Gesundheitsforen Leipzig GmbH Dr. [redacted] [redacted] Germany T: [redacted] F: [redacted]

5 Abstract

	Claims database study of utilization patterns of dimethyl fumarate in Germany, Protocol version: FINAL 1.0 Date of last version of protocol: 06 OCT 2014 Main author: [redacted], PhD [redacted], Biogen Idec [redacted], USA
Rationale and Background	Tecfidera® is a drug product containing the active ingredient dimethyl fumarate (DMF), which has been developed for the treatment of multiple sclerosis (MS).
Research Question and Objectives	The primary objective of this study is to estimate the proportion of DMF use that is prescribed “on-label” versus “off-label”. The secondary objectives of this study are to: Describe the demographic characteristics, medical history, prescription drug history, and concomitant medication use of DMF users. Describe the duration of therapy in patients newly initiating DMF treatment. Describe the medical specialties of DMF prescribers.
Study Design	Retrospective analysis of a research database, which contains German sick fund claims, to assess the usage of DMF in Germany. The data are fully pseudonymized and contain information on demographics, diagnosis, and medical prescriptions, as well as inpatient and outpatient treatment. The study data collection period will include the 6 month period prior to the German market introduction of DMF and end at 18-22 months after market introduction (depending on date of data availability). The research database is updated annually; data analyses will be based upon the first database update containing data for the initial 18 months of DMF market availability in Germany. It is assumed that a 6 month pre-DMF launch observation period is sufficient to establish baseline characteristics of patients initiating treatment with DMF and a minimum of 18 months will be sufficient to see initial uptake of DMF in the MS market, any off-label use (per product information), and subsequent potential uptake in other therapeutic areas.
Population	All new users of DMF during the study period will be eligible for the analysis. The patient index date is defined as the date of first filled prescription for DMF. New users will be defined as patients without a previous prescription for DMF in the 6 months prior to the index date. Patients for which the 6 months prior to the index date is not available will be excluded from the analysis.

Variables	The primary analysis will focus on the use of DMF, which will be identified by pharmacy claims containing the anatomical therapeutic chemical (ATC) classification system code N07XX09. “Off-label” use is defined as any DMF prescription for MS patients <18 years of age, or for patients diagnosed with non-MS indications, such as psoriasis. Discontinuation will be assessed by a calculated gap in prescriptions of 4-6 weeks, with the exact length of the medication gap defined according to the most common pack size. The date of the first pharmacy claim for DMF will be used as the index date for this study.	
Data sources	The research database is comprised of German sick fund data, which is compiled by Gesundheitsforen Leipzig (GFL). This GFL database currently contains sick fund claims data for approximately 4 million patients, which accounts for approximately 5-6% of the total sick fund population in Germany. The GFL database contains current data up to 2012 and is updated on an annual basis.	
Study size	Based on a feasibility analysis and preliminary market uptake projections, approximately 500 MS patients in the GFL research database are expected to initiate treatment with DMF within 18 months of product launch in Germany. The actual sample size of the study will depend on the actual market uptake of DMF.	
Data analysis	This study is strictly descriptive (i.e. no hypothesis testing is being conducted). Demographic characteristics, concomitant medication, medication history, time on DMF and specialty of prescribing physician will be analysed separately by “on-label” or “off-label” use. All statistical analyses will be reported in a descriptive manner. Continuous data will be described by their mean, standard deviation, median, minimum, and maximum. Categorical data will be described by absolute and relative frequencies. A detailed description of the statistical analysis will be provided in the statistical analysis plan.	
Milestones	• Final study protocol	06 October 2014
	• Start of data retrieval and data analysis	Q4 2016
	• Final study report	Q4 2017

6 Amendments und Updates

None

7 Milestones

Milestones	Planned date
Final study protocol	06 October 2014
Registration in the European Union (EU) Post-Authorization Study (PAS) register	After finalization of protocol
Start of data collection (date from which data extraction starts)	01 September 2013
End of data collection	31 December 2015
Start of data retrieval and data analysis	Q4 2016
Final study report	Q4 2017

DMF was launched in Germany in March 2014. The data collection period will include 6 months prior to the market launch of DMF (starting at 01 September 2013) and cover a minimum of 18 months after market launch of DMF (01 September 2013- 31 December 2015).

Data retrieval will start as soon as sick fund data for the data collection period (years 2013-2015) become available (anticipated in Q4 2016) and data analysis will follow.

The final study report will be submitted within 12 months after start of data retrieval. No interim analysis or interim reports will be produced.

8 Rationale and Background

Multiple sclerosis (MS) is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons(1). Considerable social and economic consequences result from this chronic and progressive disease of the central nervous system. In North America and Europe, MS is the leading cause of non-traumatic neurological disability in young adults, affecting over two million people worldwide.(2) The disease usually presents itself in adults, who are between 20 and 40 years of age, and there is a higher incidence among women.(3)

Tecfidera® is a drug product containing the active ingredient dimethyl fumarate (DMF), which has been developed for the treatment of MS. This active ingredient is rapidly converted into its primary metabolite monomethyl fumarate (MMF). DMF is the first single ester of fumaric acid ester to be investigated in clinical trials.

In subjects with MS, two randomized, controlled Phase 3 clinical studies (109MS301 and 109MS302) concluded that treatment with DMF over 2 years led to significant reductions in the frequency of relapses and the development of brain lesions associated with the disease compared to placebo. Additionally, in study 109MS301, DMF therapy significantly reduced the risk of confirmed (12-week) disability progression (as measured by Expanded Disability Status Scale scores) compared with placebo. DMF also demonstrated a positive benefit-risk balance for the proposed indication of RRMS.

Currently, the standard clinical management of MS patients varies across countries. As a number of new products have recently been introduced, it is unclear how the introduction of DMF will affect treatment patterns in routine clinical practice.

In addition, it is unclear if DMF would be used “off-label” for other inflammatory conditions, including psoriasis. Fumaderm® is a fumarate ester drug product that contains DMF in combination with three different salts of monoethyl fumarate. These salts are pharmacodynamically active and have different active metabolites than DMF. Fumaderm® has been available on the German market for the treatment of psoriasis since 1994.(4;5) Furthermore, Fumaderm® has been used “off-label” for the treatment of psoriasis in children.(6)

This study will provide information on utilization and potential off-label use of DMF, especially with regards to pediatric patients diagnosed with psoriasis. This study is part of a comprehensive risk management plan that also includes pharmacovigilance and drug safety studies.

9 Research Question and Objectives

9.1 Primary Objective

The primary objective of this study is to estimate the proportion of DMF use that is prescribed “on-label” versus “off-label” in Germany.

9.2 Secondary Objectives

The secondary objectives of this study are as follows:

- Describe the demographic characteristics and medical history of DMF users
- Describe the prescription drug history and concomitant medication use of DMF users.
- Describe the duration of therapy in patients newly initiating DMF treatment.
- Describe the medical specialties of DMF prescribers.

10 Research Methods

10.1 Study Design

The study is a non-interventional, retrospective cohort study of a German sick fund claims database to assess the usage of DMF in Germany. The data are fully pseudonymized[1] and contain information on demographics, diagnosis, and medical prescriptions, as well as inpatient and outpatient treatment.

[1] In this protocol the term “pseudonymization” will be to describe the way the data privacy is secured. By pseudonymizing the patient ID is replaced by a unique pseudo-ID in each of the different data tables enabling data sets to be linked from different data sources. It differs from anonymization where the patient ID is replaced by a (different) random number in each occurrence disabling linkage of data.

Patients will be identified based on at least one prescription of DMF. The data collection period will begin 6 months prior to the German market introduction of DMF and end at the earliest 18 months after market introduction. The exact data collection end date will be determined by the availability and completeness of data included in the annual update to the sick fund claims database. It is assumed that a 6 months pre-DMF launch observation period will be sufficient to establish baseline characteristics of patients initiating treatment with DMF and a minimum of 18 months will be sufficient to see initial uptake of DMF in the MS market, any off-label use (per product information), and subsequent potential uptake in other therapeutic areas. The primary outcome of this study is the proportion of DMF used “off-label” in Germany.

In order to observe real-life treatment patterns and “off-label” use, the retrospective research design using sick fund claims data represents a particularly well suited approach. Due to the nature of the data collection, it is assured that there is no influence on patient behavior and no interference by physicians on study procedures and data collection. The high level of detail in the German claims data, including diagnostic codes, allows the efficient and valid identification of “off-label” use, as well as the description of subsequent usage.

10.2 Setting

10.2.1 Study Population

All users of DMF in the post launch study period (time period defined in Section 10.2.3) will be retrieved from the database.

10.2.1.1 Inclusion Criteria

New users of DMF will be included in the analysis. New users are defined as patients without a previous prescription for DMF in the 6 months prior to the index date. The patient index date is defined as the date of first filled DMF prescription. Patients pretreated with products containing different fumarates (i.e. Fumaderm®) may be included in the study.

10.2.1.2 Exclusion Criteria

Patients for which data is not available for the 6 months period prior to the index date (baseline observational period) will be excluded from the analysis.

10.2.2 Research Database

The study will be conducted using data from the sick fund claims contained in a research database collected by GFL during the period 2013-2015. This database currently contains sick fund claims data for approximately 4 million patients, which accounts for approximately 5-6% of the total sick fund population in Germany.

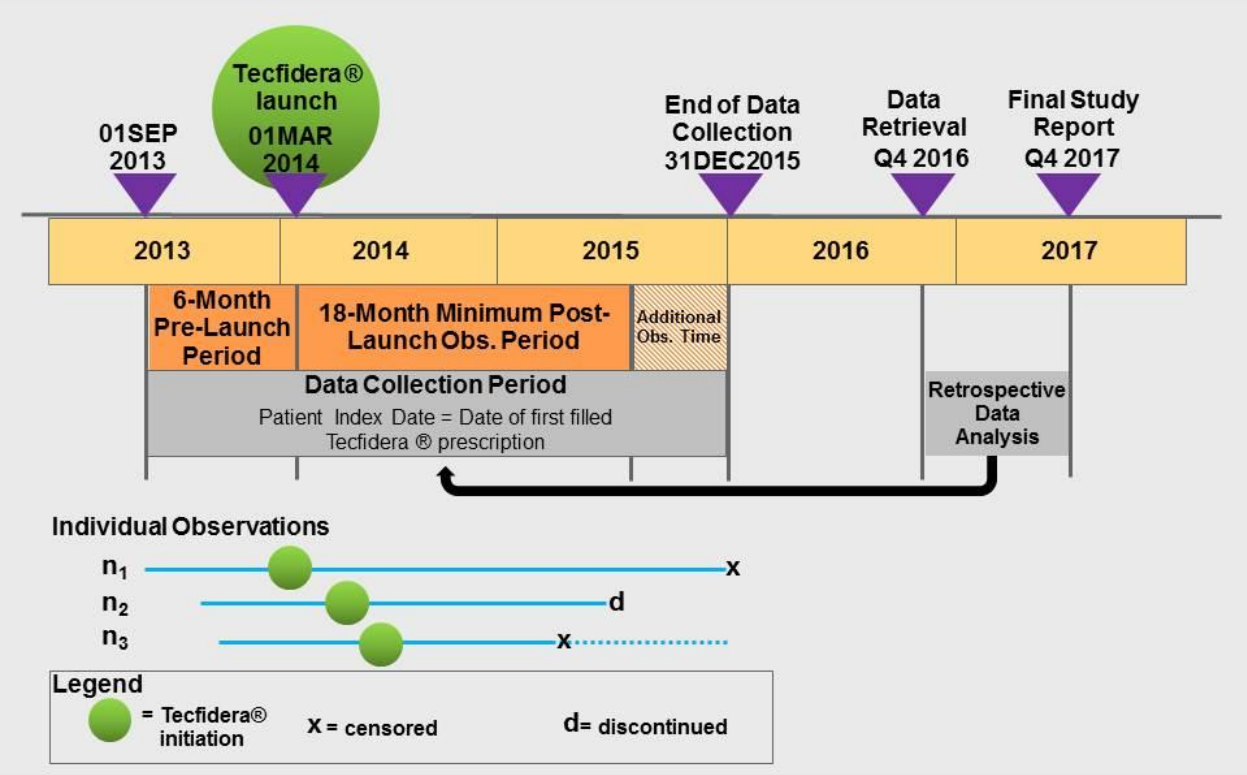
The GFL database was chosen as it provides a comprehensive source of inpatient, outpatient, and prescription drug data. Furthermore, the GFL database is fairly representative for the German sick fund market with respect to basic demographic variables. In a recent analysis, the proportion of women was similar in the GFL database compared to the general sick fund market (50.3% vs. 52.9%).(7) Finally, the data has already successfully been used to explore the treatment and cost of MS in Germany.(8-10)

10.2.3 Study Timeframe

The overall study period will include the data collection period through the final study report and is expected to be approximately 4 years.

The study data collection period will begin 6 months prior to the German market introduction of DMF and will end 18-22 months after market introduction (depending on date of data availability) (Figure 1). The research database is updated annually; data analyses will be based upon the first database update containing data for the initial 18 months of DMF market availability in Germany.

Figure 1. Study time frame



It is assumed that 6 months pre-DMF launch will be sufficient to establish baseline characteristics of patients initiating treatment with DMF. A post-launch observation time of at least 18 months will be sufficient to see initial uptake of DMF in the MS market and subsequent potential uptake in other therapeutic areas.

Analysis will begin once data is retrieved from the GFL database.

10.3 Variables

Preliminary study variables are defined below. Additional variables and further refinements of variable definition will be included in the Statistical Analysis Plan (SAP).

10.3.1 Demographic Variables

Demographic variables to be retrieved from the claims data include:

- Age
- Gender

10.3.2 Diagnosis of Comorbidities

The comorbidities at time of DMF initiation will be recorded by ICD-10 codes with three (3) digits in medication claims, or if available, associated with inpatient or outpatient treatments that are within a time window of 6 months prior to DMF initiation.

10.3.3 "On-label" and "Off-label" Use

DMF "on-label" prescriptions will be primarily defined as prescriptions for patients who are ≥18 years of age and diagnosed with MS (see Table 1). The algorithms for identifying "on-label" use will include the presence of at least one medical claim with an ICD-10 code of MS for the indicated conditions (G35.x for MS).

DMF "off-label" prescriptions will be primarily defined as prescriptions for patients without an MS diagnosis or for patients who are <18 years of age and diagnosed with MS. All non-MS prescriptions will be further characterized by use in patients with and without psoriasis (i.e. patients with no evidence of psoriasis or MS in their claims history during the of 6 months prior to DMF initiation). In addition, all non-MS prescriptions will be further categorized by use in patients <18 years of age and ≥18 years of age.

Table 1. Patient groups considered for "on-label" and "off-label" use

	MS Patients	**Non-MS Patients**	
	DMF	*Psoriasis*	*Other Diagnosis*
Age <18	Off-label	Off-label	Off-label
Age ≥18	On label	Off-label	Off-label

10.3.4 DMF Usage

DMF usage will be described with the following variables:

- DMF Initiation — Initial use will be identified by pharmacy claims containing Anatomical Therapeutic Chemical (ATC) classification system code N07XX09.
- Index date — The date of the first pharmacy claim for DMF will be used as the index date for this study.

- Baseline Observation Period: The patient baseline observation period is defined 6 months prior to the index date (Index date – 6 months)
- Discontinuation of initial DMF use: Discontinuation will be defined as a time gap between the "run out" of medication days supplied from the previous prescription to the fill date of the next prescription. The length of gaps representing a discontinuation will be dependent on pack size, but is expected to be 4-6 weeks. A final definition will be informed by the size of the most commonly prescribed packages of DMF. Details will be further specified in the SAP.
- Duration of initial treatment episode: Duration of treatment is defined as the time difference between index date and discontinuation date (Discontinuation date – Index date).
- Censoring date: Patients will be censored at the end of the data collection period, date of death, or date of discontinuation of sick fund membership
- Observation time: The patient observation time is defined as the time difference between the index date and the censoring date (Censoring date - Index date)

10.3.5 Non-DMF Medication

Prescriptions for non-DMF medications will be categorized and recorded as follows

- Prescription drug history: The class level of the ATC code of preceding medications associated with the diagnosis for which DMF is prescribed during 6 months before the initial DMF prescription
- MS disease modifying medication: The following drugs and corresponding ATC codes will be defined as MS disease modifying medications:

Generic Name	*ATC Code*
Alemtuzumab	L01XC04
Mitoxantrone	L01DB07
Interferon beta-1a	L03AB07
Interferon beta-1b	L03AB08
Glatiramer acetate	L03AX13
Natalizumab	L04AA23
Fingolimod	L04AA27
Teriflunomide	L04AA31

This list will be adapted according to the market availability of disease modifying drugs for MS in Germany at the end of the observation period

- Concomitant medication: Concomitant medications of interest (e.g. immune suppressants and potentially nephrotoxic medications) will be recorded at the class level according to the three (3) digit ATC code.

  Concomitant medications of interest prescribed anytime during a DMF treatment episode will be described. A complete list of concomitant medications of interest will be included in the SAP.

10.3.6 Specialty of Prescribing Physician

The specialty of the prescribing physician will be identified according to specialty-specific billing codes at outpatient visits. The German physician's fee schedule (Einheitlicher Bewertungsmaßstab [EBM]) provides separate billing codes for 26 different specialties.(11) These codes will be included in the SAP. It is anticipated that neurologists will be the most relevant specialty of prescribing physicians in this analysis.

10.3.7 Censoring Events

- Sick fund membership discontinuation: Sick fund membership can be discontinued for a number of reasons, aside of death. Discontinuation is recorded in the data set. The expected discontinuation rate is typically very low (<5%), particularly for patients with severe diseases such as MS (12)
- Mortality: In case of death, the mortality date is provided in the sick fund data

10.4 Data Sources

The analysis will be based on a research database comprised of German sick fund data. This database is compiled by GFL, a private research and consulting organization.

In Germany, all citizens whose annual income is below a certain level (in 2013: 52.200€) are mandatorily covered by the public health insurance. Roughly 85% of the general German population (approximately 70 million) obtains health insurance through ~130 non-for-profit sick funds, which are paid for with joint employer-employee contributions. The sick funds are mandated to provide a wide range of coverage and cannot refuse membership or otherwise discriminate on an actuarial basis. The sick funds routinely collect all information relevant for the reimbursement of the service providers. This includes data on inpatient stays, as well as prescribed medications, which are directly paid for by the sick funds. For outpatient physician services, which are reimbursed based on lump sum payments to the physician association; the information on the treatment is circled back to the sick funds.

Having started in 2007, the GFL database currently contains sick fund claims data for approximately 4 million patients, which accounts for approximately 5-6% of the total sick fund population in Germany. The GFL database contains current data up to 2012 and is updated on an annual basis. The effort of maintaining and updating the research database is performed on a voluntary basis by the sick funds. As such, the size of the database might change in the future, depending upon participation of the sick funds.

Examples of the variables contained in the database include the following:

- Demographics (e.g. sex and age)
- Inpatient and outpatient care (e.g. ICD-10 codes and prescriber specialty)
- Prescription drug dispensing (e.g. date, dose, and ATC codes)

The GFL database was chosen for this research as it provides a comprehensive source of inpatient, outpatient, and prescription drug data for a fairly representative sample of the German sick fund population.

10.5 Study Size

In a preliminary feasibility analysis, approximately 8,000 MS patients were identified in the GFL research database between 2007 and 2011. Based on market uptake projections, approximately 500 MS patients in the GFL research database would be expected to initiate treatment with DMF within 18 months of product launch in Germany. Due to the voluntary participation of German sick funds in the research database, it cannot be guaranteed that this sample size remains constant in the future. The final sample size of this study will depend on the actual market uptake of DMF and future sick fund participation.

This study is strictly descriptive (i.e. no hypothesis testing will be conducted); therefore no power calculations have been conducted.

10.6 Data Management

The raw sick fund claims data are pseudonymized by authorized personnel at each sick fund and transferred to a secured database. The transfer of the sick fund data is based on a contractual agreement between GFL and each participating sick fund according to national law (§80 Sozialgesetzbuch [SGB]). The key for the description and pseudonymization is kept by an external trustee (an external law firm). Access to the pseudonymized database is also monitored by the external law firm, which is restricted to a small number of approved personnel with GFL user profiles.

An authorized employee of GFL will access the data from the years 2013-2015 within the pseudonymized database and create an analytical data set by selecting patients with any DMF prescriptions. This data set will be the basis for further analyses based on variable definitions.

In accordance with the approved process of data access and data management, all patient level data will strictly remain at GFL. Only summary statistics and summary tables will be provided to [redacted] and Biogen Idec for inclusion in the report.

The procedures are in compliance with national law for the creation and maintenance of the research database, as well as the terms of access and analysis. Furthermore, these procedures have been approved by the responsible data safety officer.

10.7 Data Analysis

10.7.1 General Considerations

Biogen Idec and [redacted] will collaborate in planning the data retrieval and analyses. Final programming and data analysis will be performed by GFL.

Planned analyses of the primary and secondary objectives are presented in the following sections of the protocol (Section 10.7.2. to Section 10.7.4). A complete overview of planned analyses will be available in the SAP.

All analyses will be performed once the data from the years 2013-2015 are available. Hence, no interim analyses will be conducted.

All statistical analyses will be reported in a descriptive manner.

- Continuous data will be described by their mean, median, standard deviation (SD), minimum and maximum
- Categorical data will be described by absolute and relative frequencies.

10.7.2 Baseline and Study Participation data

The baseline data of all new DMF users will be analyzed at the time of their initiation:

- Age
- Gender
- Calendar year and quarter of initial uptake of DMF
- Observation time
- Percentages of censored observations

10.7.3 Primary Analysis

The primary objective of this study is to estimate the proportion of DMF use that is prescribed “on-label” versus “off-label” in Germany. The proportion of “off-label” use will be calculated as:

$$1 - \frac{\text{\# patients using DMF on-label}}{\text{Total \# of DMF patients}}$$

Analyses of “off-label” use will be further described, as shown in Table 2 below. Sensitivity analyses will be performed with regard to patients for whom the diagnostic code is missing.

Table 2. Proportions of “off-label” use (subgroups)

	MS Patients	**Non-MS**	
		Psoriasis	*Other Diagnoses (wt/wo missing diagnoses)*
Age <18	n/N [%]	n/N [%]	n/N [%]
Age ≥18	n/N [%]	n/N [%]	n/N [%]

10.7.4 Secondary Analyses

All secondary analyses will be performed for the total sample as well as by “on-label” / “off label” status. The following variables will be analyzed to address the secondary objectives of this study:

- Demographic analysis of DMF users
  - Age
  - Gender
- Medical history of DMF users
  - Comorbid conditions in the baseline observation period as defined by ICD-10 diagnoses codes and grouped at level 3 of the CCS (Clinical Classification Software) classification (13)
- Prescription history of disease specific drugs of DMF users
  - MS patients: Latest disease-modifying drug taken in the preceding 6 months prior to DMF initiation
  - Non-MS patients: Latest medication associated with same ICD code taken in the preceding 6 months prior to DMF initiation
- Duration of DMF treatment
  - Duration of initial treatment episode in days
  - Percentage of patients who discontinue DMF treatment
- Medical specialties of DMF prescribers

10.7.5 Stratified Analyses

Stratified analyses for secondary endpoints will be performed for the following stratification variables:

- By age: <18 and >=18 years of age at time of first DMF prescription.
- By indication of first DMF prescription: MS, psoriasis, and other

10.7.6 Handling of Missing Data

No imputation of missing data is planned.

10.7.7 Statistical Software

Analyses will be performed with the statistical software packages SAS 9.2 (or higher) or Mathlab.

10.7.8 Statistical Analysis Plan (SAP)

A SAP describing the complete planned statistical analyses in more detail will be prepared by [redacted] in cooperation with Biogen Idec and GFL before the analysis is performed. The SAP will be a stand-alone document as listed in Annex 1.

10.7.9 Data Ownership

This retrospective study will be conducted by GFL and [redacted] on behalf of Biogen Idec. The data, on which the analysis will be based, will remain property of GFL.

10.8 Quality Control

Claims data, such as the one used in this study, are primarily collected for the purpose of payments; this implies that they are collected using routine processes with a high level of automatization that contributes to generally high quality of data.

The development of the protocol and SAP will follow internal standard operating procedures (SOPs) of [redacted], which include detailed review rounds. Quality control of the statistical programming will follow the internal procedures of GFL.

10.9 Limitations of the Research Methods

10.9.1 General Limitations

The retrospective study design and the nature of claims data are associated with some methodological limitations:

- Presence of a claim for a filled prescription does not indicate that the medication was consumed nor that it was taken as prescribed
- Medications provided in a clinical trial or as samples by the physician will not be observed in the claims data
- Presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may have been incorrectly applied
- Important clinical information of interest is not readily available in claims data that could have an effect on study outcomes, such as certain clinical and disease-specific parameters, including e.g. results of magnetic resonance imaging (MRI) scans or further diagnostic information

10.9.2 Potential Bias

Due to the voluntary participation of German sick funds in the research data base, the GFL database contains approximately 5-6% of the total sick fund population. Furthermore, sick fund participation is mandatory by German law for those with incomes below a predetermined level. Thus, the GFL database may not be fully representative of the whole German population.

10.10 Other aspects

10.10.1 Study Funding

Biogen Idec is the Sponsor of the study and is funding the study. All financial details are provided in the separate (sub-)contracts between the CROs and Biogen Idec.

11 Protection of human subjects

The data in the GFL research database are pseudonymized and the key for potential deidentification is kept by an independent third party trustee. No separate approval needs to be obtained since the process of the data collection and pseudonomyzation has already been approved in Germany in accordance with national law. GFL is authorized to perform the analyses on the pseudonomyzed data set without additional specific ethical approvals.

12 Management and reporting of adverse events/adverse reactions

According to the EMA good pharmacovigilance practice Module VI, safety reporting is not required for studies using secondary data sources, such as claims data.((14), p22) If reports of adverse events/reactions are captured during the study they will be summarized as part of the final report.

13 Plans for disseminating and communicating study results

A final study report will be sent to Health Authorities within 12 months of data availability.

13.1 Notification of Authorities on 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.

13.2 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.

14 References

(1) Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502-17.

(2) Dutta R, Trapp BD. Mechanisms of neuronal dysfunction and degeneration in multiple sclerosis. Progress in neurobiology 2011;93:1-12.

(3) Kobelt G, Berg J, Lindgren P, Fredrikson S, Jonsson B. Costs and quality of life of patients with multiple sclerosis in Europe. Journal of neurology, neurosurgery, and psychiatry 2006;77:918-26.

(4) Reich K, Thaci D, Mrowietz U, Kamps A, Neureither M, Luger T. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis--a retrospective study (FUTURE). J Dtsch Dermatol Ges 2009;7(7):603-11.

(5) Thaci D, Weisenseel P, Philipp S, Rosenbach T, Rotterdam S, Augustin M, et al. Efficacy and safety of fumaric acid esters in patients with psoriasis on medication for comorbid conditions - a retrospective evaluation (FACTS). J Dtsch Dermatol Ges 2013;11(5):429-35.

(6) Gerdes S, Domm S, Mrowietz U. Long-term treatment with fumaric acid esters in an 11-year-old male child with psoriasis. Dermatology (Basel, Switzerland) 2011;222(3):198-200.

(7) Hapfelmeier A, Dippel FW, Schinzel S, Holz B, Seiffert A. Health care costs of multiple sclerosis in Germany, Poster presented at ISPOR 15th Annual European Congress, 3-7 Nov 2012, Berlin. 2012.

(8) Hapfelmeier A, Dippel FW, Schinzel S, Holz B, Seiffert A. Health Care Costs of Multiple Sclerosis in Germany. Value in Health 2012;15:A550.

(9) Schmidt J, Dippel FW, Kuehne S, Holz B, Larisch K. Frequency and Impact of Relapses in German Patients With Multiple Sclerosis Based on a Longitudinal Population-Based Study. Value in Health 2012;15:A547.

(10) Seiffert A, Dippel FW, Sommer G, Holz B, Trottmann M. Hospital Stays of Multiple Sclerosis Patients in Germany: Reasons, Frequencies, Duration and Impact on Drug Therapy. 2012 p. A527.

(11) Kassenärtzliche Bundesvereinigung. Einheitlicher Bewertungsmaßstab (EBM). 3 Quartal 2013. 2010. Berlin.

(12) Werner A, Reitmeir P, John J. [Switching sickness funds and risk compensation mechanisms in the statutory health insurance system in Germany--empirical results from the cooperative health research in the region of Augsburg (KORA)]. Gesundheitswesen 2005 Aug;67 Suppl 1:S158-S166.

(13) Agency for Healthcare Research and Quality (AHRQ). Clinical Classifications Software for ICD-10. 2013. 4-11-2013.

(14) European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP): Module VI - Management and reporting of adverse reactions to medical products. 2012 Jul 2. Report No.: EMA/873138/2011 .

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Not yet assigned	Not yet assigned	Statistical Analysis Plan

Annex 2 EncePP Check list for Study Protocols

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[2]	☒	☐	☐	Section 7, page13
1.1.2 End of data collection[3]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

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)	☒	☐	☐	Section 8, page 13
2.1.2 The objective(s) of the study?	☒	☐	☐	Section 9, page 14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section 10.2, page 15
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	Section 10.7.1, page 20
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	Section 10.7.1, page 20

Comments:

[2] 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.
[3] Date from which the analytical dataset is completely available.

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)	☒	☐	☐	Figure 1 and Section 10.1, page 14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	page 14
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)	☐	☐	☒	

Comments:

Measure of effect is not applicable to the current study, (Definition of off-label provided in 9.7, p.18)

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	Section 10.2, page 15
4.2 Is the planned study population defined in terms of:				Section 10.2, page 15
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Section 10.1, page 14 and Section 10.2, page 15

Comments:

Country of origin of data will be Germany but German residence of patient not used as formal exclusion criteria

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)	☒	☐	☐	Section 10.3.4, pages 17
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)	☒	☐	☐	
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:

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?	☒	☐	☐	Section 10.3, page 17
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	Section 10.3, page 17 and Section 10.4, page 19

Comments:

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)	☐	☒	☐	Section 10.3, page 17
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

There is no specific explanation on how potential confounders/effect modifiers will be addressed, as most of the information is present within the variables section. Also, confounders and effect modifiers are less relevant in a purely descriptive study such as this.

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:	☒	☐	☐	Section 10.2.2, page 15
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	Section 10.3, page 17
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.)	☒	☐	☐	Section 10.3, page 17
8.1.3 Covariates?				
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)	☒	☐	☐	Section 10.3, page 17
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 10.3, page 17

8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	Section 10.3, page 17
8.3 Is a coding system described for: 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	Section 10.3.2, page 17 and Section 10.3.3, page 17
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	Section 10.3.3, page 17 and Section 10.3.4, page 17
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

All data will be from one data source: no linkage will be needed.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	Section 10.5 , page 20

Comments:

Expected sample size based on feasibility count. No formal sample size calculation performed

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	Section 10.7, pages 21
10.2 Is the choice of statistical techniques described?	☒	☐	☐	Section 10.7, pages 21
10.3 Are descriptive analyses included?	☒	☐	☐	Section 10.7, pages 21
10.4 Are stratified analyses included?	☒	☐	☐	Section 10.7, pages 21
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	SAP inclusion
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	SAP inclusion

Comments:

9.3.7 discusses analysis of specialty of treating physician which could be an effect modifier in this study. Will be further clarified in the SAP that is to be developed.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	Section 10.7.5, page 22
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	Section 10.7.9, page 23
11.3 Are methods of quality assurance described?	☒	☐	☐	Section 10.8, page 23
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	Section 10.8, page 23

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 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)	☒ ☒	☐ ☐	☐ ☐	Section 10.9.2, page 23
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	Section 10, page14
12.3 Does the protocol address other limitations?	☒	☐	☐	Section 10.9.1, page 23

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	Section 24, page 24
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Section 24, page 24

Comments:

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?	☒	☐	☐	Section 12, page 12

Comments:

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)?	☒	☐	☐	Section 13.1, page 24
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	Section 13.2, page 24

Comments:

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

Date: / /

Signature: _____