These Clinical Study Results are provided for informational purposes only.

The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

5 Abstract

	Claims database study of utilization patterns of dimethyl fumarate in Germany Report version: FINAL 1.0 Date of last version of report: 20 Oct 2017 Main author: [redacted] Biogen 225 Binney Street Cambridge, MA 02142, USA [redacted]
Rationale and Background	Tecfidera® is a drug product containing the active ingredient dimethyl fumarate (DMF), which has been developed and is indicated for the treatment of relapsing-remitting multiple sclerosis (MS) in adult patients. This study was conducted to provide information on the utilization and potential off-label use of DMF, especially with regards to pediatric patients with MS and/or patients diagnosed with psoriasis (and without an MS diagnosis).
Research Question and Objectives	Primary objective: • To estimate the proportion of DMF use that is prescribed "on-label" versus "off-label" in Germany Secondary objectives: • To describe the demographic characteristics and medical history of DMF users • To describe the 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
Study Design	Non-interventional, retrospective cohort study of a German sick fund claims database to assess the usage of DMF in Germany The data were fully pseudonymized and contained information on demographics, diagnosis, and medical prescriptions, as well as inpatient and outpatient treatment. The study data collection period included a 6-month period prior to March 2014 when DMF was launched in Germany and ended on 31 December 2015.
Data sources	The research database that uses German sick fund data, is compiled by [redacted] This [redacted] database currently contains sick fund claims data for approximately 4 million patients, which accounts for approximately 5% of the total statutory health insurance population in Germany.

Study Population	All users of DMF in the post-launch study period were retrieved from the database. Patients were included in the study if they satisfied the following eligibility criteria: Inclusion Criterion • Treatment initiation with DMF on or after 1 March 2014 without a previous prescription for DMF in the 6 months prior to the index date Exclusion Criterion • Patients with no data available during the 6-month period prior to the index date
Variables	The primary analysis focused on the use of DMF identified by pharmacy claims containing the anatomical therapeutic chemical (ATC) classification system code N07XX09. Patient was defined to have MS if there was at least one inpatient or two outpatient codes of G35. “Off-label” use was defined as any DMF prescription for MS patients <18 years of age, or for patients diagnosed with non-MS indications, such as psoriasis. Discontinuation was assessed by a calculated gap for which the length depended on prescribed pack size. The date of the first pharmacy claim for DMF was used as the index date for this study.
Sample size	In a preliminary feasibility analysis, approximately 8,000 MS patients were identified in the [redacted] research database from 2008 to 2011. Based on a feasibility analysis and preliminary market uptake projections, approximately 500 MS patients in the [redacted] research database were expected to initiate treatment with DMF within 18 months of product launch in Germany.
Data analysis	This study was strictly descriptive (i.e., no hypothesis testing was conducted). Demographic characteristics, concomitant medication, medication history, time on DMF and specialty of prescribing physician were analyzed separately by “on-label” or “off-label” use. All statistical analyses were reported in a descriptive manner. Continuous data were described by their mean, standard deviation, median, minimum, and maximum. Categorical data were described by absolute and relative frequencies. A detailed description of the statistical analysis was provided in the statistical analysis plan.
Results	A total of 714 patients received DMF in the database from DMF launch in March 2014 to the end of 2015. Of these, only 1.4% (10/714) were cases of off-label use. DMF was mainly used on-label in adult patients with MS 98.6% (704/714) of the cases. On-label patients treated with DMF had mean age 41.4 years (SD 10.8), and were predominantly females (73.4%). Off-label patients were on average 4 years younger (37.9 years, SD 11.5) with 70.0% being females. Of the 10 off-label patients, one MS patient was [redacted] years of age at

	time of treatment initiation, one patient had psoriasis, and the remaining eight patients had an MS diagnosis at some time during the observation period but did not meet the MS definition per protocol at treatment initiation. Almost half (47.9%) of on-label users received an MS disease-modifying therapy (DMT) within the 6 months preceding DMF initiation with interferon beta 1a (21.1%) and glatiramer acetate (12.5%) being most frequently used. The most frequently prescribed concomitant medication for on-label users were drugs for acid-related disorders (34.4%), antibacterial agents (33.0%) and corticosteroids (25.7%). Among on-label users, 58.2% discontinued the treatment by the end of observation time, after allowing for gaps as according to the protocol definition. Mean treatment duration was 110.9 days (SD 134.3). DMF was predominantly initiated and prescribed in follow-up by physicians of the specialties “neurologist” or “neurology, psychiatry and psychotherapy”.	
Discussion	Claims data, which are generated using highly standardized routine processes for a large population, are generally well suited to capture drug utilization. Primary limitations are missing clinical information, missing direct link from diagnosis and prescription, and, due to concerns with the quality and consistency of the use of sub-codes from the German Modification of the International Classification of Diseases (ICD)-10, there are no means of differentiating between types of MS. In conclusion, this study demonstrated that DMF is infrequently prescribed off-label.	
Milestones	• Final study protocol	06 October 2014
	• Start of data retrieval and data analysis	Q4 2016
	• Final study report	Q4 2017

6 Amendments and Updates

None