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EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR

TECFIDERA™ / DIMETHYL FUMARATE

RMP version number:	17.0
Data lock point (DLP) for this RMP:	30 Jun 2023
Date of final sign off:	19 Aug 2024

QPPV name: Jana Hyankova, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance. The electronic signature is available on file.

Template Version 4.1

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

No other versions of the EU-RMP are currently under evaluation.

Details of currently approved RMP

Version number:	16.0
Approved with procedure:	EMEA/H/C/002601/II/0082
Procedure approval date:	26 Oct 2023 (CHMP opinion)

Rationale for submitting an updated RMP

The Tecfidera EU RMP was updated based on the results from completed Study 109MS401 and data available through the data lock point of 30 Jun 2023.

Summary of significant changes in this RMP

A summary of the significant changes implemented in Version 17.0 of this RMP is provided in the table below.

Module	Rationale for update	Summary of significant changes
Part I	Not applicable	Not applicable
Part II Module SI	Not applicable	Not applicable
Part II Module SII	Not applicable	Not applicable
Part II Module SIII	Not applicable.	Not applicable
Part II Module SIV	Completion of Study 109MS401.	Updated Table 10, titled Discussion of Exclusion Criteria Not Remaining as Contraindications in Relation to the Assessment of Missing Information, due to changes in safety concerns.
Part II Module SV	Updated postmarketing exposure data available.	Updated Table 13 with new numbers. Table 14 with country-specific exposure was deleted as this information is considered company confidential.
Part II Module SVI	Not applicable	Not applicable

Module	Rationale for update	Summary of significant changes
Part II Module SVII	Based on Study 109MS401 results, the safety concerns were reclassified.	Updated Section SVII.2.2 with information about reclassifying the safety concerns and SVII.3 in response to the reclassification.
Part II Module SVIII	Based on Study 109MS401 results, the safety concerns were reclassified.	Removed Decreases in leukocyte and lymphocyte count and Drug-induced liver injury as important identified risks, all important potential risks except for malignancies and effects on pregnancy outcome, and all topics of missing information except for long-term efficacy and safety and safety profile in patients with moderate to severe renal impairment.
Part III	Study 109MS401 completed.	Updated the number of studies pending from 2 to 1, removed 109MS401 information from Section III.2, and updated III.3 Summary Table 18 to remove 109MS401 as an ongoing study.
Part IV	Not applicable	Not applicable
Part V	Based on Study 109MS401 results, the safety concerns were reclassified.	Safety concerns noted above were removed from Tables 19 and 20.
Part VI	Based on Study 109MS401 results, the safety concerns were reclassified.	Sections II.A and II.B were updated with changes to safety concerns. Section II.C.2 deleted Study 109MS401 and the purpose of the study.

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PART VII - ANNEXES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALC	absolute lymphocyte counts
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	area under the concentration-time curve
BID	twice daily
CBC	complete blood count
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CI	confidence interval
CIS	clinically isolated syndrome
CLL	chronic lymphocytic leukaemia
CPN	chronic progressive nephropathy
CSF	cerebrospinal fluid
CSR	clinical study report
CV	Cardiovascular
CYP	cytochrome P450
DHPC	Direct Healthcare Professional Communication
DILI	drug-induced liver injury
DMF	dimethyl fumarate
DMT	disease-modifying therapy
DNA	deoxyribonucleic acid
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EMA	European Medical Agency
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies and Twins
FAS	full analysis set
GA	glatiramer acetate
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	Gastrointestinal
HCP	health care professional
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus

Abbreviation	Definition
HLA	human leukocyte antigen
HLT	High Level Term
IBD	International Birth Date
IFN	Interferon
IL	Interleukin
JCV	John Cunningham virus
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
NHANES	US National Health and Nutrition Examination Survey
NHL	non-Hodgkin's lymphoma
NOAEL	No observed adverse effect level
Nrf2	nuclear factor (erythroid derived 2)-related factor 2
PASS	post-authorisation safety study
PK	Pharmacokinetic
PL	patient leaflet
PML	progressive multifocal leukoencephalopathy
PNM	potentially nephrotoxic medication
PPMS	primary progressive multiple sclerosis
PSUR	Periodic Safety Update Report
QPPV	qualified person for pharmacovigilance
RHD	recommended human dose
RMP	risk management plan
RRMS	relapsing-remitting multiple sclerosis
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPMS	secondary progressive multiple sclerosis
TCA	tricarboxylic acid
TID	3 times daily
ULN	upper limit of normal
US	United States
WBC	white blood cell

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Dimethyl fumarate
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, other immunosuppressants (L04AX07)
Marketing Authorisation Holder	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Tecfidera™
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Fumarate ester drug product containing the active ingredient DMF. **Mode of action:** The nonclinical pharmacology studies conducted suggest that BG00012 elicits both direct neuroprotective and anti-inflammatory activities via its action on the Nrf2 antioxidant response pathway. In preclinical studies, BG00012 significantly reduced macrophage activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli and demonstrated therapeutic activity in multiple models of in vivo inflammatory injury models. In addition, BG00012 was shown to significantly improve cell viability after oxidative challenge in primary cultures of astrocytes and neurons, suggesting BG00012 directly prevented neurodegeneration in response to toxic oxidative stress. The use of in vivo acute neurotoxic injury models or genetic models of neurodegenerative disease confirmed that BG00012 provided therapeutic benefit in reducing neuronal damage resulting from various types of toxic stimuli. Evidence of the role of Nrf2 in mediating BG00012 effects was gleaned from models of Nrf2 deficiency. In these studies, the beneficial effects of BG00012 were abrogated in the absence of Nrf2.
Hyperlink to the Product Information (PI)	[Tecfidera EU SmPC]
Indication(s) in the EEA	**Current:** Tecfidera is indicated for the treatment of RRMS in adult patients and paediatric patients aged 13 years and older.
Dosage in the EEA	**Current:** The starting dose is 120 mg twice a day. After 7 days, the dose is increased to the recommended dose of 240 mg twice a day.

Pharmaceutical form(s) and strengths	**Current:** *Form:* Green and white gastro-resistant hard capsules containing microtablets printed with 'BG-12 120 mg' or 'BG-12 240 mg', respectively. *Strengths:* 120 mg and 240 mg
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Incidence and Prevalence
Despite a wealth of published epidemiological data describing the incidence and prevalence of MS across Europe, varying diagnostic criteria and survey methods make it difficult to derive an accurate overall estimate. The total number of people living with MS worldwide is approximately 2.2 million. The disease is unevenly distributed throughout the world, with age-standardised prevalence varying between < 60 per 100,000 in Asia and Latin America to > 120 cases per 100,000 in North America and some northern European countries [Collaborators GBDMS 2019].

A systematic review of studies of the incidence and prevalence of MS in Europe discovered significant heterogeneity in incidence rate and prevalence estimates between and within regions as well as across time (e.g., increasing incidence in more recent years). Some of the observed heterogeneity in more recent years could be explained by advances in methodology and study design, but increasing latitude was also a potential explanation for regional variance. The prevalence and incidence estimates tended to be higher in the northern regions of the United Kingdom and in the Nordic countries, implicating the role of latitude and the more recent studies (after the year 2000) reported higher MS prevalence and incidence estimates. In summary, estimated incidence rates across Europe and over time ranged widely, from < 1 per 100,000 to > 10 per 100,000 [Kingwell 2013].

In 2016, the overall prevalence in Europe was estimated to vary between 78,500 and 543,860 individuals [Collaborators GBDMS 2019].

Demographics of the target population in the authorised indication
MS is approximately twice as common in women as men and predominantly affects adults aged 20 to 60 years. The frequency of paediatric MS is approximately 2% to 5% [Atzori 2009; Chitnis 2009; Confavreux and Vukusic 2008; Ferreira 2008; Pohl 2007; Broland Steinborn 2020]; another analysis suggests that 2% to 10% of all patients with MS are diagnosed before their 16th birthday [Annes 2002; Ness 2007]. Aggregate data from the European Database for Multiple Sclerosis network reported a mean and median age of onset for a paediatric patient of 13.7 and 14.5 years, respectively [Renoux 2007]. Only 1% to 2% of cases occur in children younger than 10 years of age and < 0.2% before the age of 6 years [Alonso and Hernán 2008; Cole 1995; Deryck 2006; Ghezzi 1997; Ghezzi 2002; Pohl 2007; Simone 2002; Sindern 1992; Stark 2008].

Risk factors for the disease
MS is an inflammatory disease of the brain and spinal cord characterised by focal areas of inflammation that lead to destruction of the myelin sheath and varying degrees of axonal injury. While researchers do not know the exact causes of the disease, both genetic (e.g., family history of disease) and environmental (e.g., smoking, Epstein-Barr virus, latitude) risk factors are suspected aetiologies of the disease [Ramagopalan 2010].

Existing treatment options

Current therapies for MS generally fall within the following categories: treatment for acute relapses, symptomatic therapies, and DMTs. Currently available DMTs include IFN β (Betaferon®, Avonex®, Rebif®, Extavia®), pegylated IFN (Plegridy®), GA (Copaxone®), fingolimod (Gilenya®), siponimod (Mayzent®), ozanimod (Zeposia®), teriflunomide (Aubagio®), DMF (Tecfidera®), alemtuzumab (Lemtrada®), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), mitoxantrone (Novantrone®), ofatumumab (Kesimpta®), and cladribine (Mavenclad®). In addition, several antineoplastic and immunosuppressant agents, including cyclophosphamide, methotrexate, and azathioprine, are sometimes used in the treatment of MS.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Mortality in target indication: Average survival following diagnosis of MS is estimated to be 29 to 30 years.

The first clinical manifestations of MS often take the form of CIS affecting the optic nerve (optic neuritis), spinal cord (transverse myelitis), or brainstem/cerebellum. Estimates of the number of patients who eventually go on to develop MS vary widely, but in the case of optic neuritis, the presence of clinically silent brain lesions on MRI at the time of the attack indicates a greater than 80% chance of developing clinically definite MS within 10 years. Approximately 90% of individuals develop RRMS, which is characterised by episodic bouts of neurological worsening (relapses), separated by periods of relative stability (remissions). The population of patients with RRMS ranges from those with relatively "benign" inactive, noninflammatory disease to patients who experience frequent relapses and/or persistent active inflammatory disease on brain MRI.

Over a period of approximately 25 years, about 70% of individuals with RRMS will eventually enter a phase of progressive neurological decline, with or without superimposed relapses, known as SPMS. In addition, approximately 10% of patients with MS will have progression from the onset of the disease (PPMS), typically without acute relapses.

Approximately 50% of patients with MS will require assistance with walking within 15 years of their diagnosis. In addition, MS can have a substantial adverse impact on cognitive function, quality of life, productivity, and employment, and is a leading cause of disability in young adults.

Based on analyses conducted by Decision Resources, in Europe as of 2014, there were approximately 228,000 diagnosed MS patients with RRMS who are being treated with pharmacological therapy [Crowley 2015]. This represents 67% of the total diagnosed population in Europe (N = 340,000). However, despite the demonstrated efficacy of MS treatments and their widespread use, there is a substantial population of patients with relapsing MS who remain untreated for their disease. Many of these patients have disease with relatively little evidence of active inflammation clinically (relapses) or by MRI and hence choose not to initiate treatment.

Children with MS generally experience a more aggressive disease onset and increased cognitive impairment compared to adults [Alroughani and Boyko 2018]. Of paediatric MS patients, 98% present with a relapsing-remitting course, with a higher relapse frequency than adult-onset MS (2 to 3 times more frequent relapses) [Alroughani and Boyko 2018; Pena and Lotze 2013]. Children tend to recover from relapses more quickly than adults, on average over 4 weeks compared with 6 to 8 weeks in adults [Chitnis 2013]. MS disease progression, including physical disability, is slower in children. Paediatric MS eventually progresses from RRMS to secondary

progressive MS 10 years later than adult-onset MS [Alroughani and Boyko 2018; Renoux 2007; Wright 2017]. However, while there is less likelihood of secondary progression of MS in childhood, by age 35 years, half of the childhood-onset MS populations show secondary progression. Treatment in children should be started early in the disease course to reduce relapse rate and disease progression and improve long-term outlook [Alroughani 2021; Krysko 2020].

Important co-morbidities found in the target population

Pulmonary morbidity has been described in MS, especially among patients with more severe disease. The incidence of pneumonia is estimated to be twice that of the general population. Respiratory muscle function is affected by disease severity [Gosselink 1999]. Respiratory illness is also a common cause of death among patients with MS. A study of the Danish Multiple Sclerosis Registry (1998) found that MS patients were more likely to die from respiratory and infectious diseases than the general population [Koch-Henriksen 1998]. MS patients appear to have an increased history of respiratory tract infections prior to the onset of illness [Marrie 2000]. Overall, it is reasonable to conclude that the background incidence of pneumonias and respiratory tract infections in MS patients are likely to be higher than in the general population. A crude estimate, based on the MS Danish registry results, suggests that the infection rate in MS patients may be at least two times greater than the general population. Using information from the US NHANES study 1988-1994, it was found that 2.3% of the total population or 5.6 million people reported suffering from some type of pneumonia in the 12 months prior to the survey [Prevention 2012]. A much lower pneumonia hospitalisation rate, which indicates that most pneumonia is treated in an outpatient setting, has been estimated in the US using the 1981 National Health Survey. This survey reported an annual hospitalisation rate of 3.4/1000, or over 530,000 hospital admissions for pneumonia – almost 60% were in patients more than 65 years old. At this time, no estimates of pneumonia incidence rates within MS patients were found.

Urinary symptoms are very common in patients with MS. One in 10 patients may already have urinary symptoms at the time of initial diagnosis of MS. However, on average, symptoms will appear about 6 years after the onset of disease [de Seze 2007] and are estimated to be present in 64% to 68% of patients with MS. Symptoms include frequency, urgency, and urinary incontinence, which together are described as overactive bladder syndrome. Urinary tract infections are common in patients with MS and are likely to be present in 30% of MS patients. The incidence of urinary symptoms increases with disease duration. Treatment options for overactive bladder include anticholinergic agents, but none of the newer drugs in this class, which are also likely to be better tolerated, have been specifically studied in patients with MS [Nicholas 2009]. Infection needs to be excluded in any patients presenting with urinary symptoms.

An estimated 50% of MS patients visiting an outpatient department are likely to be experiencing pain, which can be directly or indirectly related to MS or MS treatments or may be coincidental.

Depression has been described as a symptom of patients with MS with a lifetime risk of about 50% [Sadovnick 1996] and appears to occur more frequently in patients with MS than in other populations with chronic disease. Treatment guidelines from general psychiatry tend to apply [Feinstein 2004].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A programme of nonclinical studies of pharmacology, PK, ADME, acute to chronic toxicology, reproduction and development, juvenile, genotoxicity, and carcinogenicity has been carried out for Tecfidera (formerly known as BG00012). Animal species used included mouse, rat, rabbit, dog, and monkey. Although the clinical formulation of Tecfidera is a gastro-resistant capsule, because of the difficulties of administration of the clinical formulation to animals, in vivo studies, with the exception of some repeat-dose dog studies, used a suspension of the active ingredient DMF. Safety pharmacology studies evaluating the effects on the central nervous, respiratory, and cardiovascular systems (including cardiac conduction and hERG channel studies) did not demonstrate effects on physiology indicative of any major risks. The transporter studies and CYP induction and inhibition studies indicated a low risk for PK drug-to-drug interactions.

Key safety findings from these studies with potential relevance to human usage are described in Table 2.

Table 2: Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity studies	
Repeat-dose toxicity Target organs identified in repeat-dose toxicology studies include the forestomach (mouse and rat), testes (rat and dog), and kidney (mouse, rat, dog, and monkey). The findings in the forestomach and testes were evaluated and concluded to be of limited concern to human risk. A summary of the kidney as well as findings in the liver, forestomach, and testes are summarised below. **Nephrotoxicity** Findings in the kidney were observed in the mouse, rat, dog, and monkey. Regeneration of the tubular epithelium was observed in all the toxicology species. Additional renal findings in the rat included an increased incidence and severity of age-related nephropathy (males), cortical tubular changes, diffuse dilation (males), hyaline droplet accumulation, nuclear/cellular hypertrophy of epithelial cells, and hypertrophy of the parietal epithelium of Bowman's capsule (males). In the dog, additional renal findings included hypertrophy of the tubular epithelium (males), dilation of cortical tubules, atrophy of the cortical parenchyma, infiltration of the renal papilla, and hyperplasia of papillary	In the human clinical trials, special urine markers of renal damage were investigated. To date, study participants treated with Tecfidera did not have a higher risk of renal or urinary events. Xenobiotics that exacerbate CPN and lead to renal tumours are not considered relevant to humans [Hard 2009]. The mouse renal tumour findings are also considered of low risk to humans. The mode of action of renal tumours was further evaluated by independent renal pathology experts. The human risk assessment further indicated that there was a low human risk in the development of renal tumours [Cohen 2012]. Given the contributory effect of a rodent-specific nephropathy, and the absence of DMF-related tubular effects in Tecfidera-treated MS patients, the relevance of rodent renal tumours to human risk is considered to be low.

SAFETY FINDING	RELEVANCE TO HUMAN USE
urothelial cells. In the monkey, additional renal findings included single cell necrosis. In the repeat-dose toxicology studies, reversibility of DMF-related kidney findings was noted. However, in the 12-month study in monkeys, interstitial fibrosis was observed in 2 male recovery animals in the highest dose group. In the rat and mouse two-year carcinogenicity studies, renal adenomas and carcinomas occurred in a dose-dependent manner. A direct genotoxic/mutagenic effect is excluded by the negative results of DMF and MMF (a primary active metabolite) in genetic toxicology assays. In the mouse and rat, the tumour incidence was associated with an exacerbation of an age-related nephropathy, also called CPN.	
Reproductive/developmental toxicity	
DMF-related effects were observed only where there was maternal toxicity. In the rat during organogenesis, reductions in maternal weight and foetal weights, and foetal variations of delayed ossification (metatarsals and hindlimb phalanges) were observed. In rabbits during organogenesis, DMF-related effects consisted of maternal weight loss and a higher incidence of abortions compared to the control. In the rat during pregnancy and lactation, lower body weight in the F1 offspring, and delays in sexual maturation (preputial separation) in male offspring were observed. It is likely that the DMF effects are secondary to maternal toxicity for all the reproductive studies.	In the context of nonclinical studies, DMF was not found to be teratogenic and DMF-related effects were observed only where there was maternal toxicity.
In juvenile toxicology studies in rats, daily oral administration of DMF at an age range comparable to 3 years and older in humans revealed similar target organ toxicities in the kidney and forestomach as observed in adult animals. DMF did not affect development, neurobehaviour or male and female fertility up to the highest dose (approximately 4.6-times the RHD based on limited AUC data in paediatric patients). Likewise, no effects on male reproductive and accessory organs were observed up to the highest DMF dose of 375 mg/kg/day in a subsequent study in male juvenile rats (about 15-times putative AUC at the RHD). There were recoverable moderate decreases in bone mineralisation and lower measures of bone mineral content and bone density in vertebrae and whole femur in males. Bone densitometry changes were also observed in juvenile rats after oral diroximel fumarate administration, another fumaric acid ester that is metabolised to MMF in vivo. These bone effects might have been related to lower food consumption, but a	The observed delay in reaching sexual maturation in male juvenile rats was due to low body weights and slower development as a result of forestomach toxicity. In addition, the delay was observed at doses considerably higher than the RHD, while no similar changes were observed at lower doses in both male and female rats; therefore, the delay is of little relevance to humans. The bone findings are of limited relevance for adult patients. With respect to the limited data in paediatric patients, the relevance remains unknown. The forestomach is a structure unique to rats and the findings secondary to forestomach toxicity are therefore of little relevance to humans. In the human clinical trials, special urine markers of renal damage

SAFETY FINDING	RELEVANCE TO HUMAN USE
direct effect of the drug on bone growth cannot be excluded, considering also that the NOAEL for bone effects was approximately 1.5 times the presumptive AUC at the recommended paediatric dose.	were investigated. To date, subjects treated with Tecfidera did not have a higher risk of renal or urinary events (see Nephrotoxicity findings above). The moderate amount of human data available to date from a completed pregnancy registry and postmarketing spontaneous reports do not suggest any negative effect of Tecfidera on pregnancy outcome. There were no reports involving lactating female subjects.
Genotoxicity	
Both DMF and MMF were negative in a battery of standard tests (ICH S2A and S2B guideline) that included the in vitro bacterial reverse mutation and chromosomal aberration assays (in mammalian cells). DMF was negative in the in vivo rat micronucleus test.	Negative results for DMF and MMF in the genotoxicity and mutagenicity assays suggest low risk to humans for genotoxicity potential.
Carcinogenicity	
DMF-related changes in the forestomach of rodents (inflammation and tumours) were observed in all treatment groups in the mouse and rat. DMF-related changes in the testes consisted of reversible degeneration of the seminiferous tubules in the dog and rat, hypospermia in the epididymis in the dog, and interstitial (Leydig) cell hyperplasia and adenoma in the rat. In stressful conditions (such as severe body weight loss), changes observed in the dog are recognised. In the rat, Leydig cell hyperplasia and adenoma could be related to disruption of androgen pathways known to occur with exposure to xenobiotics. There was also a lack of Leydig cell proliferation in 1-year chronic studies in the dog and monkey, and in the 2-year mouse carcinogenicity study. The finding of minimal to mild Leydig cell hyperplasia in the testes of the rats in the male fertility study had no adverse effects on fertility. The human risk assessment of the proliferative changes in rat testes was further considered by a carcinogenicity expert [Cohen 2012] and the expert determined a low relevance of Leydig cell changes occurring in humans with Tecfidera treatment.	The forestomach, or nonglandular stomach, is a structure unique to rats and mice, therefore, findings in this organ are of little direct relevance to humans. In the clinical setting, Tecfidera is administered as an enteric-coated microtablet that is specifically designed to avoid release in an acidic environment (i.e., the stomach), further limiting the potential of exposure of the upper GI tract. The human risk assessment of forestomach tumours in rodents are further discussed in a document prepared by a carcinogenicity expert [Cohen 2012]. The testicular changes were considered to be of limited concern for human risk as the effects in the rat and dog had different histologic patterns and were thought to be mechanistically unrelated; the seminiferous tubule degeneration in the dog was secondary to severe weight loss and this type of change is associated with malnutrition; and the testicular effects were not observed in the mouse or monkey. Leydig cell hyperplasia mode of action is known to occur in the rat and likely not applicable to humans. Given the safety margins for testicular effects observed in

SAFETY FINDING	RELEVANCE TO HUMAN USE
	dogs, the confounding body weight loss in dogs, reversibility of degeneration of the seminiferous tubules, lack of effects on fertility in rats, and the lack of testicular changes in mice and monkeys, it is considered that the testicular changes seen in animal studies are unlikely to be of relevance to humans.
Safety Pharmacology studies	
Central nervous system and respiratory safety pharmacology studies have demonstrated no drug-related adverse effects on those systems.	Not applicable.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Adult Population

The evaluations of safety presented in this EU RMP (in support of the overall risk-benefit assessment of Tecfidera) focuses primarily upon the review of integrated data from the following Phase 2 and 3 studies, conducted in relapsing-remitting MS.

Data from 4 completed studies have been integrated to comprise the placebo-controlled and long-term experience with Tecfidera in MS. These 4 studies include the Phase 2 placebo-controlled dose-ranging study (Study C-1900), the Phase 3 placebo-controlled studies (Studies 109MS301 and 109MS302), and the dose-blind Phase 3 long-term safety extension study (Study 109MS303).

For the indication of MS, 2513 participants were included in the primary pooled safety dataset. The final exposure data, stratified by duration, dose, age/gender, and ethnic origin/race, are presented in Table 3 , Table 4, Table 5 and Table 6, respectively.

Table 3: Exposure to Tecfidera by Duration (Integrated MS Trials)

Duration of exposure to Tecfidera	No. of Participants	Person-years
At least 1 dose	2513	11,318
Cumulative at least 12 weeks	2221	11,294
Cumulative at least 48 weeks (1 year)	1872	11,086
Cumulative at least 72 weeks	1706	10,915
Cumulative at least 96 weeks (2 years)	1604	10,748
Cumulative at least 120 weeks	1435	10,418
Cumulative at least 144 weeks (3 years)	1390	10,306
Cumulative at least 168 weeks	1343	10,168
Cumulative at least 192 weeks (4 years)	1304	10,034
Cumulative at least 216 weeks	1212	9683
Cumulative at least 240 weeks (5 years)	1169	9493
Cumulative at least 264 weeks	1105	9188
Cumulative at least 288 weeks (6 years)	1065	8977
Cumulative at least 360 weeks	899	7950
Cumulative at least 384 weeks	813	7329
Cumulative at least 408 weeks	671	6261
Cumulative at least 432 weeks (9 years)	576	5503
Cumulative at least 456 weeks	492	4791
Cumulative at least 480 weeks (10 years)	426	4196

Duration of exposure to Tecfidera	No. of Participants	Person-years
Cumulative at least 504 weeks	258	2619
Cumulative at least 528 weeks (11 years)	135	1412
Cumulative at least 552 weeks	47	506
Cumulative at least 576 weeks (12 years)	8	89

Integrated MS Trials include pooled cumulative data from the Phase 2 placebo-controlled dose-ranging study (Study C-1900), Parts 1 and 2, the Phase 3 placebo-controlled studies (Studies 109MS301 and 109MS302), and the long-term safety extension study (Study 109MS303). The total number of person-years exposed to study treatment is calculated as the sum of number of days exposed to study treatment/365.25.

Table 4: Exposure to Tecfidera by Dose (Integrated MS Trials)

Dose of exposure to Tecfidera	No. of Participants	Person-years
Tecfidera lower doses	128	106
Tecfidera 240 mg BID (480 mg daily)	1136	5639
Tecfidera 240 mg TID (720 mg daily)	1249	5574
Total	2513	11,318

Integrated MS Trials include pooled cumulative data from the Phase 2 placebo-controlled dose-ranging study (Study C-1900), Parts 1 and 2, the Phase 3 placebo-controlled studies (Studies 109MS301 and 109MS302), and the long-term safety extension study (Study 109MS303).

Table 5: Exposure to Tecfidera by Sex and Age Group (Integrated MS Trials)

	Male		Female	
Age group (in years)[1]	No. of Participants	Person-years	No. of Participants	Person-years
< 18	0	0	0	0
18 to 55	747	3505	1748	7560
56 to 65	2	54	16	199
> 65	0	0	0	0
Total	749	3559	1764	7759

[1]Age at first-dose of Tecfidera.
Integrated MS Trials include pooled cumulative data from the Phase 2 placebo-controlled dose-ranging study (Study C-1900), Parts 1 and 2, the Phase 3 placebo-controlled studies (Studies 109MS301 and 109MS302), and the long-term safety extension study (Study 109MS303).

Table 6: Exposure to Tecfidera by Ethnicity/Race (Integrated MS Trials)

Ethnicity/Race	No. of Participants	Person-years
White	1756	5040
Asian	197	640
Black or African American	38	148
Other	92	380
Unknown	430	5110

Integrated MS Trials include pooled cumulative data from the Phase 2 placebo-controlled dose-ranging study (Study C-1900), Parts 1 and 2, the Phase 3 placebo-controlled studies (Studies 109MS301 and 109MS302), and the long-term safety extension study (Study 109MS303).

Paediatric Population

Table 7 provides exposure in the paediatric studies, and Table 8 provides exposure by age and sex.

Table 7: Exposure to Tecfidera by Paediatric Study

Paediatric Study	No. of Participants Exposed
109MS202[a]	22
109MS306 (part 1)	78
109MS311	20
800MS301	2

[a]The 20 participants in Study 109MS311 were also in Study 109MS202.

Table 8: Cumulative Participant Exposure by Age and Sex

Age (years)	Male		Female	
	No. of Participants	Person-Years	No. of Participants	Person-Years
10	1	1.84	0	0
11	1	1.85	0	0
12	3	5.51	2	3.68
13	4	7.38	6	9.72
14	5	7.51	8	13.98
15	6	9.26	17	28.26
16	9	17.28	20	32.43
17	6	12.45	14	23.79

Studies included 109MS202, 109MS306 (part 1), 109MS311, and 800MS301.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The Tecfidera clinical development programme has employed specific exclusion criteria that were related to the evaluation of efficacy (to ensure that the appropriate target disease was studied, or to avoid confounding the efficacy evaluation), to safety (in order to protect trial patients from potential risks associated with investigational product administration), or to GCP (e.g., to ensure that proper follow-up was possible).

When evaluating the impact of these exclusion criteria in relation to the impact on the safety of patients receiving treatment with Tecfidera in the postmarketing setting, key exclusion criteria pertaining to safety from pivotal studies included in the primary pooled safety dataset are addressed by the 'Contraindications' and 'Special warnings and precautions for use' sections of the Tecfidera SmPC.

Exclusion criteria from these pivotal studies that are considered as contraindications in the SmPC, and their rationale for not being considered as missing information, are discussed in Table 9.

Table 9: Exclusion Criteria That Remain as Contraindications in Relation to the Assessment of Missing Information

Exclusion Criteria	Reason for being an exclusion criterion	Is it considered to be missing information?	Rationale
History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF.	Avoidance of serious hypersensitivity reactions	No	The current SmPC contraindicates the use of Tecfidera in patients with hypersensitivity to the active substance or to any of the excipients (as listed in SmPC Section 6.1). Considering this contraindication, use in this patient population is not considered to be relevant for inclusion as missing information.

A review of the key exclusion criteria in the pivotal studies that do not remain as contraindications for use and the appropriate justifications in relation to their relevance to be considered as missing information are presented in Table 10.

Table 10: Discussion of Exclusion Criteria Not Remaining as Contraindications in Relation to the Assessment of Missing Information

Criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
• Participants under the age of 18 years or over the age of 55 years, inclusive, at the time of informed consent	Standard age criteria for RRMS studies.	No	A review of postmarketing safety data in MS patients using 2 age cutoffs (> 55 years and ≥ 65 years) showed that the pattern and nature of the events in these age groups is consistent with that observed during clinical development and do not change the overall safety profile or benefit risk assessment of Tecfidera. Data from Study 109MS401 confirmed these findings. In addition, studies in patients aged 10 to < 18 years (109MS202, 109MS306, and 109MS311) were conducted to characterise the safety profile of Tecfidera in the paediatric population; hence, this is not missing information. However, the number of children aged < 13 years was low, so the indicated population was changed to start at age 13 years.
• Unable to perform the Timed 25-Foot Walk, Nine-Hole Peg Test with both upper extremities, and Paced Auditory Serial Addition Test. • Unable to perform visual function tests.	To ensure the optimal completion of study assessments.	No	These exclusion criteria are relevant only to patients enrolled in clinical studies in order to ensure completeness of data collection, and there is no evidence to suggest that the use of Tecfidera in patients with a more severe disease leads to a specific safety concern, or a different outcome to previously identified risks.

Criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
• History of malignancy (with the exception of basal cell carcinoma that had been completely excised)	To enable meaningful safety and efficacy evaluation during entire study period and avoid disease confounding.	No, however, malignancies are considered to be an important potential risk	Since immunomodulatory therapies have effects on the immune system, they may influence the body's capacity for tumour surveillance and thereby there is a theoretical risk that the incidence of malignancies may increase with longer durations of treatment with Tecfidera. Consequently, given these theoretical mechanistic considerations, the development of malignancies is considered to be an important potential risk for Tecfidera, rather than missing information.
• History of clinically significant disease e.g. CV, pulmonary, GI, dermatologic, psychiatric, neurologic (other than MS), and/or other major disease.	To enable meaningful safety and efficacy evaluation and avoid confounding.	• No	Based on understanding of the pharmacology and postmarketing utilisation of Tecfidera, the safety profile in patients with endocrinologic, immunologic, metabolic, CV, pulmonary, dermatologic, psychiatric, or other neurologic disease is not expected to be different to that of patients without such a disease burden, and therefore exposure in these patients is not considered to be an area of missing information requiring further characterisation. As GI events are commonly reported with Tecfidera, participants with pre-existing GI disease were thought to be at greater risk of significant clinical consequences of GI disease, but Study 109MS401 demonstrated that events experienced by those with pre-existing GI disease were consistent with the symptoms seen in the background MS population with GI disease or the experience of the total population in the postmarketing setting, those with medical comorbidities, and/or the known safety profile of Tecfidera. There were no serious GI events in patients with pre-existing GI disease in Study 109MS401.

Criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
• History of HIV infection. • Positive for hepatitis C antibody and/or positive for hepatitis B surface antigen at screening.	To reduce the risk to laboratory staff during collection/ handling of blood/tissue samples and to avoid confounding the safety assessment of Tecfidera.	No	These exclusion criteria are relevant only to patients enrolled in clinical studies in order to allow for homogeneous data collection and subsequent meaningful data interpretation, and there is no evidence to suggest that the use of Tecfidera in patients with hepatitis B, hepatitis C, and HIV infection results in a specific safety concern, or a different outcome to previously identified risks.
• Elevated liver transaminases (ALT, AST, or GGT 2 times the upper limit of normal)	Possible risk of hepatic injury due to known effect of Tecfidera on transaminases; to avoid confounding the safety assessment of Tecfidera.	• No	DMF and MMF are metabolized by extrahepatic esterases, without the involvement of the CYP system. Regular review of postmarketing data has identified relatively few cases of patients with hepatic impairment; however, a review of the types and nature of AEs reported in patients who did fulfill the criteria for hepatic impairment does not suggest the safety profile of Tecfidera differs from those with normal hepatic function. Consequently, cumulative data obtained to date, including the findings from Study 109MS401, do not indicate that the use of Tecfidera in patients with hepatic impairment impacts the overall safety profile or risk-benefit assessment of Tecfidera.

Criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
• Abnormal urinalysis (proteinuria of 1+ or greater, or haematuria or glycosuria without known aetiology • History of abnormal laboratory results indicative of any significant renal disease that would preclude participation in a clinical trial.	Animal studies have shown evidence of nephrotoxicity but no increase in serious renal injury seen during clinical development.	Yes, in relation to the following area of missing information: Safety profile in patients with moderate to severe renal impairment	Since the renal pathway is a secondary route of elimination for Tecfidera, accounting for less than 16% of the dose administered, evaluation of PK in individuals with renal impairment was not conducted, and given this mechanism of clearance, no effects or dose adjustments are anticipated. In addition, results from Study 109MS303 showed that after repeat dosing with Tecfidera, the safety profile in participants with RRMS and mild renal impairment was not different from those without renal impairment. Nevertheless, as the clinical development programme, Study 109MS401, and postmarketing experience to date have collected only limited information on patients with moderate to severe renal impairment exposed to Tecfidera, data in this population are considered important to further understand the safety profile of Tecfidera. This is therefore considered to be an area of missing information.
• Reduced WBC counts (leucocytes < 3500/mm^3)	Due to the potential risk of serious and opportunistic infections	No	Reduced WBC counts is a laboratory abnormality, not an adverse clinical outcome. The potential risk of serious and opportunistic infections related to reduced WBC counts (or decreases in leukocytes and lymphocytes) has not been demonstrated in clinical trials or the postmarketing setting. In Study 109MS401, the incidence rate of infection was overall similar between those with WBC <3.0 × 10^9/L or those with prolonged moderate to severe lymphopenia and those in the overall FAS. Thus, this topic is not considered missing information. In addition, the current SmPC includes guidance on monitoring blood counts and treatment interruption / discontinuation, while noting that Tecfidera has not been studied in patients with pre-existing low lymphocyte counts and advising caution when treating these patients.

Criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
• Prior treatment (within 6 months) with specific disease-modifying agents or immunosuppressants.	To avoid confounding the assessment of safety and efficacy of Tecfidera	No	These exclusion criteria are relevant only to patients enrolled in clinical studies in order to allow for homogeneous data collection and subsequent meaningful data interpretation.
• Female participants who were pregnant or planning pregnancy.	Animal studies have shown reproductive toxicity at Tecfidera doses exceeding the recommended dosing regimen.	No	Due to the potential for reproductive toxicity identified in non-clinical studies, and as it is not known whether Tecfidera or its metabolites are present in human milk, cautionary statements are included in Section 4.6 *(Fertility, pregnancy and lactation*) of the SmPC with regards to the avoidance of pregnancy and breastfeeding whilst receiving Tecfidera. Limited data from Study 109MS402 and the postmarketing setting so far do not support an association between Tecfidera and adverse pregnancy outcomes. However, “effects on pregnancy outcome” is still considered an important potential risk that needs to be further characterised, particularly with regard to exposure during later stages of pregnancy (beyond gestational week 6). Any pregnancy cases reported to the MAH will be followed up and regular detailed reviews of the cases will be performed in PSURs. For Vumerity, which has the same active metabolite as Tecfidera, a pregnancy registry is still ongoing to collect further data on the potential risk.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. However, a review of the limitations of the exposure to Tecfidera in the clinical development programme, and the ability to detect specific categories of adverse reactions, is provided in Table 11.

Table 11: Limitations of ADR Detection Common to Clinical Trial Development Programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	A total of 6413 MS participants have been exposed to Tecfidera in clinical trials and 2513 participants were included in the Integrated MS trials.	ADRs with a frequency of > 1/3000 could be detected assuming no background incidence.
Due to prolonged exposure, due to cumulative effects, and which have a long latency.	In the Integrated MS trials, 2513 participants were exposed to Tecfidera. Of these, 426 participants were exposed to Tecfidera for at least 480 weeks.	Exposure for at least 10 years does not appear to confer additional risk compared with overall safety profile based on integrated MS studies. No evidence for cumulative effects has been observed in the clinical trial setting. A modest number of participants have received long-term therapy beyond 10 years (426 participants were exposed to Tecfidera for at least 480 weeks as of 26 Mar 2020) from the Integrated MS studies.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 12.

Table 12: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Children	Paediatric participants were not included in the pre-authorisation clinical development programme.
Elderly patients	Participants > 55 years of age were not included in the pre-authorisation clinical development programme.
Pregnant women	Not included in the pre-authorisation clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: • Hepatic impairment	No participants with severe hepatic impairment have been identified as receiving Tecfidera in the pre-authorisation clinical development programme.

Type of special population	Exposure
Patients with relevant comorbidities: • Renal impairment	In the pre-authorisation placebo-controlled trials, 233 participants with renal impairment were reported to have received Tecfidera (based on abnormal eGFR[a] [< 90 mL/min/1.73 m^2] at baseline).
Patients with a disease severity different from inclusion criteria in clinical trials: • EDSS > 6.5	Participants with EDSS > 6.5 were not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials: • Severe active GI disease	Participants with severe active GI disease were not included in the pre-authorisation clinical development programme.
Patients with relevant different ethnic origin	The percentage of participants, by race, exposed to Tecfidera in the pivotal pre-authorisation safety pool were: • Caucasian: n = 1756 (69.9%) • Asian descent: n = 197 (7.8%) • African descent: n = 38 (1.5%) • Other: n = 92 (3.7%) • Unknown: n = 430 (17.1%)

[a] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Exposure to Tecfidera from marketing experience was calculated from monthly sales data assuming that a patient receives 1 unit (60 capsules) per month, and, based on previous forecasting, the estimated monthly discontinuation rate is 2.4%.

SV.1.2 Exposure

Cumulative postmarketing exposure to Tecfidera is presented in Table 13.

Table 13: Cumulative Patient Exposure From Marketing Experience

Source	Cumulative: IBD to 30 Jun 2023		
	Number of Patients	Units	Patient-Years
EEA Market	283,035	8,217,058	684,755
Total Exposed	589,498	16,527,740	1,377,312

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

There is no known potential for misuse of Tecfidera for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable, as this EU RMP update is not an initial submission.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.2.1 Newly identified safety concerns

No new safety concerns have been identified since the previous version of this EU RMP (Version 16.0) was submitted.

SVII.2.2 Reclassification of existing safety concerns

Following the completion of Study 109MS401, a review of the data was performed, resulting in reassessment of several safety concerns. The rationale to support these changes is presented below.

Study 109MS401 was a prospective, global, observational PASS designed to provide long-term safety data in patients with MS who were prescribed Tecfidera (DMF) in routine clinical practice. Enrolled patients who were newly prescribed Tecfidera were followed for up to 5 years ±3 months from the date of their first dose. The primary objective of the study was to determine the incidence, type, and pattern of 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 Tecfidera.

To ensure that all available data were assessed in order to confidently downgrade or remove safety concerns, data from the postmarketing setting, using information from the recent PSUR (Version 1, combined DMF/DRF report covering 27 Mar 2021 to 26 Mar 2023), were reviewed as well as Study 109MS401 findings.

In addition, a thorough review of the EMA's guideline on good pharmacovigilance practices, Module V, was undertaken to ensure that all risks were undesirable clinical outcomes.

Decreases in leukocyte and lymphocyte count – Remove as important identified risk

Lymphopenia occurs with Tecfidera. In placebo-controlled studies, decreases in mean WBC and lymphocyte counts were observed over the first year of treatment and then plateaued and remained stable. The incidence of lymphopenia and leukopenia has been well characterized in clinical trial and postmarketing experience. It is, however, a laboratory finding for which the clinical outcome could be a serious and opportunistic infection including PML. PML continues to be an important identified risk of Tecfidera. There has been no other association of lymphopenia or leukopenia with serious or opportunistic infections. Labeling and routine PV surveillance ensure proper management of patients who experience this laboratory effect.

The EMA's guideline on good pharmacovigilance practices, Module V, states that undesirable clinical outcomes should be addressed as risks. Decreases in leukocyte and lymphocyte count is a laboratory abnormality, not a clinical outcome; thus, it was removed from the product's safety concerns. It will continue to be monitored via routine PV activities.

Drug-induced Liver Injury – Downgrade to nonimportant identified risk

In its pivotal clinical trials, Tecfidera was associated with a small increase in the incidence of elevated liver transaminase levels compared with placebo. The elevations appeared to be transient, with levels remaining stable through observation, without any increase in clinically significant liver pathology. In the postmarketing setting, reversible liver function test abnormalities (transaminase elevations with hyperbilirubinemia) have been noted.

In Study 109MS401, of the 5124 patients in the FAS, 1 patient (< 1%) reported 1 serious hepatic injury event with the PT Drug-induced liver injury. The event had potential confounding circumstances, namely positive cytomegalovirus IgM serology (suggesting recent or reactivated cytomegalovirus infection), exposure to concomitant medications associated with cholestasis (pentoxifylline) and/or rare events of hepatotoxicity (bisoprolol), and signs of cholecystolithiasis in an abdominal ultrasound detected early during the event onset. Three patients (< 1%) experienced 3 AEs in the SOC Hepatobiliary disorders that resulted in discontinuation of Tecfidera, all of which were PT Drug-induced liver injury. The overall incidence rates (95% CI) of SAEs and of AEs resulting in discontinuation of Tecfidera in the SOC of Hepatobiliary disorders were 82 (95% CI: 45-148) and 74 (95% CI: 40-138) per 100,000 person-years, respectively. There were no cases of hepatic failure or liver transplantation in the study.

During the PSUR reporting period (27 Mar 2021 to 26 Mar 2023), 182 events pertaining to drug-induced liver injury were received in 174 case reports; 66 were reported by an HCP, and 61 were assessed as serious. The most frequently reported serious events included PTs Drug-induced liver injury (14 events), Hepatic failure (8 events), and Liver disorder (7 events). Of these 29 serious events, there were 7 follow-up reports, 2 with no significant new information, and 1 case of liver disease as a pregnancy complication, which resulted in induced labor. Tecfidera had been discontinued when the pregnancy was confirmed. Most of the events either provided limited information or had a confounding factor.

Although hepatic transaminase elevations and liver function abnormalities remain as ADRs based on data from placebo-controlled studies, the events appear to be reversible and have positive outcomes. Findings from Study 109MS401 and the postmarketing setting do not support severe hepatic outcomes, which would affect the benefit-risk profile. Thus, the important identified risk of drug-induced liver injury can be downgraded to a nonimportant identified risk in the RMP.

Serious and opportunistic infection (excluding PML and herpes zoster) - Remove as important potential risk

Tecfidera was associated with prolonged, severe lymphopenia in approximately 2% of the pivotal clinical trial population, which could theoretically lead to an increased risk of serious and opportunistic infection, but in placebo-controlled studies, no increased risk of infection, serious infection, or opportunistic infection was observed in participants treated with Tecfidera.

In Study 109MS401, 102 (2%) of the 5124 patients in the FAS experienced 123 SAEs in the SOC of Infections and infestations. Sixteen events were assessed as related to Tecfidera by the investigator. Of those, 6 were associated with herpes zoster, which is a known identified risk of Tecfidera and excluded from the safety concern topic. Two were related to appendicitis, 2 were related to gastroenteritis, and 2 were related to cellulitis. The others were reported in 1 patient each (bacterial infection, parasitic infection, pneumonia, and subcutaneous abscess). In the FAS,

42 patients (0.8%) experienced 44 AEs (from the SOC Infections and infestations) leading to Tecfidera discontinuation. Of these, 23 events (in 22 patients) were assessed as related to Tecfidera by the investigator; 2 were related to herpes zoster. Seven events were related to gastroenteritis, 2 to urinary tract infection, and the rest occurred in 1 patient only. Of 5124 patients in the FAS, 2 SAEs using the SMQ Opportunistic infections were reported in 2 cases, both related to herpes zoster. One patient experienced PT Infection susceptibility increased, considered related to Tecfidera by the investigator, and discontinued treatment due to the event. Using the SOC of Infections and infestations, the overall incidence rates of SAEs and of AEs resulting in discontinuation of Tecfidera were 915 (95% CI: 767-1092) and 327 (95% CI: 244-440) per 100,000 person-years, respectively (note that this includes events of herpes zoster).

In Study 109MS401, the percentage of patients with SAEs in the SOC Infections and infestations was comparable to the percentage reported in Study 109MS303, which was another long-term study of Tecfidera (2% vs. 5%). In addition, the incidence rate of serious infections with Tecfidera in Study 109MS401 was lower than or similar to published rates in persons with MS. The rate in a Swedish nationwide register-based cohort study, in which the risk of serious infections (defined as infection as the underlying or contributory cause of death or infection-related hospital admission) was assessed in 8660 patients with RRMS treated with DMTs, was 9.8 per 1000 person-years [Brand 2022]. In another Swedish nationwide register-based cohort study, in which the risk of serious infections (defined as all infections resulting in hospitalization) was assessed in 6421 patients with RRMS treated with DMTs, the incidence rate was 8.9 per 1000 person-years (95% CI: 6.4-12.1) in patients taking interferon beta or glatiramer acetate, 14.3 per 1000 person-years (95% CI: 10.8-18.5) in patients taking fingolimod, 11.4 per 1000 person-years (95% CI: 8.3-15.3) in patients taking natalizumab, and 19.7 per 1000 person-years (95% CI: 16.4-23.5) in patients taking rituximab [Luna 2020]. In a study from the US Department of Veterans Affairs system, the risk of serious infections (defined as infection-related hospitalizations and death) was assessed in 7743 patients with MS; the incidence rate in patients with RRMS was 11.6 per 1000 person-years (95% CI: 9.3-14.2) [Nelson 2015].

During the PSUR reporting period (27 Mar 2021 to 26 Mar 2023), 748 events pertaining to serious and opportunistic infections (other than PML and herpes zoster) were received in 624 case reports; 294 were reported by an HCP. The most frequently reported serious infectious events included PTs COVID-19 (109 events), Urinary tract infection (79 events), and Pneumonia (48 events). Urinary tract infection and pneumonia are both common infections in the background population with MS. COVID-19 events were not unexpected during the global pandemic. Nineteen events in 11 cases resulted in fatality during the reporting period; only 1 event (PT COVID-19) was assessed as related to Tecfidera by the HCP. The types of fatal serious infections were mostly consistent with those typically seen in patients with MS or were related to COVID-19.

Data from placebo-controlled studies, Study 109MS401, and the postmarketing setting support the removal of the important potential risk of serious and opportunistic infections (excluding PML and herpes zoster).

Interaction with nephrotoxic medications leading to renal toxicity - Remove as Important Potential Risk

Tecfidera has a low potential to cause drug interactions due to the way it is metabolized and because it has low affinity for protein binding. No potential drug interactions with Tecfidera or its primary metabolite, MMF, were identified in in vitro CYP inhibition and induction studies or in P-glycoprotein studies. Furthermore, the relatively low protein binding of Tecfidera and MMF limits the potential for AEs due to displacement from plasma proteins by concomitantly administered medications. Nevertheless, concomitant use of nephrotoxic medications was not studied in controlled clinical studies of Tecfidera, and pharmacodynamic drug interactions of polymedicated MS patients might potentiate renal effects of Tecfidera.

In Study 109MS401, 2382 patients took concomitant nephrotoxic medications and Tecfidera. Of those, 274 experienced 482 SAEs. In the Renal and urinary disorders SOC, 3 patients (< 1%) experienced acute kidney injury, 3 (< 1%) experienced nephrolithiasis, and 3 (< 1%) experienced ureterolithiasis. The acute kidney injury events were assessed as not related to Tecfidera by the investigators and had other plausible etiologies. All other SAEs in the Renal and urinary disorders SOC occurred in 1 patient each.

Of the 2382 patients taking a concomitant nephrotoxic medication, 624 experienced 1016 AEs leading to Tecfidera discontinuation. Among these, 2 patients (< 1%) had AEs in the SOC of Renal and urinary disorders that led to Tecfidera discontinuation; the PTs were Acute kidney injury and Micturition urgency.

During the PSUR reporting period (27 Mar 2021 to 26 Mar 2023), 3 events pertaining to a nephrotoxic drug interaction in 3 cases were identified but lacked sufficient information to suggest that there is additive or compounding renal events in patients taking both Tecfidera and nephrotoxic medications.

Regular reviews of postmarketing data have not identified any safety issues in patients receiving concomitant treatment with Tecfidera and nephrotoxic medications, and the safety profile observed in these patients is consistent with the known safety profile of Tecfidera. Thus, this important potential risk can be removed.

Safety profile in patients over the age of 55 years - Remove as missing information

The Tecfidera pivotal clinical trials primarily enrolled participants 18 to 55 years of age. The results of an Analysis of Variance demonstrated that age does not have a clinically significant impact on the PK of Tecfidera; however, the PK in patients aged 55 years and older were not specifically studied. In Study 109MS401, 479 patients in the FAS were older than 55 years at baseline. They experienced a numerically higher percentage of treatment-emergent SAEs than the overall FAS (14% vs. 7%), but the events were consistent with those seen in an older population (e.g., falls, syncope). The older patients also experienced a numerically higher percentage of events in the SOC Infections and infestations (5% vs. 2%), but these events occur more frequently in this population (e.g., pneumonia, sepsis, urinary tract infections). A numerically higher percentage of patients aged > 55 years discontinued Tecfidera due to a treatment-emergent AE than did the overall population, but the types of events were qualitatively similar to the overall population.

During the PSUR reporting period (27 Mar 2021 to 26 Mar 2023), 12,213 events were reported in patients > 55 years to < 65 years of age in 3606 case reports; 1306 were serious, and 3647 were reported by an HCP. The most frequently reported serious events occurring in patients > 55 years to < 65 years of age included PTs Fall (61 serious events) and Multiple sclerosis relapse (42 serious events). In patients ≥ 65 years of age, 6893 events in 2506 cases were received during the reporting period. Of those, 1374 were reported by an HCP, and 960 were considered serious. The most frequently reported serious events occurring in patients ≥ 65 years of age included PTs Fall (50 serious events), Death (43 events), and Multiple sclerosis relapse (27 serious events). In general, all the events were consistent with the known safety profile of Tecfidera (e.g., PTs Flushing, Nausea, and Diarrhoea) or comorbidities seen in patients with MS.

Data from Study 109MS401 and the postmarketing setting provide sufficient information to demonstrate that the safety profile of those aged > 55 years is consistent with the overall population exposed to Tecfidera. Thus, this topic of missing information can be removed.

Safety profile in patients with hepatic impairment - Remove as missing information

As DMF and MMF are metabolized by esterases (without the involvement of the CYP system), no formal PK studies in patients with hepatic impairment have been performed, and no patients with severe hepatic impairment are known to have received Tecfidera in pivotal clinical trials. Regular review of postmarketing data has identified relatively few cases of patients with hepatic impairment, and a review of the types and nature of AEs reported in patients who did fulfill the criteria for hepatic impairment does not suggest the safety profile of Tecfidera differs from those with normal hepatic function. Consequently, cumulative data obtained to date do not indicate that the use of Tecfidera in patients with hepatic impairment impacts the overall safety profile or risk-benefit assessment of Tecfidera; and given the nature and mechanism of clearance of Tecfidera, no effects or dose adjustments are anticipated or required.

In completed Study 109MS401, 83 patients from the FAS were identified as having hepatic impairment at baseline based on medical history of hepatic disorders. Of those, 8% experienced at least 1 SAE. One patient experienced toxic encephalopathy that was assessed as not related to Tecfidera by the Investigator. The event was reported as resolved without requiring concomitant treatment 4 days after the reported start date. Twenty-eight percent had a treatment-emergent AE that resulted in Tecfidera discontinuation. Two patients experienced events involving elevated liver function tests that resulted in discontinuation of Tecfidera; reversible elevations in liver transaminases (ALT and AST) have been observed in Tecfidera-treated patients.

During the PSUR reporting period (27 Mar 2021 to 26 Mar 2023), 859 events occurring in patients with a medical history of hepatic impairment were received in 208 case reports; 437 were reported by an HCP and 80 were serious. The most frequently reported serious events in patients with a medical history of hepatic impairment were PT Multiple sclerosis relapse (11 events), Lymphocyte count decreased (3 events), and Drug-induced liver injury (3 events); all other serious events were reported with a count of 2 events or less. In 1 case of drug-induced liver injury, the patient had a personal and family history of hepatic cancer, and limited information about the event was provided. The other 2 events were elevated liver enzyme results, which are labeled for Tecfidera; 1 in a woman with hepatitis B and 1 in a male with preexisting mildly elevated liver enzyme values. Overall, all the events were in line with the symptoms seen in the MS population with hepatic impairment and the known safety profile of Tecfidera. Review of the type and nature of the 859 events reported in patients who fulfilled the criteria for hepatic

impairment does not suggest the safety profile of Tecfidera differs from those with normal hepatic function.

Overall, data from both the postmarketing setting and Study 109MS401 demonstrate that the safety profile in patients with hepatic impairment is no longer unknown, that it does not differ from the safety profile in those with normal hepatic function, and that this topic can be removed from the product's safety concerns. Thus, this topic of missing information can be removed.

Safety profile in patients with severe active GI disease - Remove as missing information

Tecfidera is known to cause GI events, but its effect on those with pre-existing GI disease had not been studied previously. In Study 109MS401, of the 5124 patients in the FAS, 36 patients had severe or active GI disease at baseline. Five of these patients (14%) experienced 13 SAEs during the study. All the events occurred in 1 patient each, and no trends or patterns were noted with the type of events. Events ranged from malignancies to infections to dehydration; no serious GI events were reported. Of the 36 patients in the FAS with baseline severe or active GI disease, 15 experienced 20 treatment-emergent AEs resulting in discontinuation of Tecfidera. Five events were in the SOC Gastrointestinal disorders (PTs Vomiting [2 events], Abdominal pain upper, Diarrhoea, and Nausea [1 event each]). Other than PT Hypersensitivity that occurred in 2 patients, all other events were experienced by 1 patient only, and no trends or patterns were noted with the type of events.

In the postmarketing setting, cumulatively up to 26 Mar 2023, 13,369 events in patients with severe active GI disease were reported in 2860 case reports; 1321 were assessed as serious. During the PSUR reporting period (27 Mar 2021 to 26 Mar 2023), 2915 events in patients with severe active GI disease were reported in 523 cases reports; 231 were serious. The most frequently reported serious events in patients with severe active GI disease included PTs Multiple sclerosis relapse (21 events) and Diabetic ketoacidosis (14 events). Overall, the events seen are in line with the symptoms seen in the background MS population with GI disease or are consistent with the experience of the total population in the postmarketing setting, those with medical comorbidities, and/or the known safety profile of Tecfidera. There were 4 events of Crohn's disease, but review of the cases did not reveal any concerning information.

Data from Study 109MS401 and the postmarketing setting provide confidence that patients with severe active GI disease respond to Tecfidera similarly than those without GI disease. Thus, this topic of missing information can be removed.

Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies - Remove as missing information

Tecfidera has a low potential to cause drug interactions due to the way it is metabolized and because it has low affinity for protein binding. No potential drug interactions with Tecfidera or its primary metabolite, MMF, were identified in in vitro CYP inhibition and induction studies or in P-glycoprotein studies. Furthermore, the relatively low protein binding of Tecfidera and MMF limits the potential for AEs due to displacement from plasma proteins by concomitantly administered medications. Nevertheless, patients receiving anti-neoplastic or immunosuppressive therapies were not included in the Tecfidera clinical development program.

It is possible that the effect of Tecfidera on immune function may be additive when combined with known immunosuppressants or immunomodulators, leading to the theoretical possibility

that concomitant administration of Tecfidera with these therapies may increase the risk of infection or may lessen the effects of some anti-neoplastic agents as a result of the anti-inflammatory and cytoprotective effects of Tecfidera. In the Phase 2 add-on therapy study (Study 109MS201), data did not suggest an alteration in safety or tolerability when Tecfidera was combined with commonly used MS therapies, such as IFN and GA. In addition, the intermittent use of short courses of intravenous corticosteroids to treat MS relapses was not associated with a clinically relevant increase of infection in clinical studies. Tecfidera has also been given in combination with methotrexate in a study in rheumatoid arthritis with no change in the safety profile.

In Study 109MS401, 2435 patients in the FAS took immunomodulating/immunosuppressing medications concomitantly. Of those, 77 patients (3%) experienced SAEs in the SOC Infections and infestations, 32 patients (1%) experienced SAEs in the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps), 3 patients (< 1%) experienced SAEs in the SOC Investigations, and 5 patients (< 1%) experienced SAEs in the SOC Blood and lymphatic system disorders. The PTs that were experienced by at least 5 patients were consistent with the PTs seen in the overall population exposed to Tecfidera. Twenty-two percent had an AE leading to Tecfidera discontinuation. The incidence of AEs leading to discontinuation in the SOC Infections and infestations was comparable between patients concomitantly taking immunomodulating/immunosuppressing therapies and those not.

There were 83 patients concomitantly taking antineoplastic medications and Tecfidera. Of those, 14 patients experienced 17 SAEs; all PTs occurred in 1 patient each. Twenty-three patients had 38 AEs leading to Tecfidera discontinuation; most events were in the Blood and lymphatic system disorders SOC.

During the PSUR reporting period (27 Mar 2021 to 26 Mar 2023), 1 case of Tecfidera interaction with an immunosuppressive medication (methylprednisolone) was identified. The patient received methylprednisolone 1 year after starting Tecfidera. Nine days after starting methylprednisolone the patient experienced PT Lymphocyte count decreased (687/mm^3). Tecfidera was maintained, and the event resolved approximately 1 month after onset. Action taken with methylprednisolone was not reported.

Data from Study 109MS401 and the postmarketing setting demonstrate that the safety profile observed in patients receiving concomitant treatment with Tecfidera and anti-neoplastic or immunosuppressive therapies is consistent with the known safety profile of Tecfidera and not affected by the concomitant use. Thus, this topic of missing information can be removed from the safety concerns.

SVII.3 Details of important identified risks, important potential risks, and missing information

Data from completed paediatric studies have revealed that the safety profile in paediatric patients (those aged 10 years to < 18 years) show no meaningful differences compared with the safety profile in adults. No safety concerns related solely to paediatric patients were identified.

SVII.3.1 Presentation of important identified risks

SVII.3.1.1 Progressive Multifocal Leukoencephalopathy (PML)

Relevant MedDRA term: *PT Progressive multifocal leukoencephalopathy*

Potential mechanisms

PML is an opportunistic infection caused by the JCV. However, even in patients who are anti-JCV antibody positive, PML only occurs in minority of patients because JCV infection is only one of several factors required for the development of PML.

Published studies have proposed several hypotheses for the reactivation of JCV and the development of PML. These hypotheses, as well as their relevance for Tecfidera treatment are discussed below:

- Potential immunosuppression by reducing the binding of mononuclear cells to vascular cell adhesion molecule-1 thus allowing the proliferation of JCV which is undetectable to the immune system [Khatri 2015]. In preclinical and clinical studies, after oral administration of DMF only the primary metabolite MMF can be detected in circulation due to the rapid and extensive pre-systemic metabolism of DMF. MMF, even at very high concentrations (200 μM, which is 100-fold higher than the human MMF maximum observed concentration after 240 mg DMF) had no effects on adhesion molecule expression [Wallbrecht 2011].
- Host genetic factors with regard to HLA class I and II genes where different variants may influence the effectiveness of CD4+ and CD8+ T cell immune defence, have been investigated [Sundqvist 2014]. However, the methodology used in this study had several shortcomings: (i) the identified HLA associations were compared to JCV-seropositive status, and no JCV-specific T-cell responses were measured; (ii) the HLA alleles identified in this study are not biomarkers for anti-JCV antibody or T cell responses, since these HLA alleles can be found in both JCV-seropositive and JCV seronegative individuals; and (iii) genotype discordance between different platforms were observed. Finally, these results have not been replicated using a uniform genotyping platform.
- Mechanisms of cellular immunity such as IFN-γ producing CD4+ T cells and JCV-specific CD8+ cells are considered critical in preventing PML development [Calabrese 2015]. Specifically, IFN secretion by JCV specific CD8+ T-cells is known to be important in PML survival [Gheuens 2011], and IL-2 has been given to boost the immune system as a potential treatment for PML [Gheuens 2013]. A publication by de Jong describes T-cell cytokine influence mediated by MMF in purified human T cells [de Jong 1996]. Since the in vitro effect of T-cell cytokine switching was only seen at 200 μM MMF and above, it is important to note that 200 μM MMF is 2- to 6-fold and 139-fold greater than the maximal serum concentration of MMF in humans following recommended Fumaderm and Tecfidera administration, respectively. Therefore, it is unlikely that DMF or MMF would impact human T cells in the in vivo setting of standard fumaric acid ester exposure similar to the described in vitro effects characterised in the de Jong paper.
- Investigations on the potential role of JCV-specific CD8+ T [Chen 2009; Marzocchetti 2009] have resulted in variable results. A report by Gheuens et al. 2011 notes that “a

major limitation in the study of the cellular immune response to JCV is the very low frequency of specific T cells and the difficulty in detecting them in peripheral blood ex vivo" and that despite these cells being present after PML diagnosis, it was unclear whether they were present prior to PML.

Current evidence suggests that the mechanism of action of Tecfidera (as DMF) involves at least 2 pathways; activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway [Linker 2011; Scannevin 2012] and activation of the G-protein-coupled receptor hydroxycarboxylic acid receptor 2 (HCA2) [Chen 2014]. These mechanisms are consistent with preclinical and clinical evidence supporting immunomodulatory and cytoprotective effects from DMF treatment. There is nothing in the preclinical or clinical literature that suggests either of these mechanisms would confer increased risk for PML. There have been no associations of Nrf2 gain of function genetic polymorphisms with PML, nor have other structurally diverse small molecule activators of Nrf2 been associated with PML [de Zeeuw 2013].

Evidence source(s) and strength of evidence

PML case definitions (which categorise cases into Level 1 to Level 5) allow classification of cases based on various levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out (Level 5) as well as high and low suspect cases (Levels 2 and 3, respectively) and includes a category for cases with insufficient data despite exhaustive due diligence (Level 4).

Following this adjudication process, confirmed PML cases (Level 1) have been identified in association with Tecfidera use (and other products containing fumarates) in the setting of lymphopenia. PML is a contraindication in Section 4.3 (*Contraindications*) and an ADR in Section 4.8 (*Undesirable effects*) of the Tecfidera SmPC, and wording relating to the detection and management of PML is included in Section 4.4 (*Special warnings and precautions for use*).

Characterisation of the risk

This risk is characterised in Table 14.

Table 14: Characterisation of Important Identified Risk: Progressive Multifocal Leukoencephalopathy

Frequency	Clinical trials • *Placebo-controlled clinical trials:* No case of PML was identified in placebo-controlled clinical trials. • *Long-term safety extension study (Study 109MS303):* One case of PML was observed in the setting of severe and prolonged lymphopenia in a participant in the study. Postmarketing spontaneous • Cases of PML have been reported during postmarketing use in the setting of lymphopenia.
Seriousness and severity	All confirmed cases of PML were serious. PML can be fatal or result in severe disability.

Reversibility and long-term outcomes	All confirmed cases following Tecfidera exposure occurred in the setting of lymphopenia. PML can be fatal or result in severe disability.
Impact on quality of life	PML is fatal in approximately 20% of cases; however, there are limited data on the quality of life for the 80% of patients who survive. PML, like MS, is a demyelinating disease, and therefore symptoms can vary in severity and may be similar to an MS relapse. Typical symptoms associated with PML can vary in severity, are diverse, and progress over days to weeks. They can include: • Progressive weakness or clumsiness of limbs • Sensory disturbances • Personality changes or cognitive deficits • Trouble speaking • Visual disturbances • Loss of balance In some cases, the damage caused by PML can be extensive and can lead to fatality or extreme disability; however, in rare cases, the infection can be asymptomatic. Consequently, the impact on quality of life in the individual patient is difficult to assess outside of a case-by-case basis.

Risk factors and risk groups

PML can only occur in the presence of a JCV infection, with studies indicating that approximately 60% - 70% of MS patients were seropositive when screened for anti-JCV antibody [Olsson 2013]. Whilst patients who are anti-JCV antibody positive are at greater risk for developing PML than the overall population of MS patients, patients who are anti-JCV antibody negative may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result.

There are several well-recognised risk factors for PML such as immunosuppression, use of natalizumab, and a decrease in lymphocyte count. Furthermore, there are populations that have a higher risk of developing PML, including HIV patients; patients with malignancies, including NHL and CLL; patients diagnosed with SLE, sarcoidosis and autoimmune vasculitis; and patients undergoing bone marrow transplantation.

Although several hypothetical risk factors have been proposed as biomarkers to stratify PML risk, nothing has been validated to date that is not drug specific. Furthermore, even among natalizumab-treated patients, for whom there exists a well-validated PML risk algorithm, no additional JCV-specific or host-specific biomarker has been identified through exhaustive analysis of relevant information from risk characterisation (detection of mutant pathogenic JCV DNA in serum, host genetic marker, CSF IgM oligoclonal bands, serum protein signature, and CD62L/L-selectin) for development of PML in these individuals.

With regard to Tecfidera, the findings common to all confirmed cases of PML reported to date have been the presence of lymphopenia (lymphocyte counts < 0.91×10^9/L), with the majority of confirmed cases of PML occurring in the setting of moderate to severe lymphopenia for longer

than 6 months' duration. Therefore, it is considered that in Tecfidera-treated patients, lymphopenia is a risk factor.

Information from studies evaluating lymphopenia associated with Tecfidera treatment have shown that ALC was highly correlated with total T, CD4+ and CD8+ T cells, highlighting the effectiveness of the regular monitoring of lymphocyte counts in identifying patients at risk of developing lymphopenia.

Additional factors that might contribute to an increased risk for PML in the setting of lymphopenia are duration of Tecfidera therapy (cases of PML have occurred after approximately1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown); profound decreases in CD4+ and especially in CD8+ T cell counts, which are important for immunological defence; and prior immunosuppressive or immunomodulatory therapy.

Additionally, the majority of PML cases in the postmarketing setting have occurred in patients > 50 years of age.

Preventability

In Tecfidera-treated patients, lymphopenia is considered a risk factor for the development of PML; therefore, regular monitoring of lymphocyte counts provides an effective preventability measure to identify patients at risk.

Prior to initiating treatment with Tecfidera, a current complete blood count, including lymphocytes, must be performed. If lymphocyte count is found to be below the normal range, thorough assessment of possible causes should be completed prior to initiation of treatment with Tecfidera. Before initiating treatment with Tecfidera, a baseline MRI should also be available (usually within 3 months) as a reference.

After starting therapy, complete blood counts, including lymphocytes, must be performed every 3 months. Discontinue Tecfidera in patients with lymphocyte counts $< 0.5 \times 10^9$/L persisting for more than 6 months. Reassess the risk-benefit in patients who experience moderate lymphopenia for more than 6 months. Lymphocyte counts should be followed until recovery. In controlled and uncontrolled clinical studies, participants with lymphopenia who discontinued Tecfidera were monitored until their lymphocyte counts returned to normal. Refer to Section 5.1 (*Pharmacodynamic properties*) of the SmPC for data on lymphocyte recovery. Additional factors that might further augment the individual PML risk should be considered.

At the first sign or symptom suggestive of PML, treatment with Tecfidera should be withheld and appropriate diagnostic evaluations performed.

Impact on the risk-benefit balance of the product

PML continues to be a rare event related to Tecfidera use, and all reports of suspected PML are closely monitored and subject to rigorous follow-up to accurately adjudicate the cases according to level of evidence and to characterise any potential additional risk factors for PML. In addition, the MAH conducted research to characterise the impact of Tecfidera on lymphocytes. Tecfidera treatment is associated with primarily a decline in CD8+ and CD4+ T cells, and it was shown that ALC was highly correlated with total T, CD4+ and CD8+ T cells.

The Tecfidera SmPC describes the risk of lymphopenia and PML in Section 4.4 (*Special warnings and Precautions for use*), as monitoring of lymphocyte counts provides a means for early identification of those patients who are at increased risk for developing lymphopenia and its potential sequelae. These recommendations in the label are considered to be adequate measures to mitigate the risk of PML, and therefore the risk-benefit balance of the product remains favourable.

Public health impact

PML is not considered to have a major impact on public health.

SVII.3.2 Presentation of important potential risks

SVII.3.2.1 Malignancies

Relevant MedDRA terms: *SMQ Malignant or unspecified tumours*

Potential mechanisms

Based on its mechanism of action, Tecfidera is considered an immunomodulatory therapy. Since immunomodulatory therapies have effects on the immune system, they may influence the body's capacity for tumour surveillance; thereby, there is a theoretical risk that the incidence of malignancies may increase with longer durations of treatment with Tecfidera.

Evidence source(s) and strength of evidence

In 2-year rodent carcinogenicity studies with Tecfidera, renal tubular adenomas and carcinomas were observed, which were attributed to an exacerbation of rodent-specific age-related nephropathy. The nephropathy observed in aging rodents has no human correlate and since Tecfidera was not associated with an increased risk of urinary or renal events in clinical studies, these preclinical findings represent a relatively low risk to humans.

From a review of all available data, no evidence of a causal link between Tecfidera and the development of malignancies has been identified, and the types and frequencies of malignancies reported in patients treated with Tecfidera are consistent with those observed in the general US and global populations.

Characterisation of the risk

This risk is characterised in Table 15.

Table 15: Characterisation of Important Potential Risk: Malignancies

Frequency	Placebo-controlled clinical trials: Malignancy • Incidence in placebo: 0.36% (95% CI: 0.07%, 1.05%) • Incidence in Tecfidera BID: 0.26% (95% CI: 0.03%, 0.94%) • Incidence in Tecfidera TID: 0.24% (95% CI: 0.03%, 0.88%) (*Clopper Pearson exact confidence interval was used to calculate the 95% confidence intervals of event incidences.)* In the placebo-controlled trials, the overall incidence of malignancies was low and similar between the placebo group (< 1%, 3 patients), the Tecfidera BID group (< 1%, 2 patients) and the Tecfidera TID group (< 1%, 2 subjects). The incidence of malignancies in an active control GA group was 1% (4 patients). Including patients with longer-term treatment, the incidence rate for malignancies overall among all Tecfidera-treated subjects was 375.4 per 100,000 patient-years (95% CI: 218.7, 601.0), which is within expected background rates.
Seriousness and severity	The type and nature of malignancies observed were consistent with those typically seen in the general or MS populations.
Reversibility and long-term outcomes	The reversibility and long-term outcomes of malignancies observed were consistent with those typically seen in the general or MS populations.
Impact on quality of life (QoL)	The impact of developing a malignancy on quality of life can vary considerably between patients and is dependent on malignancy location, stage, and other co-morbidities affecting a patient's ability to tolerate treatment and is therefore difficult to assess outside of an individual case-by-case basis. However, as there is no evidence of an increased risk of malignancies in Tecfidera-treated patients, no impact on quality of life is anticipated.

Risk factors and risk groups

None known.

Preventability

None.

Impact on the risk-benefit balance of the product

Given the putative immunomodulatory mechanism of action of Tecfidera, malignancies were carefully evaluated in clinical studies. In the controlled MS studies, the incidence of malignancies was low and balanced across the Tecfidera and placebo groups. There was no evidence of an increased incidence rate of malignancy with continued exposure to Tecfidera for up to 9 years in the uncontrolled safety extension study. As no evidence of a causal association between Tecfidera and the development of malignancies has been identified, no impact on the risk-benefit balance of the product is currently considered.

Public health impact

As there is no evidence of increased risk of malignancy, there is no impact on public health.

SVII.3.2.2 Effects on pregnancy outcome

Relevant MedDRA terms: Not applicable. All pregnancy outcomes reporting maternal or paternal exposure to Tecfidera are reviewed.

Potential mechanisms

None known.

Evidence source(s) and strength of evidence

In reproductive studies in rats and rabbits, DMF was not found to be teratogenic (i.e., no malformation). In the rat during organogenesis, reduction in maternal weight and foetal weights, and foetal variations of ossification (metatarsals and hind limb phalanges) were observed. Different than malformation, variation is defined as a change that occurs within the normal population and is unlikely to adversely affect survival or health of the animal. In rabbits during organogenesis, DMF-related effects consisted of maternal weight loss and an increase incidence of abortions. In the rat during pregnancy and lactation, lower body weight in the F1 offspring, and delays in sexual maturation (preputial separation) in male offspring were observed. It is likely that the DMF effects are secondary to maternal toxicity for all the reproductive studies.

Current data from clinical trials and the postmarketing setting do not suggest that Tecfidera, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. In completed Study 109MS402, 289 prospectively collected pregnancy outcomes were documented in patients with MS taking Tecfidera. The median duration of exposure was 4.6 gestational weeks with limited exposure after the sixth gestational week. Exposure to Tecfidera during early pregnancy did not increase the rates of major congenital malformations compared to those reported in the general population.

Characterisation of the risk

This risk is characterised in Table 16.

Table 16: Characterisation of Important Potential Risk: Pregnancy Outcome

Frequency	Cumulatively, to 26 Mar 2021, 5104 cases (reporting 6913 events) of maternal exposure to Tecfidera during pregnancy were received of which 3159 were reported prospectively. These cases were reported from clinical studies, the MS Pregnancy Registry [Study 109MS402], and postmarketing reports. Additionally, there were 181 cases of paternal exposure (83 cases from solicited postmarketing reports and 98 cases from spontaneous postmarketing reports). Of the 5104 maternal cases, 361 were lost to follow-up or had an unknown outcome, and 1870 had an ongoing or pending pregnancy outcome. In the remaining 2873 cases, 2211 were live births without congenital anomaly. There were 73 cases of congenital anomaly, including live births (n = 59), elective termination (n = 11), and still births (n = 3). Of the 73 congenital anomaly cases, 27 cases reported either non-specific congenital anomalies or functional disorders (these cases are excluded per EUROCAT guidance). Of the remaining 46 cases, 21 were prospective and 25 were retrospective. Of the 21 prospective cases with congenital anomaly, 19 were included in the EUROCAT prevalence rate calculations, after deducting 3 cases of ectopic pregnancy. Overall, the prevalence rate for all congenital anomalies with Tecfidera, was found to be within the EUROCAT background rate of 196.89 (118.95 - 305.77) vs 208.35 (207.02 - 209.69), respectively. A frequency of abnormal pregnancies from the MS Pregnancy Registry [Study 109MS402], as of 15 Mar 2021, is estimated to be 2.3%; this is based on 8 reports of major congenital anomalies in 350 pregnancy outcomes.
Seriousness and severity	**Seriousness:** The moderate amount of human data from the Tecfidera pregnancy exposure registry, clinical studies, and postmarketing experience do not currently suggest any negative effect of Tecfidera on pregnancy outcome. The rate of spontaneous abortions, including early pregnancy losses, does not exceed the expected rate of the general population [Garcia-Enguidanos 2002]. **Severity:** To be determined
Reversibility and long-term outcomes	Reversibility would depend on the type of foetal abnormality and severity. Due to the limited human pregnancy exposure, data are currently inadequate to determine effects of Tecfidera on long-term outcomes of pregnancy exposure in the infant.
Impact on quality of life	Current data do not suggest that Tecfidera, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. No impact on quality of life is therefore anticipated.

Risk factors and risk groups

Women of childbearing potential.

Preventability

The SmPC states that Tecfidera should be used during pregnancy only if clearly needed and if the potential benefit to the mother justifies the potential risk to the foetus.

Impact on the risk-benefit balance of the product

None.

Public health impact

No potential public health risk is considered possible at this time.

SVII.3.3 Presentation of Missing Information

SVII.3.3.1 Long term efficacy and safety

Evidence source

The completed long-term safety extension study (109MS303) had participants exposed to Tecfidera and followed for up to 13 years. Completed Study 109MS401 also assessed the long-term effectiveness and safety of Tecfidera (follow up for up to 6.5 years). Both studies had adult populations and showed that Tecfidera is safe and effective over many years.

Population in need of further characterisation

The ongoing extension phase of Study 109MS306 is assessing the long-term safety and health outcomes in patients aged 10 to < 18 years.

SVII.3.3.2 Safety profile in patients with moderate to severe renal impairment

Evidence source

As the renal pathway is a secondary route of elimination for Tecfidera, no formal PK studies in patients with renal impairment have been performed, and no patients with severe renal impairment are known to have received Tecfidera in pivotal clinical trials.

Data from a long-term extension study (109MS303) with Tecfidera determined that the safety profile of participants with mild renal impairment was similar to that in participants with normal GFR. In Study 109MS401, limited data suggested that those with moderate to severe renal impairment had a similar safety profile to those with normal renal impairment, but the overall numbers were too low to be conclusive. Thus, data related to moderate-to-severe renal impairment is considered missing information.

Population in need of further characterisation

Exhalation of carbon dioxide is the primary route of Tecfidera elimination, accounting for 60% of the dose. Renal elimination is a secondary route of elimination, accounting for 16% of the dose. Therefore, on theoretical grounds, a patient with renal impairment would not be

expected to accumulate Tecfidera or its metabolites, and the safety profile of Tecfidera in such patients is not expected to be different from that in patients with normal renal function.

Regular reviews of postmarketing data have identified relatively few cases of patients with renal impairment; however, a review of the types and nature of AEs reported in those patients who did fulfil the criteria for renal impairment does not suggest the safety profile of Tecfidera differs from those with normal renal function. Consequently, cumulative data obtained to date do not indicate that the use of Tecfidera in patients with renal impairment impacts the overall safety profile or risk-benefit assessment of Tecfidera; and given the nature and mechanism of clearance of Tecfidera, no effects or dose adjustments are anticipated or required.

Nevertheless, data on the use of Tecfidera in patients with a history of renal impairment are scant; therefore, moderate to severe renal impairment will continue to be considered missing information. In the long-term extension study (109MS303), however, it was determined that the safety profile of participants with mild renal impairment was similar to that in participants with normal GFR. Mild renal impairment is no longer considered missing information.

PART II: MODULE SVIII - SUMMARY OF SAFETY CONCERNS

The Tecfidera safety specification includes the following important identified risks, important potential risks, and areas of missing information (Table 17).

Table 17: Summary of Safety Concerns

Important identified risks	• PML
Important potential risks	• Malignancies • Effects on pregnancy outcome
Missing information	• Long-term efficacy and safety • Safety profile in patients with moderate to severe renal impairment

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Biogen employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise all of the safety concerns discussed in this EU RMP.

Routine Biogen pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to assess the ongoing safety profile of Tecfidera throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent data appropriately. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

In addition to adverse reactions reporting and signal detection activities, data collection forms at different time points post-event (up to 24 months) are used for case reports of PML to aid further characterisation of the event and identification of potential risk factors. These data collection forms aim to collect detailed information relating to suspected PML events in a standardised fashion, to enable timely and robust collection of data, thereby optimising risk evaluation. Data collections forms are also used to enable timely and robust collection of data for events of malignancies, thereby optimising risk evaluation. The data collection forms are provided in Annex 4.

III.2 Additional pharmacovigilance activities

Data from 1 study is anticipated to aid the further characterisation of the safety concerns described in Part II:SVII.3. This study is summarised below.

Study 109MS306 Part 2 - Open-Label, Randomized, Multicenter, Multiple-Dose, Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension

- ***Rationale and Study Objectives:*** The primary objective of this study is to evaluate the long-term safety of BG00012 in participants who completed Week 96 in Part 1 of Study 109MS306. This study aims to address the following safety concerns: long-term safety and efficacy in paediatric participants aged 10 to < 18 years
- ***Milestones:***
  - *Final CSR: Q4 2025*

III.3 Summary table of additional pharmacovigilance activities

A summary of the studies included in the pharmacovigilance plan are summarised in Table 18.

Table 18: Ongoing and Planned Additional Pharmacovigilance Activities

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – ***Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation***				
• None				
Category 2 – ***Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances***				
• None				
Category 3 – ***Required additional pharmacovigilance activities***				
Study 109MS306 Part 2 Open-Label, Randomized, Multicenter, Multiple-Dose, Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension **Status:** Ongoing	*Primary Objective of Part 2:* • To evaluate the long-term safety of BG00012 in participants who completed Week 96 in Part 1 of Study 109MS306. *Secondary Objectives:* To describe the long-term MS outcomes of BG00012 in participants who completed Week 96 in Part 1 of Study 109MS306.	• Long-term safety and efficacy in paediatric participants aged 10 to < 18 years	Final CSR	Q4 2025

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable - there are no imposed post-authorisation efficacy studies.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine risk minimisation measures

Routine risk minimisation measures are in place in order to ensure the maintenance of a favourable risk-benefit balance to patients administered Tecfidera.

In the postmarketing setting, routine risk minimisation measures are the SmPC and PL, which are the primary tools to communicate information about the benefits and risks associated with the use of Tecfidera. These documents provide information to the prescriber and to the patient about the identified safety concerns and relevant potential safety concerns, and how these concerns should be managed in certain circumstances.

A description of the routine risk minimisation measures per safety concern are discussed in Table 19.

Table 19: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
PML	***Routine risk communication:*** • PML is listed as a contraindication in SmPC Section 4.3 (*Contraindications*) and as an ADR in SmPC Section 4.8 (*Undesirable effects*) and PL Section 4 (*Possible side effects*). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Recommendations on risk factors, detection, and management of PML and information regarding the clinical presentation of PML are included in SmPC Section 4.4 (*Special warnings and precautions for use*). • Information regarding the clinical symptoms of PML are included in PL Section 4 *(Possible side effects).* ***Other routine risk minimisation measures beyond the product information:*** • Legal status: Medicinal product subject to restricted medical prescription.
Important Potential Risks:	
Malignancies	***Routine risk communication:*** • Information regarding the findings from non-clinical carcinogenicity studies is provided in SmPC Section 5.3 (*Preclinical safety data*). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the product information:*** • Legal status: Medicinal product subject to restricted medical prescription.

Safety concern	Routine risk minimisation activities
Effects on pregnancy outcome	***Routine risk communication:*** • Information regarding the findings from non-clinical reproductive studies is provided in SmPC Section 5.3 (*Preclinical safety data*). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Information stating that as a precautionary measure, it is preferable to avoid the use of Tecfidera during pregnancy is provided in SmPC Section 4.6 (*Fertility, pregnancy and lactation*), and PL Section 2 (*What you need to know before you take Tecfidera*). ***Other routine risk minimisation measures beyond the product information:*** • Legal status: Medicinal product subject to restricted medical prescription.
Areas of Missing Information	
Long-term efficacy and safety	***Routine risk communication:*** • Text in SmPC Section 4.8 (*Undesirable effects*) describes safety profile and Section 5.1 (*Pharmacodynamic properties*) describes clinical efficacy and safety. • Text in PL Section 1 (*What Tecfidera is and what it is used for*) advises patients on what Tecfidera is used for and how it works. Section 4 (*Possible side effects*) advises patients on side effects and informing their HCP if they experience side effects. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the product information:*** • Legal status: Medicinal product subject to restricted medical prescription.
Safety profile in patients with moderate to severe renal impairment	***Routine risk communication:*** • Text in SmPC Section 4.4 (*Special warnings and precautions for use*) advises caution when treating patients with severe renal impairment • Text in PL Section 2 (*What you need to know before you take Tecfidera*) advises patients to inform their HCP if they have an existing severe kidney disease. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • None ***Other routine risk minimisation measures beyond the product information:*** • Legal status: Medicinal product subject to restricted medical prescription.

V.2 Additional Risk Minimisation Measures

There are no ongoing additional risk minimisation measures considered necessary for Tecfidera.

V.3 Summary table of risk minimisation measures

Table 20: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
PML	***Routine risk minimisation measures:*** Information in SmPC Sections 4.3 (*Contraindications*), 4.4 (*Special warnings and precautions for use*), and 4.8 (*Undesirable effects*), and PL Section 4 (*Possible side effects*). ***Additional risk minimisation measures:*** The MAH distributed a DHPC in EU countries by 12 Nov 2020 to inform HCPs about cases of PML in the setting of lymphopenia (mild).	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks:		
Malignancies	***Routine risk minimisation measures:*** Information in SmPC Section 5.3 (Preclinical safety data). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** None
Effects on pregnancy outcome	***Routine risk minimisation measures:*** Information in SmPC Sections 4.6 (*Fertility, pregnancy and lactation*) and 5.3 (*Preclinical safety data*), and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Areas of missing information		
Long-term efficacy and safety	***Routine risk minimisation measures:*** Text in SmPC Sections 4.8 (Undesirable effects) and 5.1 (Pharmacodynamic properties) ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Open-label extension (Part 2) of Study 109MS306 (in paediatric participants aged 10 to < 18 years)
Safety profile in patients with moderate to severe renal impairment	***Routine risk minimisation measures:*** SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR TECFIDERA (DIMETHYL FUMARATE)

Summary of Risk Management Plan for Tecfidera™ (dimethyl fumarate)

This is a summary of the RMP for Tecfidera. The RMP details important risks of Tecfidera, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of Tecfidera.

The Tecfidera SmPC and its PL give essential information to healthcare professionals and patients on how Tecfidera should be used.

This summary of the RMP for Tecfidera should be read in the context of all available relevant information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report.

Important new safety concerns or changes to the current described safety concerns will be included in updates of the RMP for Tecfidera.

I. The medicine and what it is used for

Tecfidera is authorised for relapsing-remitting multiple sclerosis (see SmPC for the full indication). It contains dimethyl fumarate as the active substance, and it is given orally.

Information about the evaluation of the benefits of Tecfidera can be found in the European Public Assessment Report for Tecfidera, including in its plain-language summary, available on the EMA website under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Tecfidera together with measures to minimise such risks and the proposed studies for learning more about the risks of Tecfidera are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals, respectively;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly; and
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Tecfidera is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Tecfidera are risks that need special risk management activities to further investigate or minimise the risk so that the medicinal product can be taken safely. Important risks can be categorised as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tecfidera. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that needs to be collected (e.g., on the long-term use of the medicine):

List of important risks and areas of missing information	
Important identified risks	• PML
Important potential risks	• Malignancies • Effects on pregnancy outcome
Areas of missing information	• Long-term efficacy and safety • Safety profile in patients with moderate to severe renal impairment

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks, and missing information.

Important Identified Risk(s)	
PML	
Evidence for linking the risk to the medicine	PML case definitions (which categorise cases into Level 1 to Level 5) allow classification of cases based on various levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out (Level 5) as well as high and low suspect cases (Levels 2 and 3, respectively) and includes a category for cases with insufficient data despite exhaustive due diligence (Level 4). Following this adjudication process, confirmed PML cases (Level 1) have been identified in association with Tecfidera use (and other products containing fumarates) in the setting of lymphopenia ($< 0.91 \times 10^9$/L). Consequently, PML was added as a contraindication in Section 4.3 (*Contraindications*) and a listed ADR in Section 4.8 (*Undesirable effects*) of the Tecfidera SmPC, and wording relating to the detection and management of PML was implemented in Section 4.4 (*Special warnings and precautions for use*).
Risk factors and risk groups	PML can only occur in the presence of a JCV infection, with studies indicating that approximately 60% - 70% of MS patients were seropositive when screened for anti-JCV antibody [Olsson 2013]. Whilst patients who are anti-JCV antibody positive are at greater risk for developing PML than the overall population of MS patients, patients who are anti-JCV antibody negative may still be at risk of PML for

Important Identified Risk(s)	
	reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. There are several well-recognised risk factors for PML such as immunosuppression, use of natalizumab, and a decrease in CD4 cells. Furthermore, there are populations that have a higher risk of developing PML, including HIV patients; patients with malignancies; and patients diagnosed with SLE, sarcoidosis, autoimmune vasculitis, non-Hodgkin's lymphoma, CLL, and bone marrow transplant. The common presentation in all confirmed cases of PML in Tecfidera-treated patients to date has been lymphopenia ($< 0.91 \times 10^9$/L), with the majority of confirmed cases of PML occurring in the setting of moderate to severe lymphopenia for longer than 6 months' duration. Therefore, it is considered that in Tecfidera-treated patients, lymphopenia is a risk factor. Information from studies evaluating lymphopenia associated with Tecfidera treatment have shown that ALC was highly correlated with total T, CD4+ and CD8+ T cells, highlighting the effectiveness of regular monitoring of lymphocyte counts in identifying patients at risk of developing lymphopenia. Additional factors that might contribute to an increased risk for PML in the setting of lymphopenia are duration of Tecfidera therapy (cases of PML have occurred after approximately 1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown); profound decreases in CD4+ and especially in CD8+ T cell counts, which are important for immunological defence; and prior immunosuppressive or immunomodulatory therapy. Additionally, the majority of PML cases in the postmarketing setting have occurred in patients > 50 years of age.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.3, 4.4, and 4.8 and PL Section 4. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** The MAH distributed a DHPC in EU countries by 12 Nov 2020 to inform HCPs about cases of PML in the setting of lymphopenia (mild).

Important Potential Risk(s):	
Malignancies	
Evidence for linking the risk to the medicine	In 2-year rodent carcinogenicity studies with Tecfidera, renal tubular adenomas and carcinomas were observed, which were attributed to an exacerbation of rodent-specific age-related nephropathy. The nephropathy observed in aging rodents has no human correlate and since Tecfidera was not associated with an increased risk of urinary or renal events in clinical studies, these preclinical findings represent a relatively low risk to humans. From a review of all available data, no evidence of a causal link between Tecfidera and the development of malignancies has been identified, and the types and frequencies of malignancies reported in patients treated with Tecfidera are consistent with those observed in the general population.
Risk factors and risk groups	None known
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 5.3 Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	***None***
Effects on pregnancy outcome	
Evidence for linking the risk to the medicine	In reproductive studies in rats and rabbits, DMF was not found to be teratogenic (i.e., no malformation. In the rat during organogenesis, reduction in maternal weight and foetal weights, and foetal variations of ossification (metatarsals and hindlimb phalanges) were observed. Different than malformation, variation is defined as a change that occurs within the normal population and is unlikely to adversely affect survival or health of the animal. In rabbits during organogenesis, DMF-related effects consisted of maternal weight loss and an increase incidence of abortions. In the rat during pregnancy and lactation, lower body weight in the F1 offspring, and delays in sexual maturation (preputial separation) in male offspring were observed. It is likely that the DMF effects are secondary to maternal toxicity for all the reproductive studies. Current data from clinical trials and the postmarketing setting do not suggest that Tecfidera, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. In completed Study 109MS402, 289 prospectively collected pregnancy outcomes were documented in patients with MS taking Tecfidera. The median duration of exposure was 4.6 gestational weeks with limited exposure after the sixth gestational week. Exposure to Tecfidera during early pregnancy did not increase the rates of major congenital malformations compared to those reported in the general population.
Risk factors and risk groups	Women of childbearing potential.

Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.6 and 5.3 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	None

Areas of Missing Information	
Long-term efficacy and safety	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.8 and 5.1, and PL Sections 1 and 4. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Open-label extension (Part 2) of Study 109MS306 (in paediatric participants aged 10 to < 18 years)
Safety profile in patients with moderate to severe renal impairment	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription.
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies that are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for Tecfidera.

II.C.2 Other studies in post-authorisation development plan

Other studies in the post-authorisation development plan are as follows:

- **Study 109MS306 Part 2:**
  - *Purpose of the study:* Evaluate the long-term safety and MS outcomes in children with MS who are aged 10 to < 18 years.

ANNEX 4 - SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Adverse event follow-up forms will be distributed for potential/confirmed events of progressive multifocal leukoencephalopathy and for malignancies; see Part III [Pharmacovigilance Plan] of the European Union Risk Management Plan for details).

The follow-up forms for distribution are provided in this Annex below:

- Multiple Sclerosis Suspect Progressive Multifocal Leukoencephalopathy Data Collection Tool
- Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 3 and 6
- Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 12 and 24
- Malignancies Data Collection Tool

Biogen	Multiple Sclerosis Suspect Progressive Multifocal Leukoencephalopathy Data Collection Tool (Governed by DEV-SOP-836)	RD-FORM-2067 Version: 9.0 Page 1 of 10

Biogen Unique Case ID#: Case ID #

I. → Patient Information

Patient Initials: ☐☐☐☐☐ → DOB: ☐☐☐☐☐ (DD/MMM/YYYY) Gender: ☐☐☐☐☐

Height: ☐☐☐☐☐ → Weight: ☐☐☐☐☐ BMI: ☐☐☐☐☐

II. → Primary Neurologist:

Name: ☐☐☐☐☐ → Email: ☐☐☐☐☐

Address: ☐☐☐☐☐

Phone: ☐☐☐☐☐ → Fax: ☐☐☐☐☐

III. → Treating Physician (if different from primary neurologist):

Name: ☐☐☐☐☐ → Email: ☐☐☐☐☐

Address: ☐☐☐☐☐

Phone: ☐☐☐☐☐ → Fax: ☐☐☐☐☐

IV. → Primary Suspect Product

Select the product you believe to be the Primary Suspect Product:

☐ Tysabri → ☐ Avonex → ☐ Tecfidera → ☐ Other: ☐☐☐☐☐

☐ Fampyra/Ampyra ☐ Plegridy → ☐ Vumerity → ☐ dimethyl fumarate (authorized generic) distributed by Teva

Is this patient receiving Tysabri at an extended interval dosing (e.g. >4 weeks)?

☐ Yes ☐ No

Provide additional details on the dosing and frequency of the Primary Suspect Product, including information on the use of multiple regimens:

Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Dose	Route	Frequency of Dosing	Number of Administered Doses (Tysabri)	Lot/ Batch #
☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

In your assessment, is the suspected PML related to the Primary Suspect Product?

☐ Yes ☐ No

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Biogen Unique Case ID#: Case ID #

- **V. → Secondary Suspect Product (if applicable)**

Select the product you believe to be the Secondary Suspect Product:

☐ Tysabri → ☐ Avonex → ☐ Tecfidera → ☐ Other: [redacted]

☐ Fampyra/Ampyra → ☐ Plegridy → ☐ Vumerity → ☐ dimethyl fumarate (authorized generic) distributed by Teva

Provide additional details on the dosing and frequency of the Secondary Suspect Product, including information on the use of multiple regimens:

Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Dose	Route	Frequency	Lot/Batch #
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In your assessment, is the suspected PML related to the Secondary Suspect Product? ☐ Yes ☐ No

Since discontinuation of Biogen suspect product, is the patient being treated with any other MS therapy? ☐ Yes ☐ No If yes, specify: [redacted]

- **VI. → Multiple Sclerosis History**

1) → MS diagnosis date: [redacted] → (DD/MMM/YYYY)

2) → Provide the MS therapies used prior to Primary Suspect Product:

Medication	Dose	Route	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3) Has the patient received prior immunosuppressant therapy, radiation therapy, antineoplastic or immunomodulatory therapy for a condition other than MS?

☐ Yes ☐ No

If yes, list the drug and include the indication:

4) Is this patient immunocompromised from any other cause?

☐ Yes ☐ No

If yes, provide diagnosis:

5) Has the patient ever been or currently is enrolled in a Biogen Clinical Trial?

☐ Yes ☐ No

If yes, specify the trial name/number: Provide the patient's study ID:

VII. PML Suspicion

1) Indicate the reason(s) the patient is being evaluated for PML:

- Patient presented with clinical signs and symptoms? ☐ Yes ☐ No (Asymptomatic)
- Patient presented with radiological findings consistent with PML? ☐ Yes ☐ No
- Reason for MRI: (Check all that apply)

☐ MS standard of care ☐ PML surveillance ☐ Patient request ☐ Other:

2) List earliest presenting signs and symptoms that led to the evaluation for possible PML (even if identified in retrospect):

Symptoms	Date (DD/MMM/YYYY)

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3) Provide copies of MRI reports for 6 months prior to PML suspicion. If not possible, provide detailed MRI results including lesion characteristics and location.

a. MRI at the time of the suspected PML diagnosis:

Date of MRI: _____ (DD/MMM/YYYY)

Detailed description: _____

b. MRI prior to suspected PML diagnosis

Date of MRI: _____ (DD/MMM/YYYY)

Detailed description: _____

4) Provide copies of CSF JCV DNA reports, if not possible provide details of lumbar puncture (LP) and CSF sample collection (provide all tests, even if multiple assays are performed on a single puncture):

	Test 1	**Test 2**	**Test 3**
Date of LP (DD/MMM/YYYY)	_____	_____	_____
LP performed Pre-PLEX (if applicable)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
CSF JCV DNA Result	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate
Quantitative (copies/mL)	_____	_____	_____
Laboratory Name and Limit of Detection	_____	_____	_____

5) Has a CSF analysis been performed? (cell count, protein, glucose, albumin, various viral PCR testing, etc.)

☐ Yes ☐ No → Date of Test: _____ (DD/MMM/YYYY)

Provide cell count: _____

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6) **Provide details of <u>all</u> serum anti-JCV antibody testing:**

(Provide copies of the anti-JCV antibody test results)

Date of Test: (DD/MMM/YYYY)	Result of Test: (positive, negative, pending)	Index Value Available:	Index Value:	Laboratory Name:
°°°°°	☐ Positive ☐ Negative ☐ Pending	☐ Yes ☐ No	°°°°°	☐ Focus/Quest ☐ Unilabs ☐ Other °°°°°
°°°°°	☐ Positive ☐ Negative ☐ Pending	☐ Yes ☐ No	°°°°°	☐ Focus/Quest ☐ Unilabs ☐ Other °°°°°
°°°°°	☐ Positive ☐ Negative ☐ Pending	☐ Yes ☐ No	°°°°°	☐ Focus/Quest ☐ Unilabs ☐ Other °°°°°
°°°°°	☐ Positive ☐ Negative ☐ Pending	☐ Yes ☐ No	°°°°°	☐ Focus/Quest ☐ Unilabs ☐ Other °°°°°

7) **Was a brain biopsy performed?** ☐ Yes ☐ No

Date of Test: °°°°° (DD/MMM/YYYY)

(If yes, provide a copy of the brain biopsy report.)

8) **HIV status:** ☐ Positive ☐ Negative ☐ Unknown

Date of Test: °°°°° (DD/MMM/YYYY)

9) **Was patient lymphopenic within 12 months prior to PML suspicion?** ☐ Yes ☐ No

Date (DD/MMM/YYYY)	WBC	Lymphocyte (%)	Absolute Lymphocyte Count	Lymphocyte Subset Analysis: (CD4, CD8, CD4/CD8 ratio, etc.)	
°°°°°	°°°°°	°°°°°	°°°°°	°°°°°	Not Performed ☐
°°°°°	°°°°°	°°°°°	°°°°°	°°°°°	Not Performed ☐
°°°°°	°°°°°	°°°°°	°°°°°	°°°°°	Not Performed ☐
°°°°°	°°°°°	°°°°°	°°°°°	°°°°°	Not Performed ☐
°°°°°	°°°°°	°°°°°	°°°°°	°°°°°	Not Performed ☐

VIII. → Current Treatment

1) → Has the patient received steroids within the past 3 months? ☐ Yes ☐ No

Drug	Dose	Route	Frequency	Start date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Reason for steroids

2) → PML Treatment: (check all that apply)

Medication	Dose	Route	Frequency	Start date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
☐ Mefloquine					
☐ Cidofovir					
☐ Mirtazapine					
☐ Other:					
☐ Other:					

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3) PLEX / IA:

Plasma Exchange (PLEX): ☐ Yes ☐ No → Immunoadsorption (IA): ☐ Yes ☐ No

Session	Date (DD/MMM/YYYY)	Volume
1		
2		
3		
4		
5		

IX. Patient's Location

Patient's current location: (check appropriate box)

☐ Hospital → ☐ Home → ☐ Nursing Home
☐ Intensive Care Unit → ☐ Hospice → ☐ Rehabilitation Facility
☐ N/A (Patient is deceased)

If patient is deceased, provide the following information:

Date of Death: (DD/MMM/YYYY)

Reported Cause of Death:

Was an autopsy performed? ☐ Yes ☐ No *(If yes, provide a copy of the autopsy report)*

In your assessment, was the patient's death related to the Primary Suspect Product?

☐ Yes ☐ No

If applicable, in your assessment, was the patient's death related to the Secondary Suspect Product? ☐ Yes ☐ No

X. → Functional Scores

Provide the patient's functional status scores
On Primary Suspect Product prior to PML

EDSS: _____ Date: _____ (DD/MMM/YYYY)
Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)
Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

At the time of PML suspicion:
EDSS: _____ Date: _____ (DD/MMM/YYYY)
Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)
Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

Modified Rankin Score	
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

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Karnofsky Performance Status Scale Definitions/Criteria		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

XI. → Rule Out PML

1) → Based on your evaluation, was PML ruled out? ··· ☐ Yes ··· ☐ No ☐ Still under investigation

2) → If PML was ruled out, provide the final diagnosis (if available): _____

3) → Was the final diagnosis related to the Primary Suspect Product? ····· ☐ Yes ····· ☐ No

a. → Was the final diagnosis related to the Secondary Suspect Product? (if applicable)

☐ Yes ··· ☐ No

b. → Provide the outcome for the final diagnosis: _____

☐ Fatal ☐ Recovered ☐ Recovered with sequelae ☐ Not recovered ☐ Unknown

4) → What MS therapy is planned or is the patient currently on? _____

Biogen Unique Case ID#: Case ID #

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

(When signing electronically, check "Lock Document After Signing" in the Sign Document window).

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Biogen Unique Case ID#: Case ID #

I. Patient Demographics

Patient Initials: _____ DOB: _____ (DD/MMM/YYYY)

II. Is the Patient alive? ☐ Yes ☐ No

If yes, provide the patient's current location (check appropriate box):

☐ Hospital ☐ Home ☐ Nursing Home

☐ Intensive Care Unit ☐ Hospice ☐ Rehabilitation Facility

If no, provide the following information:

Date of Death: _____ (DD/MMM/YYYY)

Reported Cause of Death: _____

Was an autopsy performed? ☐ Yes ☐ No
(If yes, provide a copy of the autopsy report)

III. In your assessment, was the patient's death related to one of the following products?

☐ Yes ☐ No

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex ☐ dimethyl fumarate (authorized generic) distributed by Teva

IV. Functional status post-PML diagnosis: (see tables below)

EDSS: _____ Date: _____ (DD/MMM/YYYY)
Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)
Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

Biogen Unique Case ID#: Case ID #

Modified Rankin Score	
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Karnofsky Performance Status Scale Definitions/Criteria		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not Imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

V. → Test results post-PML diagnosis: *(provide a copy of test results)*

Provide copies of MRI reports, including most recent MRI report. If not possible, provide detailed MRI results including lesion characteristics and location:

Date of MRI: ☐☐☐☐☐ (DD/MMM/YYYY)

Detailed description: ☐☐☐☐☐

Provide copies of CSF JCV DNA reports. If not possible, provide details of lumbar puncture (LP) and CSF sample collection (provide all tests, even if multiple assays are performed on a single puncture).

	Test 1	Test 2	Test 3
Date of LP (DD/MMM/YYYY)	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
LP performed Pre-PLEX (if applicable)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
CSF JCV DNA Result	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate	☐ Positive ☐ Negative ☐ Inconclusive/ Indeterminate
Quantitative (copies/mL)	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
Laboratory Name and Limit of Detection	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

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Date (DD/MMM/YYYY)	WBC	Lymphocyte (%)	Absolute Lymphocyte Count	Lymphocyte Subset Analysis: (CD4, CD8, CD4/CD8 ratio, etc.)	
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐
					Not Performed ☐

VI. → Is your patient currently on another therapy for Multiple Sclerosis? ☐ Yes ☐ No

If yes, what is the therapy?

Include start date and dosing regimen:

Provide patient's EDSS at time of new DMT onset:

VII. → PML Treatment:

Plasma Exchange (PLEX): ☐ Yes ☐ No → Immunoadsorption (IA): ☐ Yes ☐ No

Session	Date (DD/MMM/YYYY)	Volume
1		
2		
3		
4		
5		

Biogen	Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 3 and 6 (Governed by DEV-SOP-836)	RD-FORM-2065 Version: 8.0 Page # of #

Biogen Unique Case ID#: Case ID #

Medication	Dose	Route	Frequency	Start date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
☐ Mefloquine					
☐ Cidofovir					
☐ Mirtazapine					
☐ Other:					
☐ Other:					

VIII. → PML Outcome:

a. → What is the outcome of the patient's PML?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown
☐ Fatal

Provide the date of the assessed outcome: _____ (DD/MMM/YYYY)

IX. → Was the patient diagnosed with PML-IRIS?

☐ Yes; onset date (DD/MMM/YYYY): _____ ☐ No

a. → Any new or worsening symptoms? ☐ Yes ☐ No

If yes, specify the symptoms:

Onset date of IRIS symptoms:

b. → Any contrast enhancements or MRI at time of PML-IRIS? ☐ Yes ☐ No

c. → Any mass effect or edema on MRI? ☐ Yes ☐ No

X. → PML-IRIS Treatment:

a. → Did the patient receive corticosteroids pre-PML-IRIS onset? ☐ Yes ☐ No

b. → Did the patient receive corticosteroids post-PML-IRIS onset? ☐ Yes ☐ No

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Biogen Unique Case ID#: Case ID #

Specify all treatments the patient received for PML-IRIS: (*including corticosteroid regimens*):

Medication	Dose	Route	Frequency	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Specify if treatment is pre- or post-PML-IRIS

XI. → PML-IRIS Outcome:

a. → What is the outcome of the patient's PML-IRIS?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown
☐ Fatal

Provide the date of the assessed outcome of PML-IRIS: _____ (DD/MMM/YYYY)

b. → What is the causality of the PML-IRIS to the following Biogen products?

☐ Related → → ☐ Not Related ☐ Unknown

☐ Tysabri → → ☐ Tecfidera ☐ Vumerity →

☐ Fampyra/Ampyra → ☐ Plegridy → ☐ Avonex → ☐ dimethylfumarate (authorized generic) distributed by Teva

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

(When signing electronically, check "Lock Document After Signing" in the Sign Document window).

Biogen	Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 12 and 24 (Governed by DEV-SOP-836)	RD-FORM-2066 Version: 9.0 Page 1 of 4

Biogen Unique Case ID#: Case ID#

I. Patient Information

Patient Initials: _____ DOB: _____ (DD/MMM/YYYY)

II. Is the Patient alive? ☐ Yes ☐ No

If yes, provide the patient's current location (check appropriate box):

☐ Hospital ☐ Home ☐ Nursing Home

☐ Intensive Care Unit ☐ Hospice ☐ Rehabilitation Facility

If no, provide the following information:

Date of Death: _____ (DD/MMM/YYYY)

Reported Cause of Death: _____

Was an autopsy performed? ☐ Yes ☐ No
(If yes, provide a copy of the autopsy report)

III. In your assessment, was the patient's death related to one of the following products?

☐ Yes ☐ No

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex ☐ dimethylfumarate (authorized generic) distributed by Teva

IV. Functional Status post-PML Diagnosis (see tables below):

EDSS: _____ Date: _____ (DD/MMM/YYYY)
Karnofsky score: _____ Date: _____ (DD/MMM/YYYY)
Modified Rankin Score: _____ Date: _____ (DD/MMM/YYYY)

Page Break

Modified Rankin Score	
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Karnofsky Performance Status Scale Definitions/Criteria		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not Imminent.
	20	Very sick; hospital admission necessary; active supportive treatment Necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Biogen	Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 12 and 24 (Governed by DEV-SOP-836)	RD-FORM-2066 Version: 9.0 Page 3 of 4

Biogen Unique Case ID#: Case ID#

V. → Test results post-PML diagnosis: *(provide a copy of test results)*

Provide copies of MRI reports, including most recent MRI report. If not possible, provide detailed MRI results including lesion characteristics and location:

Date of MRI: ..... (DD/MMM/YYYY)

Detailed description: .....

Date (DD/MMM/YYYY)	WBC	Lymphocyte (%)	Absolute Lymphocyte Count	Lymphocyte Subset Analysis: (CD4, CD8, CD4/CD8 ratio, etc.)	
.....	.....	.....	.....	.....	Not Performed ☐
.....	.....	.....	.....	.....	Not Performed ☐
.....	.....	.....	.....	.....	Not Performed ☐
.....	.....	.....	.....	.....	Not Performed ☐
.....	.....	.....	.....	.....	Not Performed ☐

VI. → Is your patient currently on another therapy for Multiple Sclerosis? ☐ Yes ☐ No

If yes, what is the therapy? .....

Include start date and dosing regimen: .....

Provide patient's EDSS at time of new DMT onset: .....

VII. → PML Outcome:

a. → What is the outcome of the patient's PML?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Fatal

Provide the date of the assessed outcome: ..... (DD/MMM/YYYY)

Biogen	Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 12 and 24 (Governed by DEV-SOP-836)	RD-FORM-2066 Version: 9.0 Page # of #

Biogen Unique Case ID#: Case ID#

VIII. → PML-IRIS Outcome:

a. → What is the outcome of the patient's PML-IRIS?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Fatal

Provide the date of the assessed outcome of PML-IRIS: _____ (DD/MMM/YYYY)

b. → What is the causality of the PML-IRIS to the following Biogen products?

☐ Related → ☐ Not Related → ☐ Unknown

☐ Tysabri → ☐ Tecfidera → ☐ Vumerity

☐ Fampyra/Ampyra → ☐ Plegridy → ☐ Avonex → ☐ dimethylfumarate (authorized generic) distributed by Teva

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

(When signing electronically, check "Lock Document After Signing" in the Sign Document window).

Tecfidera Breast Cancer

To provide consistency in our due diligence of Tecfidera breast cancer reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of breast cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please provide any medical history risk factors the patient had for breast cancer (e.g., family history, hormone replacement therapy, breast cancer (BRCA) gene mutations, history of proliferative benign breast disease or breast carcinoma, etc.).
4. Please provide any social risk factors for breast cancer (e.g., smoking, alcohol consumption).
5. Please list the medications the patient has taken in the past 2 years.
6. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
7. If a tissue biopsy was performed, please provide the findings.
8. Please provide results from all imaging studies such as mammogram, ultrasound, or magnetic resonance imaging (MRI).
9. Was the patient tested for estrogen receptor, progesterone receptor, or human epidermal growth factor receptor 2 (HER-2/neu) protein? If so, please provide test results.
10. Please provide results from the physical exam.
11. If the patient was hospitalized, please provide discharge report.
12. Please provide any treatments the patient received for the event.
13. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Cervical Cancer

To provide consistency in our due diligence of Tecfidera cervical cancer reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of cervical cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient had any recent infections (bacterial, fungal, spirochetes, etc.).
4. Please indicate if the patient has a history of cancer.
5. Please provide any medical history risk factors the patient had for cervical cancer (e.g., smoking, family history of cervical cancer, human papillomavirus (HPV) infection, or oral contraceptive use > 5 years, etc.).
6. Please indicate the dates if the patient received either the Cervarix or Gardasil HPV vaccination.
7. Please list the medications the patient has taken in the past 2 years.
8. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
9. Please provide results and dates from all pathology or cytology studies.
10. Please provide results from all imaging studies.
11. Please provide results from physical examination.
12. If the patient was hospitalized, please provide discharge report.
13. Please provide any treatments the patient received for the event.
14. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Colon Cancer

To provide consistency in our due diligence of Tecfidera colon cancer reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of colon cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
4. Please provide any medical history risk factors the patient had for colon cancer (e.g., family, or personal history of colorectal cancer or adenomatous polyps, obesity, smoking, alcohol consumption, etc.).
5. Please list all medications the patient has taken in the past 2 years.
6. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
7. If a tissue biopsy was performed, please provide the findings and the date it was performed.
8. If tumor markers were analyzed, please provide the name of the marker(s) which were found and the date of the analysis.
9. Please provide results and dates from all pathology or cytology studies.
10. Please provide results from all imaging studies.
11. Please provide results from physical examination.
12. If the patient was hospitalized, please provide discharge report.
13. Please provide any treatments the patient received for the event.
14. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Endometrial Cancer

To provide consistency in our due diligence of Tecfidera endometrial cancer reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of endometrial cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please provide any medical history risk factors the patient had for endometrial cancer (e.g., personal or family history, diabetes, early menarche, late menopause, polycystic ovary syndrome, estrogen therapy, tamoxifen use, nulliparity, etc.).
4. Please list the medications the patient has taken in the past 2 years.
5. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
6. Please provide results from all pathology or cytology studies.
7. Please provide results from all imaging studies.
8. Please provide results from physical examination.
9. If the patient was hospitalized, please provide discharge report.
10. Please provide any treatments the patient received for the event.
11. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera General Malignancy

To provide consistency in our due diligence of Tecfidera general malignancy reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
4. Please indicate if the patient has a history of cancer.
5. Please provide any medical history risk factors the patient had for a general malignancy (e.g., family history of malignancies, radiation exposure, smoking, diabetes mellitus, etc.).
6. Please list all medications the patient has taken in the past 2 years.
7. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
8. Please provide all signs and symptoms related to the malignancy.
9. If a tissue biopsy was performed, please provide the findings and the date it was performed.
10. Please provide results from all pathology or cytology studies.
11. Please provide results from all imaging studies.
12. Please provide results from physical examination.
13. If the patient was hospitalized, please provide discharge report.
14. Please provide any treatments the patient received for the event.
15. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Lymphoma

To provide consistency in our due diligence of Tecfidera lymphoma reports, please ask the follow-up questions below.

1. Please specify the patient's type and stage of lymphoma.
2. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
3. Please indicate if the patient has a history of cancer.
4. Please provide any medical history risk factors the patient had for lymphoma (e.g., family history, chromosomal abnormalities, transplantation, rheumatoid arthritis, etc.).
5. Please list the medications the patient has taken in the past 2 years.
6. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
7. If a tissue biopsy was performed, please provide the findings.
8. Please provide results from all imaging studies.
9. Please provide results from physical examination.
10. Please provide results from all laboratory tests. Please include baseline values as well as reference ranges for any and all lab tests.
11. If the patient was hospitalized, please provide discharge report.
12. Please provide any treatments the patient received for the event.
13. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Melanoma

To provide consistency in our due diligence of Tecfidera melanoma reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of melanoma.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
4. Please indicate if the patient has a history of cancer.
5. Please provide any medical history risk factors the patient had for melanoma (e.g., ultraviolet light exposure, family history of melanoma, pigmented lesions, etc.).
6. Please indicate if the patient has a family history of melanoma skin cancer and describe the family history.
7. Please list all medications the patient has taken in the past 2 years.
8. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
9. If a tissue biopsy was performed, please provide the findings and the date it was performed.
10. If tumor markers were analyzed, please provide the name of the marker(s) which were found and the date of the analysis.
11. Please provide results from all imaging studies.
12. Please provide results from physical examination.
13. If the patient was hospitalized, please provide discharge report.
14. Please provide any treatments the patient received for the event.

Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Non-Melanoma Skin Cancer

To provide consistency in our due diligence of Tecfidera non-melanoma reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade on non-melanoma skin cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
4. Please indicate if the patient was exposed to ultraviolet (UV) light, arsenic, or ionizing radiation.
5. Please provide any medical history risk factors the patient had for non-melanoma (e.g., family history or non-melanoma skin cancer, immunosuppression, genetic factors, etc.).
6. Please indicate if the patient has a family history of non-melanoma skin cancer and describe the family history.
7. Please list the medications the patient has taken in the past 2 years.
8. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
9. If a tissue biopsy was performed, please provide the findings and the date it was performed.
10. If tumor markers were analyzed, please provide the name of the marker(s) which were found and the date of the analysis.
11. Please provide results from all imaging studies.
12. Please provide results from physical examination.
13. If the patient was hospitalized, please provide discharge report.
14. Please provide any treatments the patient received for the event.
15. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Non-Small Cell Lung Cancer

To provide consistency in our due diligence of Tecfidera non-small cell lung cancer reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of non-small cell lung cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient was exposed to tobacco smoke, how many packs per year they smoke, if they currently smoke, if they are exposed to second-hand smoke, or if they have a remote history of smoking.
4. Please indicate if the patient had occupation or environmental exposure to hazardous chemicals (e.g., arsenic, chromium, asbestos, haloethers, radon gas, nickel, polycyclic aromatic hydrocarbons, etc.).
5. Please indicate if the patient has any other lung diseases, such as chronic obstructive pulmonary disease (COPD), lung fibrosis, tuberculosis, etc.
6. Please indicate if the patient has a family history of lung cancer and describe the family history.
7. Please list the medications the patient has taken in the past 2 years.
8. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
9. If a tissue biopsy was performed, please provide the findings and the date it was performed.
10. If tumor markers were analyzed, please provide the name of the marker(s) which were found and the date of the analysis.
11. Please provide results from all imaging studies.
12. Please provide results from physical examination.
13. Please provide the patient's pulmonary function test results and the date they were performed.
14. If the patient was hospitalized, please provide discharge report.
15. Please provide any treatments the patient received for the event.
16. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Prostate Cancer

To provide consistency in our due diligence of Tecfidera prostate cancer reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of prostate cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
4. Please indicate if the patient has a history of cancer.
5. Please indicate if the patient has a history of right or left sided heart failure.
6. Please provide any medical history risk factors the patient had for prostate cancer (e.g., family history, breast cancer (BRCA) 1 or BRCA 2 gene mutations, high testosterone levels, high insulin-like growth factor 1 levels, high intake of calcium, high fat diet, etc.).
7. Please list the medications the patient has taken in the past 2 years.
8. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
9. If a tissue biopsy was performed, please provide the findings.
10. Please provide results from all imaging studies.
11. Please provide results from physical examination.
12. Please provide the patient's prostate specific antigen (PSA) level and the date it was taken. Please include baseline values as well as reference ranges for any and all lab tests.
13. If the patient was hospitalized, please provide discharge report.
14. Please provide any treatments the patient received for the event.
15. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Renal Cell Carcinoma

To provide consistency in our due diligence of Tecfidera renal cell carcinoma reports, please ask the follow-up questions below.

1. Please provide any medical history risk factors the patient had for renal cell carcinoma (e.g., family history, polycystic kidney disease, chronic hemodialysis, anemia, tuberous sclerosis, erythrocytosis, obesity, hypertension, etc.).
2. Please provide any available information on the histological type of cancer (e.g., clear cell vs papillary).
3. Please list the medications the patient has taken in the past 2 years.
4. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
5. Please provide the clinical signs and symptoms of the patient and the date at which each sign or symptom began.
6. Please provide the below laboratory results for the patient. Include reference ranges, baseline levels and levels for the treatment and management of the event.
    a. Liver function tests
    b. Renal function tests
    c. Coagulation profile
    d. Complete blood count with differential
    e. Creatinine Clearance (CrCl)
    f. Any other tests related to the diagnosis or management of renal cell carcinoma.
7. Please provide results from urinalysis or state that it was not performed.
8. If a tissue biopsy was performed, please provide the findings.
9. Please provide results from all imaging studies.
10. Please provide results from the physical exam.
11. If the patient was hospitalized, please provide discharge report.
12. Please provide any treatments the patient received for the event.
13. Please provide outcome for event and date of resolution if applicable. If the patient recovered with sequelae, please describe the sequelae.

Tecfidera Small Cell Lung Cancer

To provide consistency in our due diligence of Tecfidera small cell lung cancer reports, please ask the follow-up questions below.

1. Please specify the patient's type, stage, and grade of small cell lung cancer.
2. Did the patient develop lymphopenia while on Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient was exposed to tobacco smoke, how many packs per year they smoke, if they currently smoke, if they are exposed to second-hand smoke, or if they have a remote history of smoking.
4. Please indicate if the patient had occupation or environmental exposure to hazardous chemicals (e.g., arsenic, chromium, asbestos, haloethers, radon gas, nickel, polycyclic aromatic hydrocarbons, etc.).
5. Please indicate if the patient has any other lung diseases, such as chronic obstructive pulmonary disease (COPD), lung fibrosis, tuberculosis, etc.
6. Please indicate if the patient has a family history of lung cancer and describe the family history.
7. Please list the medications the patient has taken in the past 2 years.
8. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
9. If a tissue biopsy was performed, please provide the findings and the date it was performed.
10. If sputum cytology was performed, please provide the findings and the date it was performed.
11. If tumor markers were analyzed, please provide the name of the marker(s) which were found and the date of the analysis.
12. Please provide results from all imaging studies.
13. Please provide results from physical examination.
14. Please provide the patient's pulmonary function test results and the date they were performed. Please include baseline values as well as reference ranges for any and all results.
15. If the patient was hospitalized, please provide discharge report.
16. Please provide any treatments the patient received for the event.
17. Please provide outcome for event and date of resolution if applicable. If the event recovered with sequelae, please describe the sequelae.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

For the important identified risk of progressive multifocal leukoencephalopathy (PML), the Marketing Authorisation Holder distributed a Direct Healthcare Professional Communication in European Union countries by 12 Nov 2020 as an additional risk minimisation measure to inform healthcare professionals about cases of PML in the setting of lymphopenia (mild). The following key elements were included:

- Cases of PML in the setting of mild lymphopenia (lymphocyte count $\geq 0.8 \times 10^9$/L and below the lower limit of normal) have been reported in patients treated with Tecfidera; previously, PML had been confirmed only in the setting of moderate to severe lymphopenia.
- Tecfidera is contraindicated in patients with suspected or confirmed PML.
- Tecfidera should not be initiated in patients with severe lymphopenia (lymphocyte counts $< 0.5 \times 10^9$/L).
- If the lymphocyte count is below the normal range, a thorough assessment of possible causes should be completed before initiating treatment with Tecfidera.
- Tecfidera should be discontinued in patients with severe lymphopenia (lymphocyte counts $< 0.5 \times 10^9$/L) persisting for more than 6 months.
- If a patient develops PML, Tecfidera must be permanently discontinued.
- Advise patients to inform their partner or caregivers about their treatment and symptoms suggestive of PML, since they may notice symptoms of which the patient is not aware.
- Among over 475,000 patients exposed to Tecfidera, 11 cases of PML have been confirmed.
- As currently recommended, all patients should have absolute lymphocyte counts (ALC) measured before initiating treatment and every 3 months thereafter.
- In patients with lymphocyte counts below the lower limit of normal as defined by local laboratory reference range, enhanced vigilance is now recommended and additional factors that may potentially contribute to an increased risk for PML in patients with lymphopenia should be considered. These include:
  - Duration of Tecfidera therapy. Cases of PML have occurred after approximately 1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown.
  - Profound decreases in CD4+ and especially in CD8+ T cell counts.
  - Prior immunosuppressive or immunomodulatory therapy.

- In patients with sustained moderate reductions of absolute lymphocyte counts ≥ 0.5 × 10^9/L and < 0.8 × 10^9/L for more than 6 months, the benefit/risk of Tecfidera treatment should be re-assessed.
- Physicians should evaluate their patients to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML.
- At the first sign or symptom suggestive of PML, Tecfidera should be withheld and appropriate diagnostic evaluations carried out, including determination of JCV DNA in cerebrospinal fluid (CSF) by quantitative polymerase chain reaction (PCR) methodology.
- It is important to note that patients developing PML following recent discontinuation of natalizumab may not present with lymphopenia.