Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR VUMERITY™ (DIROXIMEL FUMARATE)

RMP version number:	3.0
Data lock point for this RMP:	30 Jun 2023
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QPPV name: Jana Hyankova, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

Template Version 4.1

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

Not applicable – No other version of this Vumerity European Union (EU) Risk Management Plan (RMP) is currently under evaluation.

Details of currently approved RMP

Version number:	1.2
Approved with procedures:	EMEA/H/C/005437/II/0005
Date of approval:	27 Oct 2022

Rationale for submitting an updated RMP

This Vumerity EU RMP (Version 3.0) was updated based on results from completed Tecfidera 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 3.0 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	Change to Tecfidera RMP related to completion of Study 109MS402	Updated pregnancy text in Table 2 to be consistent with Tecfidera RMP where applicable.
Part II, Module SIII	Not applicable	Not applicable
Part II, Module SIV	Completion of Study 109MS401	Updated Table 12, titled Discussion of Tecfidera or DRF exclusion criteria not remaining as contraindications for DRF in relation to the assessment of missing information, and Table 13, titled Discussion of DRF 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 Tables 16 and 17 with new numbers, removed tables with country-specific data.
Part II, Module SVI	Not applicable	None

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 information about data collection forms and removed or recategorised 109MS401 information from Section III.2.
Part IV	Not applicable	None
Part V	Based on Study 109MS401 results, the safety concerns were reclassified.	Safety concerns noted above were removed from Tables 25 and 26.
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
AE	adverse event
AEDs	antiepileptic drugs
AESI	adverse event of special interest
ALC	absolute lymphocyte counts
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	area under the concentration-time curve
BID	twice daily
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukaemia
C_{max}	maximum observed concentration
CSR	clinical study report
CYP	cytochrome P450
DILI	drug-induced liver injury
DLP	data lock point
DMF	dimethyl fumarate
DMT	disease-modifying therapy
DR	delayed release
DRF	diroximel fumarate
ECG	electrocardiogram
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FAS	full analysis set
GA	glatiramer acetate
GFR	glomerular filtration rate
GI	gastrointestinal
HAART	highly active antiretroviral therapy
HCP	health care provider

Abbreviation	Definition
hERG	human ether-à-go-go-related gene
HES	2-hydroxyethyl succinimide
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
IC_{50}	concentration resulting in 50% inhibition of response
JCV	John Cunningham virus
LLN	lower limit of normal
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MMF	monomethyl fumarate
MRHD	maximum recommended human dose
MRI	magnetic resonance imaging
MS	multiple sclerosis
NHANES	United States National Health and Nutrition Examination Survey
Nrf2	nuclear factor (erythroid-derived 2)-related factor 2
PASS	post-authorisation safety study
PK	pharmacokinetic(s)
PL	Patient Leaflet
PML	progressive multifocal leukoencephalopathy
PND	postnatal day
PNM	potentially nephrotoxic medication
PT	preferred term
Q	quartile
QoL	quality of life
QTc	QT interval corrected
RHD	recommended human dose
RMP	Risk Management Plan
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SMR	standardised mortality ratio
TCA	tricarboxylic acid
TID	3 times daily
ULN	upper limit of normal
US	United States
WBC	white blood cell

I: PART I: PRODUCT OVERVIEW

Table 1: Product overview

Active substance (INN or common name)	Diroximel fumarate
Pharmacotherapeutic group (ATC Code)	Immunosuppressants, other immunosuppressants (L04AX09)
Marketing Authorisation Holder	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	2
Invented name in the EEA	Vumerity
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Fumarate ester drug product containing the active ingredient DRF. **Mode of action:** DRF and DMF undergo rapid hydrolysis prior to systemic circulation by esterases and are converted to the primary active metabolite, MMF. Controlled clinical studies have identified treatment regimens for DRF and DMF that yield bioequivalent exposure to MMF. Therefore, DRF is assumed to have the same effects on MS pathophysiology and resulting safety profile as DMF. This enables the utilisation of established DMF safety data to further understand the risks associated with DRF and complement the DRF development programme. Nonclinical pharmacology studies conducted suggest that DRF and DMF elicit both direct neuroprotective and anti-inflammatory activities via its action on the Nrf2 antioxidant response pathway. In preclinical studies, DMF significantly reduced macrophage activation and subsequent release of proinflammatory cytokines in response to inflammatory stimuli and demonstrated therapeutic activity in multiple models of in vivo inflammatory injury. In addition, DMF was shown to significantly improve cell viability after oxidative challenge in primary cultures of astrocytes and neurons, suggesting that DMF 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 DMF provided therapeutic benefit in reducing neuronal damage resulting from various types of toxic stimuli. Evidence of the role of Nrf2 in mediating DMF effects was gleaned from models of Nrf2 deficiency. In these studies, the beneficial effects of DMF were abrogated in the absence of Nrf2. DMF has also been shown to upregulate Nrf2-dependent antioxidant genes in participants, confirming clinical pharmacodynamic activity in humans. However, the mechanism by which DRF and DMF exert therapeutic effects in MS is not fully understood.

	Important information about composition: The active drug substance is DRF. Crospovidone promotes the disintegration of the minitablet and allows for release of the drug substance. Microcrystalline cellulose is a binder that aids the minitablet compression process. Nonbovine magnesium stearate is a lubricant used during the minitablet compression process. Colloidal silicon dioxide aids flow during compression and is a suspending agent during coating. Methacrylic acid and ethyl acrylate copolymer provide the DR profile. Triethyl citrate is a plasticiser, and talc is an antitack agent, both required to allow application of the DR coating.
Hyperlink to the Product Information	Vumerity EU SmPC
Indication in the EEA	**Current:** Vumerity is indicated for the treatment of adult patients with RRMS.
Dosage in the EEA	**Current (if applicable):** The starting dosage is 231 mg BID orally. After 7 days, the dosage should be increased to the recommended maintenance dose of 462 mg (administered as two 231 mg capsules) BID orally. Temporary dose reductions to 231 mg BID may be considered for individuals who do not tolerate the maintenance dose. Within 1 month, the recommended dosage of 462 mg BID should be resumed.
Pharmaceutical form and strengths	**Current:** *Form:* gastro-resistant hard capsule *Strength:* 231 mg The capsules contain enteric-coated minitablets designed to provide a DR gastro-resistant profile. The coated minitablets contain the drug substance DRF and are encapsulated within a white, 2-piece, HPMC capsule shell. The capsule body has the following text printed radially in black ink: “DRF 231 mg.”
Is/will the product be subject to additional monitoring in the EU?	No

II: PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATIONS

SI.1 Epidemiology of multiple sclerosis

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 to 2.5 million [Compston and Coles 2002; Reich 2018; Wallin 2019]. The disease is unevenly distributed throughout the world, with age-standardised prevalence varying from < 60 per 100,000 cases in Asia and Latin America to > 120 cases per 100,000 in North America and some northern European countries [GBD 2016 Multiple Sclerosis Collaborators 2019]. In a recent population-based study utilizing administrative health claims databases, the 2010 prevalence in the US was estimated to be 309.2 per 100,000 cases, representing approximately 800,000 cases of MS in the US as of 2010 [Wallin 2019]. The prevalence was estimated in 2017 to range from 337.9 to 362.6 per 100,000. European country-specific prevalence estimates have been reported to range from <20 to 289 per 100,000 persons, with estimates between 11 to 383 per 100,000 for women and 10 to 167 per 100,000 for men [Kingwell 2015; Petersen 2014; Pugliatti 2008; Pugliatti 2006].

The worldwide incidence of MS in 2016 was estimated to be 0.9 per 100,000 [Vos 2017; Clarivate]. 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) [Kingwell 2013]. 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 year 2000) reported higher MS prevalence and incidence estimates. The annual incidence rate of MS in Europe is estimated to range from 0.7 to 12.2 per 100,000 persons, with country-specific variations [Dean 2002; Kingwell 2013; Nicoletti 2005; Pugliatti 2006].

Demographics of the population in the authorised indication and risk factors for the disease

The mean age of MS diagnosis is 30 years old, with twice as many women affected as men [Reich 2018; Wallin 2019].

MS is an inflammatory disease of the brain and spinal cord characterized 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 etiologies of the disease [Ramagopalan 2010].

Main existing treatment options

Current therapies for MS generally fall within the following categories: treatment for acute relapses, symptomatic therapies, and DMTs. In addition, several antineoplastic and immunosuppressant agents 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 usually take the form of a clinically isolated syndrome 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 25 years, approximately 70% of individuals with RRMS will eventually enter a phase of progressive neurological decline, with or without superimposed relapses, known as secondary progressive MS. In addition, approximately 10% of patients with MS will have progression from the onset of the disease (primary progressive MS), 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, QoL, 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 MS patients diagnosed 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, a substantial population of patients with relapsing MS remains untreated for the 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.

Important comorbidities found in the target population

Pulmonary morbidity has been described in MS, especially among patients with advanced disease. Respiratory muscle function is affected by disease severity [Gosselink 1999]. Even among ambulatory patients, respiratory muscle fatigue is noted in later stages of MS [Bosnak-Guclu 2012; Mutluay 2005]. MS patients appear to have an increased history of respiratory tract infections prior to the onset of illness [Marrie 2000]. A crude estimate, based on the Danish Multiple Sclerosis Registry results, suggests that the infection rate in MS patients may be at least

2 times greater than that in the general population [Kingwell 2020]. A large electronic medical record study evaluated the prevalence of asthma among persons with MS (n=141,800) compared with persons without MS (n=56,416,790) and observed that the prevalence was significantly greater in those with MS (prevalence rate 2.97, 95% confidence interval 2.96 to 2.97) [Hill 2019]. Even after adjusting for age and sex, asthma was 3 times more common in the MS cohort compared with the controls. Complications from a respiratory illness are also a common cause of death among patients with MS. A cohort study that used prospectively collected data from the United Kingdom General Practice Research Database found that pneumonia was the second most recorded cause of death across all age groups [Jick 2014]. Utilizing patient records from the Manitoba Vital Statistics Death Database and Manitoba provincial health department, Marrie and colleagues found respiratory disease to be one of the most common causes of death for MS patients [Marrie 2015].

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; de Sèze 2007] and are estimated to be present in 64% to 68% of patients with MS [Mahajan 2010]. 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 [Phé 2016]. 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.

A 2008 systematic review found the point prevalence of pain in persons with MS to be nearly 50% and about 75% of persons with MS reported having pain within 1 month of assessment [O'Connor 2008]. Nearly 20% of patients experienced pain at disease onset. There are several types of pain associated with MS, such as central neuropathic pain, musculoskeletal pain, intermittent central neuropathic pain, and mixed neuropathic and non-neuropathic pain. Nearly 50% of persons with MS are reported to have central neuropathic pain, which makes it the most common pain syndrome among this population [Solaro 2013]. An estimated 50% of patients with MS 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. Depending on the type of pain, treatment options include AEDs, tricyclic antidepressants, and standard pain medication. Pain related to spasticity may improve with physiotherapy but can also be treated with baclofen, tizanidine, or AEDs. Severe spasticity may be treated with botulinum toxin or intrathecal baclofen [Pöllmann and Feneberg 2008].

Depression has been frequently described in patients with MS, with a lifetime risk of about 50% [Sadovnick 1996]. A Swedish population-based study of depressive symptoms in persons with MS showed that 19% (28/149) of the patients were depressed [Gottberg 2006]. Similarly, a Canadian study that utilized data from a large-scale national survey found that 15.7% (n=322) of persons with MS had major depression [Patten 2003]. A meta-analysis estimated the prevalence of depressive symptoms among persons with MS to be 17% (n=87,756) compared with the 6% estimated for the general public [Boeschoten 2017]. A large multi-center, cross-sectional study (n=1011) estimated that 30% of persons with MS had depressive symptoms [Solaro 2016]. Through additional multi-variate analyses, Solaro and colleagues found that Expanded Disability

Status Scale and disease course are the most significant risk factors associated with depressive symptoms.

In addition to the higher prevalence of depression among persons with MS, there is an increased risk of suicidal intent [Dickstein 2015]. A large multi-registry study of nearly 30,000 persons with MS in Sweden concluded that persons with MS have an elevated risk for attempted suicide and completed suicide compared with the general public [Brenner 2016]. In that study, the incidence of attempted suicide and completed suicide was 116.53 and 30.31 per 100,000 person-years, respectively. The increased risk of suicide among this population was further confirmed in a literature review along evidence of geographical and ethnoracial variation [Scalfari 2013]. A study of 3823 patients with MS seen at the Cleveland Clinic Epilepsy and Multiple Sclerosis Centers found that 14.7% (n=562) had “thoughts of death or self-harm at least once” [Dickstein 2015]. A multi-registry study of Danish persons with MS also found that the suicide risk among persons with MS was more than twice that of the general population (SMR = 2.12) and that the increased risk was particularly high during the first year after MS diagnosis (SMR = 3.15) [Brønnum-Hansen 2005].

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety programme of DRF included safety pharmacology, repeat-dose general toxicology, genotoxicity, carcinogenicity, developmental and reproductive toxicity, local tolerability, juvenile toxicity, and impurity qualification studies conducted in compliance with GLP regulations.

The findings noted in nonclinical safety studies with DRF (e.g., QTc increases in monkeys; renal, heart, bone, and testicular effects in mice, rats, and/or monkeys) present a low risk to human safety due to lack of correlates in humans with either DRF or DMF, lack of human relevance of the target (e.g., mucosal hyperplasia in nonglandular stomach of rodents; testicular Leydig cell adenomas in rats), or lack of association with doses higher than the maximum recommended human dose (MRHD).

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

Table 2: Key safety findings from nonclinical studies in DRF and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity studies	
In general toxicology studies evaluating DRF, target organ effects were observed in the kidney, GI tract, heart, bone, and testes. **Nephrotoxicity** Kidney toxicity was observed in mice, rats, and monkeys. The findings in wild-type littermates of *ras*H2 transgenic mice in the 28-day study were limited to increased kidney weights and minimal-to-mild hypertrophy of tubular epithelial cells in the renal cortex of female mice. In subchronic and chronic toxicology studies in rats and monkeys, kidney findings consisted of higher kidney weights; changes in clinical pathology parameters indicative of renal functional changes (changes in urine volume and specific gravity); as well as histopathological tubular degeneration/necrosis with regeneration, tubular hypertrophy, and/or interstitial fibrosis. Changes in biomarkers of kidney injury were also observed in the chronic toxicology studies in rats and monkeys. These kidney findings were partially or fully reversible. Histological changes in the kidney occurred in both rats and monkeys in shorter duration studies (e.g., 2 weeks) and were with limited severity, no functional clinical pathology correlates, and reversible. Adverse	**Nephrotoxicity** In the human clinical trials, special urine markers of renal damage were investigated. To date, study participants treated with DRF or DMF did not have a higher risk of renal or urinary events, suggesting that findings in animals do not translate to humans, although proteinuria is commonly observed at therapeutic doses. **GI Toxicity** GI effects were observed across animal studies in the range of clinical exposures. Findings in the nonglandular stomach of rats and mice may not have clinical relevance due to anatomical differences in the stomach between the human and rodent [Kararli 1995]. GI-related clinical signs observed in monkeys could be clinically relevant. GI events are known ADRs for both DRF and DMF. **Cardiovascular Toxicity** Cardiovascular effects were observed only in rats at doses exceeding the MRHD. No clinical correlates in humans have been observed during DRF or DMF use, suggesting they are not relevant at the therapeutic dose in humans.

SAFETY FINDING	RELEVANCE TO HUMAN USE
renal effects occurred in the chronic toxicology studies in monkeys at MMF/HES exposure (AUC) approximately 3/1× the respective clinical exposure at the MRHD of DRF and in rats at ≥ 1/1× the respective clinical exposure. Similar kidney effects were also observed in animal studies for DMF. **GI Toxicity** GI toxicity was observed in mice, rats, and monkeys. Decreased body and food consumption were observed in wild-type littermates of *ras*H2 transgenic mice and rats, with correlating histological changes of mucosal hyperplasia in the nonglandular stomach. In rats, mucosal hyperplasia was also observed in duodenum, with increased stomach weight. The GI findings in rodents were reversible and were generally not adverse. In monkeys, the GI-related clinical signs were observed in the high-dose group. The monkeys in the high-dose group in the chronic toxicology study only displayed salivation, while emesis, inappetence, and thin body condition/lower body weight were observed in the subchronic and 2-week studies. In the range-finding study (single dose and 5-day dosing), monkeys in the high-dose group and some monkeys in the mid-dose group showed emesis and watery faeces, with histological change of inflammation and glandular dilatation in the stomach. No histological changes were observed in 2-week, subchronic, and chronic monkey studies. GI effects occurred in animal studies at MMF/HES exposure (AUC) ≥ 2/2× the respective clinical exposure at the MRHD of DRF. Similar GI effects were also observed in animal studies for DMF. **Cardiovascular Toxicity** Three male rats in the high-dose group in the subchronic toxicology study were euthanised in moribund condition during DRF treatment due to cardiac inflammation/necrosis. These histological findings in the heart were associated with MMF/HES exposure (AUC) of approximately 4.3/4× the respective clinical exposure at the MRHD of DRF. No histopathological changes in the heart were observed in any other animals in the subchronic rat study or in any other general toxicology studies in mice, rats, and monkeys.	**Bone Toxicity** Physeal dysplasia in monkeys might be related to antiangiogenic effects or the potential impact of fumarate esters on bone homeostasis and was observed only at doses exceeding the MRHD. No clinical correlates in humans have been observed in DRF or DMF, suggesting they are not relevant at the therapeutic dose in humans. **Testicular Toxicity** DRF did not affect male fertility in rats, and the testicular effects were observed in mice at doses exceeding the MRHD and, therefore, were considered to be of limited concern for human risk at the therapeutic dose. No clinical correlations in humans have been observed for DRF or DMF, suggesting they are not relevant at therapeutic doses in humans.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Bone Toxicity The monkeys in the high-dose group in the subchronic toxicology study showed physeal dysplasia of the proximal and distal femur and the proximal tibia at MMF/HES exposure (AUC) of ≥ 15/4× the clinical exposure at the MRHD of DRF. No physeal changes were observed in monkey after a 28-day drug-free recovery period. **Testicular Toxicity** In wild-type littermates of *ras*H2 transgenic mice of the 28-day study, minimal degeneration was observed in the male mice in the high-dose group, which included an increased incidence of giant spermatids and a slight decrease in spermatids in the tubular epithelium, correlated with decreases in the testes weight. The findings in the testes were considered adverse. Additionally, a nonadverse increase in cellular debris in the tubules of the epididymides was observed in the mice of both mid and high dose groups. The adverse testicular findings in mice were associated with MMF/HES exposure (AUC) of 15/6× the clinical exposure at the MRHD of DRF. No DRF-related effects on male mating, fertility, and copulation indices or spermatogenesis were observed in the male fertility study conducted in rats at MMF/HES exposure (AUC) up to 7/4× the clinical exposure at the MRHD of DRF. Similar testicular effects were also observed in animal studies for DMF.	
Reproductive/developmental toxicity	
Developmental and reproductive toxicity studies evaluating the effects of DRF on fertility indices showed no adverse findings at the highest doses, which yielded MMF and HES exposures (AUC) that were approximately 7× and 4×, respectively, clinical exposures in male rats (AT-5108-19), respectively, at the MRHD of DRF and approximately 9× and 4× clinical exposures, respectively, in female rats (AT-5108-20). Evaluation of developmental toxicity in rabbits (AT-5108-22) indicated that DRF was associated with foetal skeletal malformations (vertebral central anomaly and severely malaligned sternebra[e]) at MMF and HES exposures (AUC) that were approximately 6× and 2× clinical exposures, respectively, at the MRHD of DRF;	In the context of nonclinical studies, DRF did not affect male and female fertility at dose levels significantly higher than the MRHD. DRF was not found to be teratogenic at clinically relevant doses. Foetal skeletal effects observed in the embryofoetal development studies and effects on the pup weight in the pre- and postnatal development study were observed at dose levels greater than the MRHD, which was considered to be related to the active metabolite MMF, not the inactive metabolite HES, with unknown relevance to humans at the therapeutic dose. Similar developmental findings have been reported for DMF.

SAFETY FINDING	RELEVANCE TO HUMAN USE
the incidence of skeletal malformations at these exposure margins was within or only slightly above the historical control range for the test facility (AT-5108-22). At higher AUC exposures of MMF and HES (i.e., approximately 13× and 4× clinical exposures, respectively), increased postimplantation loss, with a corresponding lower mean litter proportion of viable foetuses, and developmental variations (13th full rib[s]) were noted in addition to the skeletal malformations. The No-Observed-Adverse-Effect-Level (NOAEL) was associated with MMF and HES AUC that were approximately 2× and 0.7× clinical exposures, respectively, at the MRHD of DRF. In the rat embryo-foetal development study (AT-5108-21), DRF was associated with lower foetal body weights and foetal skeletal ossification variations at MMF and HES exposures that were approximately 10× and 5× clinical exposures, respectively. The NOAEL was associated with MMF and HES AUC that were approximately 2× clinical exposures at the MRHD of DRF. In the pre- and postnatal development study in rats (AT-5108-30), DRF-related decreases in pup birth weights and body weights/weight gains during the preweaning period were noted at the high dose of 400 mg/kg; no changes in postweaning development, behaviour, or reproductive function were observed at any dose level. At 400 mg/kg, AUC exposures of MMF and HES were approximately 10× and 3× clinical exposures, respectively. The NOAEL was associated with MMF and HES AUC that were approximately 3× and equal to clinical exposures, respectively, at the MRHD of DRF. In juvenile rats, oral DRF administration from PND 25 through PND 63 produced no effects on neurobehaviour, sperm motility/counts/morphology, oestrous cycle and cycle length, or reproductive performance and outcome. Kidney, GI tract (nonglandular stomach), and bone were also the target organs, with the effects considered adverse being observed at MMF and HES AUC exposure that was at least 6× and 5× the respective clinical exposure. Later vaginal opening attainment was seen in females at the same exposure multiples	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; the effect of DRF on pregnancy outcome is unknown and being studied. There were no reports involving lactating female participants. In juvenile animals, DRF did not affect neurobehaviour and reproductive parameters at dose levels significantly higher than the MHRD. Findings in the kidney and GI tract are similar to those observed in adult animals; the human relevance of these findings has been described in the general toxicology section above. Delayed growth (lower body weight), likely secondary to the GI events, played a role in the delayed attainment of vaginal opening in females. The densitometry changes in the bone might be secondary to lower body weight and decreased food consumption associated with the GI effects, but a direct effect of fumarates on bone development cannot be excluded. These findings were observed at ≥ 1.4× MMF AUC and at ≥ 1.5× HES AUC at the MRHD but are of limited relevance to adult humans at therapeutic doses. The relevance for paediatric patients is unknown.

SAFETY FINDING	RELEVANCE TO HUMAN USE
due to growth delay (lower body weight), which was not an effect on sexual maturation. Similar reproductive and developmental findings have been reported for DMF.	
SAFETY FINDING	**RELEVANCE TO HUMAN USE**
Genotoxicity	
Results from in vitro genotoxicity studies indicated that DRF was not mutagenic (AT-5108-11) but was clastogenic in the presence or absence of a hepatic metabolic activation system (AT-5108-12). In the in vivo micronucleus/Comet assay (AT-5108-23), DRF was not clastogenic and did not induce DNA damage in duodenal or liver cells at MMF and HES exposures (AUC) up to 33× and 8× clinical exposures, respectively, at the MRHD of DRF.	Even though DRF was positive for clastogenicity in vitro, it was negative for mutagenicity in the AMES assay and was also negative in 2 in vivo assays (micronucleus and comet) in rats, suggesting low risk to humans for genotoxicity potential.
Carcinogenicity	
DRF was evaluated for carcinogenicity in 26-week *ras*H2 transgenic mouse (AT-5108-31) and 2-year rat (AT-5108-26) studies. In the mouse study, no DRF-related mortality or increased incidence of tumours occurred at any dose level. Systemic exposures (AUC) of MMF and HES at the high dose (300 mg/kg) in male mice were approximately 3× and 1× clinical exposures, respectively, at the MRHD of DRF; at the high dose in females (1000 mg/kg), MMF and HES exposures were approximately 13× and 4× clinical exposures, respectively. In the 2-year rat study, there was a DRF-related increase in mortality in high-dose males (150 mg/kg) that was attributed to non-neoplastic renal lesions; in addition, an increased incidence of neoplastic Leydig cell adenomas in the testes was observed at this dose and considered related to DRF treatment. The AUC exposures of MMF and HES at 150 mg/kg were approximately 2× clinical exposures at the MRHD of DRF. Leydig cell adenomas have also been reported in male rats after treatment with DMF.	Leydig cell tumour mode of action is known to occur in the rat and likely not applicable to humans [Steinbach 2015].
Safety pharmacology	
<u>Cardiovascular system:</u> Neither DRF nor its major inactive metabolite HES inhibited hERG channel activity in vitro (IC_{50} > 300 μM). In addition, MMF, which is the	The hERG results for DRF, HES, and MMF suggest a low potential for increased QTc in humans at the MRHD of DRF.

SAFETY FINDING	RELEVANCE TO HUMAN USE
major active metabolite of DRF, does not inhibit hERG channel activity (IC_{50} > 1500 μM). When the IC_{50} values were expressed relative to respective clinical C_{max} values at the MRHD of DRF, the exposure multiples approached infinity for DRF and were approximately 4× and 120× for HES and MMF, respectively. In the single-dose cardiovascular safety pharmacology study in monkeys, small, statistically significant increases in QTc occurred at MMF and HES exposures (C_{max}/AUC basis) that were ≥ 30× and ≥ 7× of respective clinical exposures at the MRHD of DRF. In general toxicology studies conducted in monkeys, QTc was evaluated following repeated administration of DRF. In the 2-week study (AT-5108-07), small, statistically significant increases in QTc were noted in high-dose (400 mg/kg) females, consistent with results from the cardiovascular safety pharmacology study at the same dose level; MMF and HES exposures (C_{max}/AUC) in AT-5108-07 were ≥ 32× and ≥ 5×, respectively, corresponding clinical exposures at the MRHD of DRF. In subsequent 91-day (AT-5108-14) and 39-week (AT-5108-16) monkey studies, no changes in QTc were observed at any dose level; C_{max}/AUC exposures for MMF were ≥ 15× and ≥ 9× clinical exposures, respectively, and for HES were ≥ 4× and ≥ 3× clinical exposures, respectively.	Small increases in QTc were only observed in monkeys on a considerably higher DRF dose than the MRHD. Analysis of completed clinical studies, including the thorough QT study, indicated that DRF treatment did not have a clinically relevant effect on QTc in humans.
Respiratory and neurobehavioural: There were no DRF-related effects on respiratory or neurobehavioural parameters in rats at doses up to 600 mg/kg, which was associated with C_{max} values that were 29× and 14× and AUC values 14× and 8× for MMF and HES, respectively, relative to the MRHD of DRF.	Not applicable.
Mechanistic studies	
DRF was compared with DMF and MMF in the Lewis rat experimental autoimmune encephalomyelitis model of MS using the same MMF AUC exposure levels. Results indicated that the administration of DRF elicited a significant reduction in disease severity that was similar to the reduction in disease severity observed with administration of MMF and DMF treatment.	In humans, DRF and DMF undergo hydrolysis to produce the active metabolite MMF; DRF undergoes additional hydrolysis to yield the inactive metabolite HES. In patients with MS at steady state, on average, HES had a C_{max} 6.6× higher and an AUC 21× higher than that of MMF. These ratios are similar to those observed in nonclinical studies, and the AUC exposure of HES in this nonclinical study was 3× greater than

SAFETY FINDING	RELEVANCE TO HUMAN USE
Furthermore, HES had no effect on MMF at a 12× greater AUC exposure ratio of HES to MMF.	the exposure levels described in clinical trials; therefore, HES is not expected to interfere with MMF therapeutic activity clinically.
The potential for HES to elicit pharmacological activity in vitro was evaluated at a concentration of 300 µM in a Cerep panel. Inhibition (or stimulation for assays performed based on basal conditions) levels greater than 50% were considered to represent a significant effect. HES at a concentration of 300 µM did not significantly inhibit binding or activity in any of the receptor-, transporter-, or enzyme-binding/inhibition assays. In vitro experiments were performed to evaluate whether HES interferes with cellular responses (protein biomarkers and functional activities) that are induced by MMF. Results from the in vitro platform (BioMAP Diversity PLUS panel of human primary cell systems and clinically relevant biomarker endpoints) showed that HES had no meaningful effect on cellular activity alone or on the activity of MMF in a range of cell types (e.g., lymphocytes, monocytes, fibroblasts, and endothelial, epithelial, and smooth muscle cells) that model aspects of vascular, immune, inflammation, lung, skin, and tissue biology.	As observed from in vivo nonclinical studies, results from these in vitro studies imply that HES is not expected to interfere with MMF therapeutic activity clinically.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

The evaluation of safety and the pharmacovigilance plan presented in this EU RMP focuses primarily upon the review of integrated data from the following Phase 3 studies:

- Two Phase 3 studies in participants with RRMS:
  - One 5-week, double-blind Phase 3 study comparing the GI tolerability of DRF and Tecfidera (Study ALK8700-A302).
  - One 96-week, open-label study to evaluate the long-term safety and tolerability of ALKS 8700 (Study ALK8700-A301).

Safety data relevant to DRF from the following Tecfidera studies are also included:

- One Phase 2 placebo-controlled dose-ranging study (Study C-1900; Parts 1 and 2).
- Three Phase 3 studies; 2 placebo-controlled (Studies 109MS301 and 109MS302) and a dose-blind long-term safety extension study (Study 109MS303).
- One multicentre, global, observational study to collect information on safety and drug utilisation of Tecfidera when used in routine medical practice (Study 109MS401).

Data from 1071 participants were included in the pooled safety dataset for DRF (Studies ALK8700-302 and ALK8700-A301). In the tables, a month is 28 days, and 1 participant-year is 365.25 days. Data are final as of 11 Nov 2021 (the date of last patient out of Study ALK8700-A301). Exposure data (Table 3), stratified by age and sex/gender (Table 4), dose (Table 5), and racial group (Table 6) are presented.

Table 3: Exposure to DRF by Duration

Duration of exposure	Number of participants n (%)	Person-years
MS[a]		
> 0 to < 1 month	26 (2.4)	0.95
1 month to < 3 months	33 (3.1)	4.60
3 months to < 6 months	39 (3.6)	13.18
6 months to < 9 months	25 (2.3)	13.83
9 months to < 12 months	33 (3.1)	25.11
12 months to < 18 months	48 (4.5)	53.17
18 months to < 24 months	177 (16.5)	310.35
≥ 24 months	690 (64.4)	1292.90
Total	1071 (100)	1714.10

Table 4: Exposure to DRF by Age Group and Sex/Gender

Age group	Number of participants			Person-years		
	Male n (%)	Female n (%)	Total n (%)	Male	Female	Total
< 18 years	0	0	0	0	0	0
18 to 55 years	259 (87.2)	673 (87.0)	932 (87.0)	432.30	1062.63	1494.93
56 to 65 years	38 (12.8)	101 (13.0)	139 (13.0)	62.69	156.47	219.17
> 65 years	0	0	0	0	0	0
Not reported	0	0	0	0	0	0
Total	297 (100)	774 (100)	1071 (100)	494.99	1219.11	1714.10

Person-years were rounded to 2 decimal places.

Table 5: Exposure to DRF by Dose

Dose of exposure	Number of participants n (%)	Person-years
Delayed Release 462 mg	1071 (100)	1714.10
Total	1071 (100)	1714.10

Table 6: Exposure to DRF by Racial Group

Racial group	Number of participants n (%)	Person-years
White	985 (92.0)	1600.32
Black or African American	73 (6.8)	93.65
Asian	5 (0.5)	6.13
Other	7 (0.7)	12.92
Native Hawaiian or Other Pacific Islander	1 (< 0.1)	1.07
Total	1071 (100)	1714.10

For the analysis of relevant information from Tecfidera studies, data from 4 pivotal studies have been integrated to comprise the placebo-controlled and long-term experience with Tecfidera in MS. The integrated analysis included data from the Phase 2 placebo-controlled dose-ranging study (Study C-1900), the Phase 3 placebo-controlled studies (Studies 109MS301 and 109MS302), and the Phase 3 dose-blind long-term safety extension study (Study 109MS303).

For the indication of MS, 2513 patients were included in the Tecfidera primary pooled safety dataset. Exposure data (Table 7) stratified by age and sex/gender (Table 8), dose (Table 9), and racial group (Table 10) are presented.

Table 7: Exposure to Tecfidera by Duration (Integrated MS Studies[1])

Duration of exposure	Number of participants	Person-years[2]
At least 1 dose	2513	11318.02
Cumulative at least 12 weeks	2221	11294.34
Cumulative at least 48 weeks (1 year)	1872	11086.38
Cumulative at least 72 weeks	1706	10915.13
Cumulative at least 96 weeks (2 years)	1604	10748.16
Cumulative at least 120 weeks	1435	10418.33
Cumulative at least 144 weeks (3 years)	1390	10306.23
Cumulative at least 168 weeks	1343	10168.45
Cumulative at least 192 weeks (4 years)	1304	10033.85
Cumulative at least 216 weeks	1212	9682.90
Cumulative at least 240 weeks (5 years)	1169	9493.01
Cumulative at least 264 weeks	1105	9188.52
Cumulative at least 288 weeks (6 years)	1065	8976.88
Cumulative at least 360 weeks	899	7949.60
Cumulative at least 384 weeks	813	7329.07
Cumulative at least 408 weeks	671	6260.56
Cumulative at least 432 weeks (9 years)	576	5503.39
Cumulative at least 456 weeks	492	4790.81
Cumulative at least 480 weeks (10 years)	426	4196.22
Cumulative at least 504 weeks	258	2618.76
Cumulative at least 528 weeks (11 years)	135	1412.27
Cumulative at least 552 weeks	47	505.95
Cumulative at least 576 weeks (12 years)	8	88.75

[1]Integrated MS studies include pooled cumulative data from Phase 2 placebo-controlled dose-ranging study (Study C-1900), Parts 1 and 2, and Phase 3 placebo-controlled studies (Studies 109MS301 and 109MS302) and the long-term safety extension study (Study 109MS303).
[2]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 8: Exposure to Tecfidera by Age Group and Sex/Gender (Integrated MS Studies[1])

	Male		Female	
Age group (in years)	**Number of Participants**	**Person-years[2]**	**Number of Participants**	**Person-years[2]**
<18	0	0	0	0
18-55	747	3504.58	1748	7560.19
56-65	2	53.96	16	199.29
>65	0	0	0	0
Total	749	3558.54	1764	7759.48

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

Table 9: Exposure to Tecfidera by Dose (Integrated MS Studies[1])

Duration of exposure	**Number of participants**	**Person-years[2]**
Tecfidera lower doses	128	105.63
Tecfidera 240 mg BID (480 mg daily)	1136	5638.86
Tecfidera 240 mg TID (720 mg daily)	1249	5573.52
Total	2513	11,318.02

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

Table 10: Exposure to Tecfidera by Ethnicity/Race (Integrated MS Studies[1])

Racial group	**Number of participants**	**Person-years[2]**
Asian	197	639.52
Black	38	148.29
White	1756	5040.25
Other	92	380.40
Unknown	430	5109.55
Total	2513	11,318.02

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

[2]Total number of person-years exposed to study treatment is calculated as the sum of number of days exposed to study treatment/365.25 and rounded to 2 decimal places.

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

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

The DRF clinical development programme has employed specific exclusion criteria that were primarily related to the evaluation of safety (to protect trial participants from potential risks associated with investigational product administration; Studies ALK8700-A302 and ALK8700-A301). Within these pivotal studies, additional efficacy analyses were conducted, and specific exclusion criteria were employed to ensure that the appropriate target disease was studied.

When evaluating the impact of these exclusion criteria in relation to the impact on the safety of patients receiving treatment with DRF in the postmarketing setting, key exclusion criteria pertaining to safety from DRF pivotal studies are addressed by the "Contraindications" and "Special warnings and precautions for use" sections of the DRF SmPC. Relevant data from Tecfidera pivotal studies and postmarketing experience are present within Table 11, Table 12, and Table 13 given the bioequivalence of the common active metabolite, MMF, between DRF and Tecfidera. Therefore, DRF is assumed to have the same effects on MS pathophysiology and the same resulting safety profile as Tecfidera. This enables the utilisation of established Tecfidera safety data to further understand the risks associated with DRF and complement the DRF development programme.

Exclusion criteria from these pivotal studies that are considered as contraindications in the DRF SmPC and a rationale for not being considered as missing information are discussed in Table 11.

Table 11: Exclusion criteria that remain as contraindications for DRF 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 DRF.	Avoidance of serious hypersensitivity reactions.	No	The SmPC contraindicates the use of DRF in patients with hypersensitivity to the active substance or to any of the excipients or other fumaric acid esters (as listed in the SmPC). 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 DRF and Tecfidera studies that do not remain as contraindications for use, and the appropriate justifications in relation to their relevance to be considered as missing information so that participants are not excluded for reasons of contraindication are presented in Table 12 for DRF and Tecfidera and in Table 13 for DRF only.

Table 12: Discussion of Tecfidera or DRF exclusion criteria not remaining as contraindications for DRF in relation to the assessment of missing information

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
Tecfidera: Participants under the age of 18 years or over the age of 55 years, inclusive, at the time of informed consent DRF: Participants under the age of 18 years or over the age of 65 years at Screening, inclusive, at the time of informed consent.	Standard age criteria for a pivotal efficacy trial in MS used for Tecfidera studies. Broader age range used for DRF studies due to study-specific objectives.	No	As DRF is indicated only in patients aged 18 years and over, exposure in the pediatric population is not considered missing information. A review of postmarketing Tecfidera safety data in MS participants 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 risk-benefit assessment of Tecfidera. Data from Study 109MS401 confirmed these findings. In addition, Study ALK8700-A301, which enrolled participants older than 55 years, addressed the safety profile of Vumerity in participants up to 65 years of age and found no difference in the safety profile between older and younger patients. Therefore, the safety in participants > 65 years of age is not considered an area of missing information.
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 participants enrolled in clinical studies to ensure completeness of data collection, and there is no evidence to suggest that the use of DRF and Tecfidera in participants with a more severe disease leads to a specific safety concern or a different outcome to previously identified risks.

Exclusion 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 the entire study period and to avoid disease confounding.	No, however, "Malignancies" are an important potential risk.	In Study 109MS303, participants received Tecfidera for up to 12 years (including the parent studies) and the overall incidence of malignancy was low (3%) and without any specific malignancy disproportionately represented. The incidence rate of malignancy, excluding basal cell carcinoma and squamous cell carcinoma, was 397.77 per 100,000 person-years. The background rate of malignancy in the general US population is 442.0 per 100,000 person-years. The incidence rate in the EU population is 268.6 per 100,000 person-years (age-standardised to the world population). Postmarketing data also do not provide evidence of an association between malignancies and Tecfidera, consistent with what was found in the clinical development programme. Since immunomodulatory therapies have effects on the immune system, they may influence the body's capacity for tumour surveillance. Thus, there is a theoretical risk that the incidence of malignancies may increase with longer durations of treatment with DRF. Consequently, the development of malignancies is considered to be an important potential risk for Vumerity, rather than missing information.

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
History of clinically significant disease, e.g., cardiovascular, pulmonary, GI, dermatologic, psychiatric, neurologic (other than MS), and/or other major disease.	To enable meaningful safety and efficacy evaluation during the entire study period and to avoid disease confounding.	No	Based on understanding of the pharmacology of DRF and DMF, plus the postmarketing utilisation of Tecfidera, the safety profile in participants with endocrinologic, immunologic, metabolic, cardiovascular, pulmonary, dermatologic, psychiatric, or other neurologic disease is not expected to be different from that in participants without such a disease burden, and therefore, exposure in these participants 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. Participants with severe active GI disease were not included in the preauthorisation clinical development programme for Tecfidera or the clinical development programme for DRF. Study ALK8700-A302 was a formal study of GI tolerability of Tecfidera and DRF, and participants with prior GI disease were excluded to avoid a confounding data set. The rollover study (Study ALK8700-A301) continued with this exclusion criterion to ensure that the population of De Novo and Rollover participants remained similar. However, Study 109MS401 in patients taking Tecfidera 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.

Exclusion 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 or DRF.	No	These exclusion criteria are relevant only to participants enrolled in clinical studies to allow for homogeneous data collection and subsequent meaningful data interpretation and are included in part to protect the study site staff involved in blood sampling of trial participants. There is no evidence to suggest that the use of DRF or in participants with controlled hepatitis B, hepatitis C, or HIV infection results in a specific safety concern or a different outcome to previously identified risks.
Elevated liver transaminases (ALT, AST, or gamma-glutamyl transferase 2× ULN).	Possible risk of hepatic injury due to known effect of Tecfidera or DRF on transaminases; to avoid confounding the safety assessment of Tecfidera or DRF.	No	As DMF, DRF, and MMF are metabolised by extrahepatic esterases, without the involvement of the CYP system, a formal study of PK parameters in participants with hepatic impairment was not performed. Given this mechanism of clearance, no effects or dose adjustments are anticipated. 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.The results are also relevant for DRF.

Exclusion 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 was seen during clinical development.	Yes, in relation to the following area of missing information: Safety profile in participants with moderate-to-severe renal impairment.	After a single dose of DRF to healthy participants, approximately 60% of the total administered dose is recovered as the inactive metabolite HES in the urine. DRF undergoes hydrolysis to the inactive metabolite HES, which is 100% renally excreted. In a single-dose study of DRF in participants with mild-to-severe renal impairment, the degree of renal impairment had no effect on exposure to MMF. Furthermore, nonclinical studies have shown that HES did not impact the biological function of MMF across a range of platforms (Table 2). Study ALK8700-A301 showed that, after repeated dosing with DRF, the safety profile in participants with RRMS and mild renal impairment was not different from that in those without renal impairment. The same results were observed in Study 109MS303 (with Tecfidera). 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 or Vumerity, this population is considered an area of missing information.

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
Reduced WBC counts (leukocytes < 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 SmPC for DRF contains guidance on monitoring blood counts and treatment interruption, whilst noting that DRF and Tecfidera have not been studied in participants with pre-existing low lymphocyte counts and advising caution when treating these participants.
Prior treatment (within 6 months) with specific disease-modifying agents or immunosuppressants.	To avoid confounding the assessment of safety and efficacy of DRF or Tecfidera.	No	These exclusion criteria are relevant only to participants enrolled in clinical studies to allow for homogeneous data collection and subsequent meaningful data interpretation.
If female, pregnant or planning pregnancy.	Animal studies have shown reproductive toxicity at DRF and Tecfidera doses exceeding the recommended dosing regimen.	No – however, DRF effects on pregnancy outcome in humans is considered an important potential risk.	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 in patients taking DRF. A prospective observational pregnancy exposure registry (Study 272MS401) is ongoing to characterise how DRF may affect pregnancy and infant outcomes.

Table 13: Discussion of DRF exclusion criteria not remaining as contraindications in relation to the assessment of missing information

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
Diagnosis of primary progressive MS and secondary progressive MS.	Study design is for DRF use in RRMS.	No	DRF is to be indicated for RRMS.
History of clinically significant cardiovascular, pulmonary, GI (e.g., inflammatory bowel disease, peptic ulcer disease), dermatologic, psychiatric, neurologic (other than MS), endocrine, renal, and/or other major disease that would preclude participation in a clinical trial.	To enable meaningful safety and efficacy evaluation during the entire study period and to avoid disease confounding.	No	See Table 12.
History of clinically significant recurring or active GI symptoms (e.g., nausea, diarrhoea, dyspepsia, constipation) within 3 months of Screening, including symptoms that necessitate the initiation of symptomatic medical treatment (e.g., initiation of a medication to treat gastro-oesophageal reflux	To enable meaningful safety and efficacy evaluation during the entire study period and to avoid disease confounding.	No	See Table 12.

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
disease) or a change in symptomatic medical treatment (e.g., an increase in dose) within 3 months of Screening.			
History of malignancy, unless an exception is granted by the Medical Monitor (e.g., participants with basal cell carcinoma that has been completely excised prior to study entry remain eligible).	To enable meaningful safety and efficacy evaluation during the entire study period and to avoid disease confounding.	No, however, "Malignancies" are an important potential risk.	In Study 109MS303, participants received Tecfidera for up to 12 years (including the parent studies) and the overall incidence of malignancy was low (3%) and without any specific malignancy disproportionately represented. The incidence rate of malignancy, excluding basal cell carcinoma and squamous cell carcinoma, was 397.77 per 100,000 person-years. The background rate of malignancy in the general US population is 442.0 per 100,000 person-years. The incidence rate in the EU population is 268.6 per 100,000 person-years (age-standardised to the world population). Postmarketing data also do not provide evidence of an association between malignancies and Tecfidera, consistent with what was found in the clinical development programme. Since immunomodulatory therapies have effects on the immune system, they may influence the body's capacity for tumour surveillance. Thus, there is a theoretical risk that the incidence of malignancies may increase with longer durations of treatment with DRF. Consequently, the development of malignancies is considered to be an important potential risk for Vumerity, rather than missing information.
Clinically significant medical condition or observed abnormality at Screening (e.g., clinically	To enable meaningful safety and efficacy evaluation during the	No	Based on the understanding of the pharmacology of DRF and postmarketing utilisation of Tecfidera, the safety profile in participants with abnormal clinically significant results (e.g., physical examination findings, vital sign,

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
significant physical examination finding, vital sign result, ECG result, or laboratory test result).	entire study period and to avoid disease confounding.		ECG, or laboratory tests) is not expected to be different from that of participants without such disease burden, and therefore, exposure in these participants is not considered to be an area of missing information requiring further characterisation.
History of a myocardial infarction, including a silent myocardial infarction identified on ECG, or unstable angina.	To enable meaningful safety and efficacy evaluation and to avoid disease confounding.	No	Based on the understanding of the pharmacology of DRF and postmarketing utilisation of Tecfidera, the safety profile in participants with myocardial infarction is not expected to be different from that of participants without such disease burden, and therefore, exposure in these participants is not considered to be an area of missing information requiring further characterisation.
History of clinically significant drug or alcohol abuse within the past year (per Investigator judgment).	To enable meaningful safety and efficacy evaluation and to avoid disease confounding.	No	Based on the understanding of the pharmacology of DRF and postmarketing utilisation of Tecfidera, the safety profile in participants with alcohol abuse is not expected to be different from that of participants without such disease burden, and therefore, exposure in these participants is not considered to be an area of missing information requiring further characterisation.
Positive serology test for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody at Screening.	To reduce the risk to laboratory staff during collection/ handling of blood/tissue samples, and to avoid confounding the safety assessment of DRF.	No	These exclusion criteria are relevant only to participants enrolled in clinical studies in order to allow for homogeneous data collection and subsequent meaningful data interpretation and are included in part to protect the study site staff involved in blood sampling of trial participants. There is no evidence to suggest that the use of DRF in participants with controlled hepatitis B, hepatitis C, and HIV infection results in a specific safety concern, or a different outcome to previously identified risks.

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
Has any of the following abnormal blood tests at Screening: • ALT or AST ≥ 2×ULN • Thyroid-stimulating hormone level > 10% of the ULN at Screening • eGFR ≤ 60 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation) [Levey 2009] • Lymphocyte count < 0.9 × 10^3/µL • Beta-2 microglobulin > 0.3 µg/mL • Albumin to creatinine ratio > 200 mg/g	To enable meaningful safety and efficacy evaluation during the entire study period and to avoid disease confounding.	No, with the exception of use in participants with eGFR ≤ 60 mL/min/1.73 m^2	Based on the understanding of the pharmacology of DRF and postmarketing utilisation of Tecfidera, the safety profile in participants with these findings is not expected to be different from that of participants without such disease burden, and therefore, exposure in these participants is not considered to be an area of missing information requiring further characterisation. Due to the renal excretion of the inactive metabolite HES that is not present in Tecfidera metabolism, long-term safety in participants with moderate-to-severe renal impairment is considered an area of missing information for DRF.
If female, pregnant or planning pregnancy.	Animal studies have shown reproductive toxicity at DRF doses exceeding the recommended dosing regimen.	No – however, DRF effects on pregnancy outcome in humans is considered an important potential risk.	See Table 12.
Clinically significant history of suicidal ideation or suicidal behaviour	To enable meaningful safety and efficacy evaluation during the	No	Based on the understanding of the pharmacology of DRF and postmarketing utilisation of Tecfidera, the safety profile in participants with history of suicidal ideation or

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
occurring in the past 12 months as assessed by the Columbia Suicide Severity Rating Scale at Screening.	entire study period and to avoid disease confounding.		suicidal behaviour is not expected to be different from that of participants without such disease burden, and therefore, exposure in these participants is not considered to be an area of missing information requiring further characterisation.
Previous discontinuation of treatment with Tecfidera due to tolerability issues and/or lack of efficacy.	To enable meaningful safety and efficacy evaluation during the entire study period.	No	Based on the understanding of the pharmacology of DRF, the safety profile of DRF in participants who have discontinued Tecfidera due to tolerability issues is not expected to be different from those who have not previously taken Tecfidera, and therefore, this is not considered an area of missing information that needs further characterisation. Due to bioequivalence of the active metabolite for both DRF and Tecfidera, DRF should not be utilised in participants who have discontinued Tecfidera for the reason of lack of efficacy.
History of treatment with or has received the following: • Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, total body irradiation, or total lymphoid irradiation at any time. • Natalizumab within 2 months prior to Visit 2 or any prior use of alemtuzumab. • Fingolimod within 90 days prior to Visit 2.	To enable meaningful safety and efficacy evaluation during the entire study period and to avoid confounding of previous immune suppressive agent use.	No	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. Data from clinical studies 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.

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
• Daclizumab within 6 months prior to Visit 2. • B-cell–targeted therapies for the treatment of MS (e.g., ocrelizumab, rituximab) within 12 months of Screening; greater than 12 months of Screening is permissible with evidence that the CD19 cells have returned to within normal range (per local laboratory reference range). • Eligibility related to prior treatment with an investigational drug and/or a commercially available drug for the treatment of MS not listed above within the past 24 months will be determined on a case-by-case basis by the Medical Monitor. • Steroids, with the exception of topical or inhaled steroids or intravenous			

Exclusion criteria	Reason for being an exclusion criterion	Is it considered to be included as missing information?	Rationale
immunoglobulin within 30 days prior to Visit 2.			

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

Due to the relatively small clinical trial exposure and short pivotal trial duration, the DRF clinical development programme may not 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, there has been extensive clinical and postmarketing experience with Tecfidera in participants with MS, and the DRF clinical development programme has demonstrated bioequivalent levels of exposure with Tecfidera with respect to the major active metabolite, MMF. Therefore, the safety profile of DRF is expected to be similar to that of Tecfidera, thus mitigating such limitations.

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 14.

Table 14: Limitations of ADR Detection Common to DRF and Tecfidera 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 1461 participants were exposed to DRF in clinical trials. Of these, 1071 were participants in MS Phase 3 clinical trials, representing 1714.10 person-years of exposure. A total of 4791 MS participants were exposed to Tecfidera in clinical trials and 2513 participants were included in the Integrated MS studies (11 Nov 2021).	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.	Participants were exposed to DRF for a maximum of 96 weeks in the DRF Phase 3 clinical trials. In the Tecfidera Integrated MS studies, a total of 2513 participants have been exposed to Tecfidera. Of these, 426 participants have been exposed to Tecfidera for at least 480 weeks (Table 7).	Currently, the maximum time of exposure to DRF does not provide a sufficient opportunity to assess cumulative effects that may or may not have a long latency in isolation. However, given the bioequivalence in MMF exposure between DRF and Tecfidera and consistency in safety data between the 96-week DRF Study ALK8700-A301 and the long-term Tecfidera safety extension study, Study 109MS303, it is assumed that DRF will have a similar long-term safety profile to that of Tecfidera. Exposure for at least 10 years to Tecfidera does not appear to confer additional risk compared with overall

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
		safety profile based on integrated MS studies. No evidence for cumulative effects has been observed in the Tecfidera clinical trial setting.

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

The degree of exposure of populations typically under-represented in the DRF clinical development programme is provided in Table 15 below. Relevant information from the Tecfidera clinical development programme is also discussed.

Table 15: Exposure of special populations included or not in Tecfidera and DRF clinical trial development programmes

Type of special population	Exposure
Children	Not included in the preauthorisation clinical development programmes.
Elderly participants	A limited number of participants > 55 years of age at enrolment were included in the preauthorisation clinical development programme for DRF but not for Tecfidera.
Pregnant women	Not included in the preauthorisation clinical development programmes.
Breastfeeding women	Not included in the preauthorisation clinical development programmes.
Participants with relevant comorbidities: • Hepatic impairment	Not included in the preauthorisation clinical development programmes.

Type of special population	Exposure
Participants with relevant comorbidities: • Renal impairment	A single-dose DRF clinical study in participants with mild, moderate, and severe renal impairment demonstrated no effect of renal impairment on PK exposures of MMF; as such, no dosage adjustment is necessary (ALK8700-A108). The inactive metabolite HES demonstrated slowed clearance with respect to renal impairment severity, especially with moderate and severe renal impairment in this study. The mean plasma HES AUC from time 0 to time of the last measurable concentration and AUC from time 0 to infinity increased with renal impairment and was highest in participants with severe renal impairment, but no correlation with renal impairment was identified for C_{max}. Total exposure as measured by AUC in the severe renal impairment cohort was approximately 2.6-fold higher than that in the healthy participants. In this study, HES did not appear to have any clinically relevant impact on the safety profile of DRF. In the Tecfidera preauthorisation 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).
Participants with relevant comorbidities: • Cardiovascular impairment	Not included in the preauthorisation clinical development programmes.
Participants with relevant comorbidities: • Immunocompromised participants	Not included in the preauthorisation clinical development programmes.
Participants with a disease severity different from inclusion criteria in clinical trials: • Expanded Disability Status Scale score > 6.5	Not included in the preauthorisation clinical development programmes.
Participants with a disease severity different from inclusion criteria in clinical trials: • Severe active GI disease	Not included in the preauthorisation clinical development programmes.

Type of special population	Exposure
Participants with relevant different race	The number and percentage of participants, by race, exposed to DRF in the preauthorisation safety pool were as follows: • White: n = 985 (92.0%) • Black or African American: n = 73 (6.8%) • Asian: n = 5 (0.5%) • Other: n = 7 (0.7%) • Native Hawaiian or other Pacific Islander: n = 1 (< 0.1%) The number and percentage of participants, by race, exposed to Tecfidera in the preauthorisation safety pool were as follows: • White: n = 1756 (69.9%) • Asian: n = 197 (7.8%) • Black: n = 38 (1.5%) • Other: n = 92 (3.7%) • Not reported or missing information: n = 430 (17.1%)
Subpopulations carrying relevant genetic polymorphisms	Not included in the preauthorisation clinical development programmes.
Females and males of reproductive potential	There are no clinical data related to fertility. Although under-represented, this is not a concern with DRF or Tecfidera.

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

PART II: MODULE SV – POSTAUTHORISATION EXPERIENCE

SV.1 Postauthorisation exposure

DRF was first granted approval in the US on 29 Oct 2019 for the treatment of relapsing forms of MS, to include clinically isolated syndrome, RRMS, and active secondary progressive MS, in adults. It has since been approved in many countries. The cumulative postmarketing exposure to Vumerity through 30 Jun 2023 is presented in Table 16. Exposure to Vumerity from marketing experience was calculated from monthly sales data, assuming that a patient receives 1 unit (120 capsules) per month, and based on previous forecasting, the estimated monthly discontinuation rate is 1.8%.

Table 16: Cumulative patient exposure from marketing experience with Vumerity as of 30 Jun 2023

Setting	Number of patients	Units	Person-years
European Economic Area	8678	76,143	6345
Global	37,887	556,080	46,340

The cumulative postmarketing exposure to Tecfidera through 30 Jun 2023 is presented in Table 17. 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%.

Table 17: Cumulative patient exposure from marketing experience with Tecfidera, as of 30 Jun 2023

Setting	Number of patients	Units	Person-years
European Economic Area	283,035	8,217,058	684,755
Global	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 DRF for illegal purposes.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

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

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

No potential risks have been classified for DRF. A summary of the rationale for not including identified risks in the list of safety concerns (at the time of the initial marketing authorisation application) is presented below. All identified and potential risks are followed within the framework of Biogen pharmacovigilance processes.

Known risks that do not impact the risk-benefit profile:

Herpes zoster infection has been reported with Tecfidera administration in clinical trials and postmarketing experience, with an incidence of 5.1% reported in a long-term Tecfidera extension study (Study 109MS303). The majority of reported cases are nonserious, and of mild or moderate severity. These events may occur at any time during treatment. Patients receiving DRF are to be monitored for signs and symptoms of herpes zoster. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered. DRF treatment is to be withheld in patients with serious infections. Overall, the risk-benefit profile of DRF remains positive.

All important identified and important potential risks are followed within the framework of the Biogen pharmacovigilance processes.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 18: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk category: Risk	Scientific evidence and risk-benefit impact
Important identified risk: PML	Confirmed PML cases have been identified in association with Tecfidera use in the setting of lymphopenia (< 0.91×10^9/L). Consequently, PML is an important identified risk for DRF. The DRF SmPC describes the risk of lymphopenia and PML in Section 4.4 (*Special warnings and precautions for use*), and 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 SmPC are considered adequate measures to mitigate the risk of PML, and therefore, the risk-benefit balance of DRF remains favourable.

Risk category: Risk	Scientific evidence and risk-benefit impact
Important identified risk: Decreases in leukocytes and lymphocytes	As with Tecfidera, DRF has the potential to lower lymphocyte counts, and lymphopenia is a known risk factor for infections, including opportunistic infections. In placebo-controlled studies with Tecfidera, most patients (> 98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with Tecfidera, mean lymphocyte counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. In DRF Study ALK8700-A301, as of 01 September 2020, overall mean changes from baseline in lymphocyte count and leukocyte count were -0.53 × 10^3/μL and -0.63 × 10^3/μL at Week 96, respectively. Overall, 57.6% (602/1045) of participants always had ALC ≥ LLN (0.91 × 10^9/L), 6.2% (65/1045) of participants had mild lymphopenia (< 0.91 × 10^9/L) for 6 months, and 13.7% (143/1045) of participants had moderate lymphopenia (< 0.8 × 10^9/L) for 6 months.
Important identified risk: Drug-induced liver injury	In placebo-controlled studies with Tecfidera, elevations of hepatic transaminases were observed. The majority of patients with elevations had hepatic transaminases that were < 3 times the ULN. Postmarketing reports of increase of liver enzymes and cases of drug-induced liver injury (i.e., elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN), which resolved upon treatment discontinuation, have been identified following Tecfidera administration. Consequently, drug-induced liver injury was added as an ADR in Section 4.8 (*Undesirable effects*) of the Tecfidera SmPC, and advice relating to the monitoring of liver function prior to and during treatment was included in Section 4.4 (*Special warnings and precautions for use*). In Study ALK8700-A301 with DRF, as of 01 September 2020, postbaseline ALT values of > 3 × ULN were observed in 2.0% (21/1057) of participants overall, and postbaseline AST values of > 3 × ULN were observed in 1.1% (12/1057) of participants overall. The DRF SmPC describes the risk of DILI in Section 4.4 (*Special warnings and precautions for use*) and PL in Section 2 (*What you need to know before you take Vumerity*) and Section 4 (*Possible side effects*). Considering that the nature of the suspected reported events involves overall reversibility, favourable outcomes, and early recognition of cases by prescribers, the risk-benefit balance of DRF remains favourable.

Risk category: Risk	Scientific evidence and risk-benefit impact
Important potential risk: Serious and opportunistic infections (other than PML and herpes zoster)	Tecfidera has been associated with a risk of 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. However, to date, the incidence of serious infections and opportunistic infections (excluding PML and herpes zoster) is similar in patients treated with placebo versus those treated with Tecfidera. Therefore, excluding PML infection and herpes zoster, no evidence of an increased risk of other serious or opportunistic infections has been demonstrated. In Study ALK8700-A301 with DRF, as of 01 September 2020, no participants experienced prolonged severe lymphopenia (ALC $< 0.5 \times 10^9$/L and sustained for 6 months or more) or had AESIs of serious infection or opportunistic infection. The DRF SmPC provides guidance on the monitoring of lymphocyte counts, which provides a means for early identification of those patients who are at increased risk for developing lymphopenia and thereby any potential sequelae. These recommendations in the SmPC are considered adequate measures to mitigate the potential risk of serious and opportunistic infections; therefore, the risk-benefit balance of DRF remains favourable.
Important potential risk: Malignancies	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. Given the putative immunomodulatory mechanism of action of Tecfidera and DRF, malignancies were carefully evaluated in clinical studies. In the controlled MS studies with Tecfidera, 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 13 years in the uncontrolled safety extension study. From Study ALK8700-A301, as of the 01 September 2020 data cut, the number of malignancies was low (n = 5), and no malignancy was seen in more than 1 participant. As no evidence of a causal association between Tecfidera, DRF, and the development of malignancies has been identified, no impact on the risk-benefit balance of the product is currently considered.

Risk category: Risk	Scientific evidence and risk-benefit impact
Important potential risk: Pregnancy outcome	Current data from clinical trials, postmarketing experience, and the ongoing Biogen Multiple Sclerosis Pregnancy Exposure Registry (Study 109MS402) do not suggest that Tecfidera, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. Further characterisation is being investigated in Study 109MS402. There are no adequate data on the developmental risk associated with the use of DRF in pregnant women. Because animal reproduction studies are not always predictive of human response, the SmPC states that this drug should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. The impact of DRF on pregnancy outcome is being evaluated in a prospective pregnancy registry (Study 272MS401). No impact on the risk-benefit balance of the product is currently considered.
Important potential risk: Interaction with nephrotoxic medications leading to renal toxicity	Results of a subgroup analysis within the placebo-controlled studies show that there was an increased incidence of renal and urinary AEs (primarily AEs of proteinuria) in participants with concomitant PNM compared to those participants who did not receive potentially nephrotoxic drugs. In Study ALK8700-A301 with DRF, as of 01 September 2020, the overall incidence of AESIs in the renal injury category was low (3.4% [36/1057] of participants). The incidence was low across all groups. All events in this category were mild or moderate in severity and nonserious, with the most common event being proteinuria, which was experienced by 1.3% (14/1057) of participants. The evaluation of the events does not suggest or provide any evidence of renal injury associated with DRF. No impact to the risk-benefit balance of DRF is anticipated.

Risk category: Risk	Scientific evidence and risk-benefit impact
Missing information: Long-term efficacy and safety	Interim data from the long-term extension study (Study 109MS303) have demonstrated consistent efficacy in patients treated with Tecfidera for up to approximately 11 years. Among participants who continued treatment with Tecfidera from the parent studies, the incidence of serious infections and malignancies remained low, and white blood cell and lymphocyte counts remained stable overall. Treatment discontinuation due to adverse events (AEs), MS progression, and MS relapse was 14%, 2%, and 2%, respectively. Subjects who discontinue for any reason and have an absolute lymphocyte count less than the lower limit of normal will continue to have follow-up post-treatment until lymphocyte reconstitution has occurred or for at least 48 weeks. The study was completed in Q4 2020. Long latency potential risks such as malignancies and lymphopenia will continue to be monitored through routine pharmacovigilance activities. In addition, ongoing studies with Tecfidera (Study 109MS401) and DRF (Study ALK8700-A301) aim to provide long-term data. A registry-based Category 3 post-authorisation safety study also will be conducted to assess long-term safety. Long latency potential risks such as malignancies will continue to be monitored through routine pharmacovigilance activities. The risk-benefit balance of DRF remains favourable.
Missing information: Safety profile in patients older than 65 years	Available evidence does not indicate that the use of DRF in patients older than 65 years presents a specific concern; the absence of scientific evidence has led to inclusion in this section. A Tecfidera postauthorisation safety study (Study 109MS401) is ongoing to address this area of missing information; the safety profile of DRF in participants older than 65 years will remain as a safety concern until such time that the results of this study are available. The risk-benefit balance of DRF remains favourable.

Risk category: Risk	Scientific evidence and risk-benefit impact
Missing information: Safety profile in patients with moderate to severe renal impairment	Regular reviews of Tecfidera 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 participants who did fulfil the criteria for renal impairment does not suggest that the safety profile of Tecfidera in participants with renal impairment differs from that in participants with normal renal function. In Study ALK8700-A301 with DRF, as of 01 September 2020, 205 participants were identified with mild renal impairment (eGFR $\geq$ 60 mL/min/1.73 m^2 and to < 90 mL/min/1.73 m^2). When compared with participants with normal GFR ($\geq$ 90 mL/min/1.73 m^2), the safety profile was similar with that of the overall population. Consequently, cumulative data obtained to date do not indicate that the use of DRF in participants with renal impairment impacts the overall safety profile or risk-benefit assessment of DRF. Given the nature and mechanism of clearance of DRF, no effects or dose adjustments are anticipated/required. The risk-benefit balance of DRF remains favourable.
Missing information: Safety profile in patients with hepatic impairment	Regular review of postmarketing data has identified relatively few cases of patients with hepatic impairment exposed to Tecfidera; however, a review of the types and nature of AEs reported in those patients who did fulfil 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; given bioequivalence and the nature and mechanism of clearance of DRF, no effects or dose adjustments are anticipated/required. The risk-benefit balance of DRF remains favourable.

Risk category: Risk	Scientific evidence and risk-benefit impact
Missing information: Safety profile in patients with severe active GI disease	Participants with severe active GI disease were not included in the preauthorisation clinical development programme. Available evidence does not indicate that the use of DRF in patients with severe active GI disease presents a specific concern; the absence of scientific evidence has led to inclusion in this section. A completed DRF study (Study ALK8700-A302) evaluated the GI tolerability of DRF compared with Tecfidera and showed that there were fewer GI AEs and discontinuations due to GI AEs along with fewer and less severe self-reported GI events in the DRF group. No participants were enrolled with severe active GI disease into this study, and clinically significant recurring or active GI symptoms was an exclusion criterion from 96-week DRF Study ALK8700-A301. The risk-benefit balance of DRF remains favourable.
Missing information: Increased risk of infection in patients concomitantly taking antineoplastic or immunosuppressive therapies	Tecfidera has a low potential to cause drug interactions due to the way it is metabolised and its low affinity for protein binding, and 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, participants receiving anti-neoplastic or immunosuppressive therapies were not included in the Tecfidera clinical development programme. A Tecfidera postauthorisation safety study (Study 109MS401) is currently ongoing to address this area of missing information, and results may be applied to DRF given bioequivalent exposure of MMF between DRF and Tecfidera. The safety profile of DRF in this patient population will remain as a safety concern until such time that the results of this study are available. The risk-benefit balance of DRF remains favourable.

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

SVII.2.1 Newly identified safety concerns

There are no newly identified safety concerns reported in this EU RMP.

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. The study results may be applied to DRF given the bioequivalent exposure of MMF between DRF and Tecfidera.

To ensure that all available data were assessed in order to confidently downgrade or remove safety concerns, data from the postmarketing setting, using Tecfidera 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 Vumerity and Tecfidera. In Tecfidera 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 Vumerity. 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 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.

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 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 the 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 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

Vumerity 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 Vumerity, 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 or Vumerity and nephrotoxic medications, and the safety profile observed in these patients is consistent with the known safety profile of the drug. Thus, this important potential risk can be removed.

Safety profile in patients over the age of 65 years - Remove as missing information

The Vumerity clinical trials primarily enrolled participants aged 18 to 65 years. In Tecfidera pivotal studies, the age range was 18 to 55 years. 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), 6893 events in 2506 patients ≥ 65 years of age were noted. 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 > 65 years is consistent with the overall population exposed to Tecfidera. In addition, data from Vumerity Study ALK8700-A301 included 13% of participants aged > 55 years, with a mean exposure to DRF of 20.4 months. Evaluation of these data showed the safety profile in this population to be similar to that of the overall population in the study. Thus, this topic of missing information can be removed.

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

As DRF, DMF, and MMF are metabolized by esterases (without the involvement of the CYP system), no formal PK studies in patients with hepatic impairment were 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 Vumerity differs from those with normal hepatic function. Consequently, cumulative data obtained to date do not indicate that the use of Vumerity in patients with hepatic impairment impacts the overall safety profile or risk-benefit assessment of Vumerity; and given the nature and mechanism of clearance of Vumerity, 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. 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 PTs 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 (and thus Vumerity) 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 case 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 serious events of Crohn's disease, but review of the cases did not reveal any concerning information.

A completed DRF study (Study ALK8700-A302) evaluated the GI tolerability of DRF compared with Tecfidera and showed that there were fewer GI AEs and discontinuations due to GI AEs, along with self-reported fewer and less severe GI events in the DRF group.

Data from Study 109MS401 and the postmarketing setting provide confidence that patients with severe active GI disease respond to Tecfidera (and Vumerity) 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

Vumerity and Tecfidera have a low potential to cause drug interactions due to the way they are metabolized and because they have 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 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 Vumerity or Tecfidera on immune function may be additive when combined with known immunosuppressants or immunomodulators, leading to the theoretical possibility that concomitant administration of Vumerity or 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 drugs' anti-inflammatory and cytoprotective effects. 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 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 Vumerity) 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

SVII.3.1 Presentation of important identified risks

Important Identified Risk: Progressive multifocal leukoencephalopathy

Relevant MedDRA term: *PT: Progressive multifocal leukoencephalopathy*

Potential mechanisms

PML is an opportunistic infection caused by JCV. However, even in patients who are anti-JCV antibody positive, PML occurs in only a minority of patients because JCV infection is only one of several factors required for the development of PML. Although the exact mechanism of PML development is unknown, it is believed that after initial infection with JCV, the virus becomes dormant but is able to reactivate in the setting of immune alteration that creates circumstances favourable for the virus to undergo a mutation and trigger progressive white matter infection in the brain.

Published studies have proposed several hypotheses for the development of PML [Calabrese 2015; Chen 2009; Marzocchetti 2009; Sundqvist 2014; Wallbrecht 2011]; however, there are currently no conclusive data to support the mechanism by which DMF or DRF increases risk for PML.

Evidence suggests that the mechanism of action of DMF involves at least 2 pathways: activation of the Nrf2 pathway [Linker 2011; Scannevin 2012] and activation of the G protein-coupled receptor hydroxycarboxylic acid receptor 2 [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 that either

of these mechanisms would confer increased risk for PML. There have been no associations of Nrf2 gain of function genetic polymorphisms with PML, and no other structurally diverse small molecule activators of Nrf2 have been associated with PML [de Zeeuw 2013]. Given the bioequivalence of DRF with DMF, it is reasonable to conclude that these data also apply to DRF.

Evidence source and strength of evidence

Similar to Tecfidera, DRF has the potential to lower lymphocyte counts, and lymphopenia is a known risk factor for infections, including opportunistic infections. PML has occurred in the setting of lymphopenia (lymphocyte counts < 0.91×10^9/L) after Tecfidera administration.

Biogen utilises a framework that uses standardised criteria and case definitions to differentiate and classify reported cases of PML by levels of diagnostic certainty. This objective adjudication process was developed with external PML expert input and has been used to evaluate PML case reports for Tysabri (natalizumab) for more than 10 years.

PML case definitions (which categorise cases into Level 1 to Level 5) allow classification of cases based on varying levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out cases (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 fumaric acid esters) in the setting of lymphopenia (< 0.91×10^9/L). Consequently, PML is an important identified risk for DRF and wording relating to the detection and management of PML is included in the DRF SmPC (Section 4.4 [*Special warnings and precautions for use*]).

Characterisation of the risk

This risk is characterised in Table 19 below.

Table 19: Characterisation of important identified risk: PML

Frequency	Clinical trials • *Placebo-controlled clinical trials:* No cases of PML were identified in Tecfidera placebo-controlled clinical trials. • *Long-term safety extension study (Study 109MS303):* One case of PML was observed in the setting of prolonged, severe lymphopenia in a study participant. • *Long-term safety and tolerability study (Study ALK8700-A301):* No cases of PML have been identified in the 96-week DRF study. Postmarketing spontaneous • There are limited postmarketing data for DRF, but there have been no confirmed cases of PML with DRF. • PML has been reported in Tecfidera-exposed patients, predominantly in the setting of prolonged moderate-to-severe lymphopenia.

Absolute risk and relative risk	There are no estimates of PML in the MS population not receiving DMT. PML among those without known risk factors is rare at < 3 cases per million person-years [Hirsch 2013]. PML has been most frequently diagnosed in the context of HIV infection. The reported prevalence of PML among HIV-infected participants in the era before HAART varied from 0.3% to 8%. In a Swiss HIV cohort study, the incidence in the pre-HAART era of PML was 0.24%. After the introduction of HAART, this reduced the incidence of PML to 0.06%. An incidence rate of 1.3 cases per 1000 person-years was reported in a Danish population-based cohort of participants with HIV. In a study in non-HIV participants in the US, the incidence rate per 100,000 person-years was found to be 2.4, 10.8, 11.1, 8.3, and 35.4 for participants diagnosed with SLE, autoimmune vasculitis, non-Hodgkin's lymphoma, CLL, and those undergoing bone marrow transplantation, respectively. Severe lymphopenia as a risk factor for PML has been reported in several diseases, including HIV, autoimmune rheumatic diseases, and idiopathic CD4+ lymphocytopenia [De Raedt 2008; Gheuens 2013; Jamilloux 2014; Molloy and Calabrese 2009], and PML is associated with therapies in addition to Tecfidera that result in lymphopenia (e.g., rituximab, fingolimod, and fumaric acid esters).
Seriousness and severity	All confirmed cases of PML in Tecfidera-exposed participants 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 QoL	PML can be fatal, and in survivors, there is usually significant impact on QoL. However, there are limited data on the QoL of participants who survive. PML, like MS, is a demyelinating disease; 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 the following: • 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 death or extreme disability; however, in rare cases, the infection can be asymptomatic. Consequently, the impact on QoL 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% to 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, those 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, some patient populations have a higher risk of developing PML, including those with HIV; those with malignancies (including non-Hodgkin's lymphoma and CLL); those diagnosed with SLE, sarcoidosis, or autoimmune vasculitis; and those undergoing bone marrow transplantation.

With regard to Tecfidera, the finding common to all confirmed cases of PML reported to date has been the presence of 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- and DRF-treated participants, lymphopenia is a risk factor.

Information from studies evaluating lymphopenia associated with Tecfidera treatment have shown that ALC was highly correlated with total, 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 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.

Preventability

In DRF-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 participants at risk.

Routine monitoring of CBC including lymphocytes identifies participants at risk of developing lymphopenia. Prior to initiating treatment with DRF, a CBC 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 DRF. DRF should not be initiated in patients with severe lymphopenia (lymphocyte counts $< 0.5 \times 10^9$/L).

After starting therapy, CBCs, including lymphocytes, must be performed every 3 months. Discontinue DRF in participants with lymphocyte counts $< 0.5 \times 10^9$/L persisting for more than 6 months. Lymphocyte counts should be followed until recovery. Assess the risk-benefit in participants who experience moderate lymphopenia for more than 6 months.

The majority of cases of PML have occurred in the setting of prolonged moderate-to-severe lymphopenia. Routine monitoring of CBC and differential may serve to mitigate the risk through early detection of events of lymphopenia and identification of participants at risk of developing lymphopenia.

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

Impact on the risk-benefit balance of the product

PML has not been observed in any DRF studies; however, PML continues to be a rare event related to use of Tecfidera and other medicinal products containing fumaric acid esters. 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, a robust clinical research plan aimed to characterise the impact of DRF on lymphocytes has been established.

The DRF SmPC describes the risk of lymphopenia and PML in Section 4.4 (*Special warnings and precautions for use*) and monitoring of lymphocyte counts provides a means for early identification of those participants 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 in the context of DRF use is not considered to have a major impact on public health.

SVII.3.2 Presentation of important potential risks

Important Potential Risk: Malignancies

Relevant MedDRA terms: *SMQ: Malignant or unspecified tumours*

Potential mechanisms

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

Evidence sources and strength of evidence

Characterisation of the risk

This risk is characterised in Table 20.

Table 20: Characterisation of important potential risk: Malignancies

Frequency	In Study ALK8700-A301, the number of malignancies in participants treated with DRF was low (n = 5), and no malignancy was seen in more than 1 participant. Tecfidera 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 among 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.
Absolute risk and relative risk	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 and DRF are consistent with those observed in the general US and global populations.
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 QoL	The impact of developing a malignancy on QoL can vary considerably between patients and is dependent on malignancy location, stage, and other comorbidities affecting a patient's ability to tolerate treatment; impact on QoL, therefore, is difficult to assess outside of an individual case-by-case basis. However, as there is no evidence of an increased risk of malignancies in patients treated with Tecfidera or DRF, no impact on QoL 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 and DRF, malignancies were carefully evaluated in clinical studies. In the controlled MS studies with Tecfidera, 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.

In Study ALK8700-A301, the number of malignancies was low (n = 5), and no malignancy was seen in more than 1 participant.

As no evidence of a causal association between Tecfidera, DRF, 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.

Important Potential Risk: Effects on pregnancy outcome

Relevant MedDRA terms: Not applicable; all pregnancy outcomes reporting maternal or paternal exposure to DRF and Tecfidera are reviewed.

Potential mechanisms

None known.

Evidence source

Reproductive toxicology studies conducted with DRF revealed no impairment of male and female fertility in rats, no teratogenicity in rats and rabbits, and no pre- and postnatal development toxicity in rats at MMF and HES exposure (AUC) at least 2 times the RHD of DRF. At maternal toxic doses, the offspring of DMF treatment to pregnant female animals exhibited skeletal variations in rats and skeletal variations/malformations in rabbits; these findings occurred at MMF AUC that was approximately 10 times in rats and ≥ 6 times in rabbits, relative to the RHD of DRF. At a toxic dose to pregnant rats, with MMF exposure (AUC) that was approximately 10 times that at the RHD of DRF, decreased birth weights and body weights/weight gains during the preweaning period were noted in the offspring. With the exception of skeletal malformations in rabbits, similar embryo-foetal developmental findings have been reported for DMF.

There are, however, no adequate data on the developmental risk associated with the use of DRF in pregnant women. Because animal reproduction studies are not always predictive of human response, the SmPC states that this drug should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus.

Ten pregnancies have been reported in the DRF clinical study programme. One pregnancy was reported in the DRF Phase 1 ALK8700-A110 study, and 9 pregnancies were reported in the DRF ALK8700-A301 study. The outcome of 6 pregnancies was the delivery of 7 healthy, full-term infants (5 singletons, 1 twin gestation); 2 pregnancies resulted in spontaneous abortions (gestational ages unknown); and 2 pregnancies were terminated by elective abortions at 8 weeks and at 10 weeks of gestation. The impact of DRF on pregnancy outcome is being evaluated in a

prospective pregnancy registry (Study 272MS401). The effects of DRF on labour and delivery are unknown.

Current data from clinical trials, postmarketing, and the completed Biogen Multiple Sclerosis Pregnancy Exposure Registry (Study 109MS402) do not suggest that Tecfidera, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. The observations from these studies are relevant to DRF, given the shared common active metabolite, MMF, with Tecfidera.

Characterisation of the risk

This risk is characterised below (Table 21).

Table 21: Characterisation of important potential risk: Pregnancy outcome

Frequency	The impact of DRF on pregnancy outcomes has not been formally established, so frequency cannot be determined. However, the impact of DRF on pregnancy outcomes is being evaluated in a prospective pregnancy registry (Study 272MS401).
Seriousness and severity	**Seriousness:** The 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 and Vumerity on long-term outcomes of pregnancy exposure in the infant.
Impact on QoL	Current data from clinical trials, postmarketing, and the completed Pregnancy Registry (Study 109MS402) do not suggest that Tecfidera, when taken early in pregnancy, has a negative effect on pregnancy outcome. No impact on QoL is therefore anticipated.

Risk factors and risk groups

Women of childbearing potential.

Preventability

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

Impact on the risk-benefit balance of the product

None anticipated, pending completion of the pregnancy exposure registry.

Public health impact

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

SVII.3.3 Presentation of missing information

Missing Information: Long-term efficacy and safety

Evidence source

There is low risk that patients with long-term exposure to Tecfidera may be at increased risk of experiencing an AE. The completed long-term safety extension study (Study 109MS303) had participants exposed to Tecfidera and followed for up to 13 years. Among participants who continued treatment with Tecfidera from the parent studies, the incidence of serious infections and malignancies remained low, and WBC and lymphocyte counts remained stable overall. In addition, Study 109MS401 demonstrated a positive benefit-risk profile of long-term exposure to Tecfidera (up to 6.5 years) in patients with MS who were prescribed Tecfidera under routine clinical care. Results were consistent with findings from other Tecfidera studies.

With Vumerity, results from the completed Study ALK8700-A301 presented no new safety concerns. A registry-based Category 3 PASS (Vumerity Study 272MS403) also will be conducted to provide long-term safety data. The risk-benefit balance of Vumerity remains favourable.

Population in need of further characterisation

The registry-based PASS (272MS403) will add to the base of evidence to characterise Vumerity's long-term safety and efficacy.

Missing Information: Safety profile in patients with moderate to severe renal impairment

Evidence source

A single-dose clinical study investigating the effect of renal impairment on the PK of the DRF metabolites MMF and HES was conducted. The study included cohorts with mild, moderate, and severe renal impairment and a healthy cohort and found no clinically relevant changes in MMF exposure. HES exposure increased by 1.3-, 1.8-, and 2.7-fold with mild, moderate, and severe renal impairment, respectively. In Study ALK8700-A301, 19.4% participants had mild renal impairment (GFR < 90 mL/min/1.74 cm^3 and ≥ 60 mL/min/1.74 cm^3) at the time of data cutoff, and there were no clinically relevant differences in safety findings in this group compared with participants with no renal impairment. There are no data available on long-term use of DRF in participants with moderate or severe renal impairment.

Data from a long-term safety extension study of Tecfidera (Study 109MS303) determined that the safety profile of participants with mild renal impairment was similar to that in participants without renal impairment, but data related to moderate-to-severe renal impairment are considered missing information.

Population in need of further characterisation

After a single dose of DRF to healthy participants, approximately 60% of the total administered dose is recovered as the inactive metabolite HES in the urine, with a negligible recovery of the active metabolite MMF (< 0.3% of the dose). DRF undergoes hydrolysis to the inactive metabolite HES, which is 100% renally excreted. A clinical study in participants with mild, moderate, and severe renal impairment demonstrated no effect of renal impairment on PK exposures of MMF, the active metabolite of DRF; however, there is a reduction in the rate of

clearance of HES in participants with renal impairment that is proportionate to the degree of renal impairment. Therefore, long-term safety in participants with moderate-to-severe renal impairment remains an area of missing information.

Regular reviews of Tecfidera postmarketing data have identified relatively few cases of participants with renal impairment; however, a review of the types and nature of AEs reported in those participants who did fulfil the criteria for renal impairment does not suggest that the safety profile of Tecfidera in participants with renal impairment differs from that in participants with normal renal function.

In DRF Study ALK8700-301, 205 participants were identified with mild renal impairment (eGFR $\geq$ 60 mL/min/1.73 m^2 and to < 90 mL/min/1.73 m^2). When compared with participants with normal GFR ($\geq$ 90 mL/min/1.73 m^2), the safety profile was similar to that of the overall population. Consequently, cumulative data obtained do not indicate that the use of DRF in participants with renal impairment impacts the overall safety profile or risk-benefit assessment of DRF, and, given the nature and mechanism of clearance of DRF, no effects or dose adjustments are anticipated/required.

PART II: MODULE SVIII – SUMMARY OF SAFETY CONCERNS

The DRF safety specification includes the following important identified risks, important potential risks, and areas of missing information (Table 22).

Table 22: Summary of safety concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III. 1 Routine pharmacovigilance activities

Biogen uses routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline to further characterise all 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 DRF throughout clinical development and in the postauthorisation 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, the following routine pharmacovigilance activities are also used in order to provide further characterisation data for specific safety concerns:

PSUR reporting on PML cases Standardised criteria and case definitions for the reporting and assessment of PML cases for DRF as for DMF are used to further risk characterize the events and optimise assessment through consistent evaluation.

Specific adverse drug reaction follow-up questionnaires Data collection questionnaires at different timepoints after the 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 collection questionnaires are also used to enable timely and robust collection of data for events of malignancies, thereby optimising evaluation.

All data collection questionnaires are provided in Annex 4.

III. 2 Additional pharmacovigilance activities

Data from planned or ongoing studies are anticipated to aid the further characterisation of some of the safety concerns for DRF described in Part II:SVII.3. DRF and DMF share the same major active metabolite, MMF; therefore, the important safety risks for DRF are also defined based on the established safety profile of DMF, which has extensive clinical trial and postmarketing experience in patients with MS.

A prospective observational pregnancy exposure registry cohort analysis (Study 272MS401) and a registry-based Category 3 post-authorisation safety study (Study 272MS403) will assess long-term safety of Vumerity.

A brief outline of each study is included in Table 23.

Table 23: Study Details

Protocol number	272MS401
Short name	Pregnancy Registry (The protocol does not specify short name.)
Study title	Vumerity (Diroximel Fumarate) Prospective MS Pregnancy Exposure Registry
Rationale	Women of childbearing potential are a considerable segment of the patient population affected by MS and may be exposed to DRF around the time of conception and during pregnancy. Therefore, it is important to evaluate, in a global pregnancy registry, how exposure to DRF may affect pregnancy and infant outcomes.
Study design	This is a prospective, observational registry in pregnant women with MS who were exposed to DRF at any time from 2 weeks after the first day of their LMP through any time during pregnancy. At enrolment, the Coordinating Centre (CC) investigator will obtain demographic, medical history, and contact information from the patient. Once per trimester, the CC will contact the patient for any updates. The CC also will contact the patient's obstetric Health Care Provider (HCP) and neurologist at 6 to 7 months of gestation for the Prenatal Follow-Up and at approximately 4 weeks after the estimated delivery date for the Pregnancy Outcome Follow-Up. At approximately 4, 12, and 52 weeks after birth, the CC will contact the paediatric HCP for a Paediatric Follow-Up.
Study objectives	The purpose of this pregnancy registry is to better characterise how DRF may affect pregnancy and infant outcomes. The primary objectives of the study are as follows: • Estimate the risk of major congenital malformation (MCM) in infants born to women with MS who were exposed to DRF at any time from 2 weeks after the first day of their last menstrual period (LMP) through the first trimester of pregnancy. • Comparatively evaluate pregnancy outcomes with MCMs in women with MS who were exposed to DRF at any time from 2 weeks after the first day of their LMP through the first trimester of pregnancy with the following: i) women with MS who were unexposed to DMTs and ii) women with MS who were exposed to other DMTs (e.g., Avonex and

Protocol number	272MS401
	Tysabri pregnancy registries [DMF was not included given that it is the reference drug of DRF.]). The secondary objective of the study is as follows: • Evaluate pregnancy outcomes in women with DRF exposure at any time from 2 weeks after the first day of their LMP through the end of pregnancy compared with the following: i) women with MS who were unexposed to DMTs, ii) women with DMF exposure, iii) women with MS who were exposed to other DMTs (e.g., Avonex and Tysabri Pregnancy Registries; NOTE: DMF not included given that it is the reference drug of DRF), and iv) women without MS (e.g., women from external, general population comparators). DMT-unexposed is defined as one of the following: • never received a DMT • discontinued treatment with DRF at least 1 day before 2 weeks after the first day of their LMP • discontinued a non-Registry-specified MS DMT more than 5 times its half-life prior to 2 weeks after the first day of their LMP
Study population	It is anticipated that approximately 383 to 454 pregnant women exposed to DRF will be enrolled to observe a combined 363 prospective live births or pregnancy losses. This study is being conducted in pregnant women with MS who were exposed to DRF at any time from 2 weeks after the first day of their LMP through any time during pregnancy and compared with pregnancies among women with MS who were exposed to DMF, women with MS who were exposed to other DMTs (e.g., Avonex and Tysabri pregnancy registries [DMF was not included given that it is the reference drug of DRF.]), women with MS who were unexposed to DMTs, and women without MS.
Location	Global
Milestones	• First Patient In: Oct 2023 • Study completion: 2032; final CSR submission: 2033

Protocol number	272MS403
Short name	• PASS Safety Registry
Study title	• An Observational Study Utilising Data From Big MS Data Registries to Evaluate the Long-Term Safety of Vumerity and Tecfidera
Rationale	• The purpose of this study is to further evaluate the long-term safety of Vumerity
Study design	• This is a noninterventional, observational cohort study using data from registries that are part of the Big MS Data network. The study will be based on secondary data analysis and will include, where possible, retrospective data for all patients of interest that have been collected from the initiation of treatment and, for example, from the index date where systematic safety data were collected in the respective registries.
Study objectives	• The primary objective of the study is to estimate the incidence rate of SAEs, including but not limited to malignancies and serious and opportunistic infections, among patients with MS treated with Vumerity, Tecfidera, other selected DMTs (teriflunomide, beta-interferons, or glatiramer acetate), or Vumerity after switching from Tecfidera. • The secondary objective is to compare the incidence rate of SAEs, including but not limited to malignancies and serious and opportunistic infections, among MS patients treated with Vumerity, Tecfidera, and Vumerity after switching from Tecfidera with the incidence rate of MS patients treated with other selected DMTs (teriflunomide, beta-interferons, or glatiramer acetate), if the sample size allows.
Study population	• All MS patients ≥ 18 years of age who have been prescribed with Vumerity, Tecfidera, or other selected DMTs (teriflunomide, beta-interferons, or glatiramer acetate) and whose data have been captured from treatment initiation after the date of systematic data collection as part of registries participating in the Big MS Data network.

Protocol number	272MS403
Location	• National MS registries based in the Czech Republic, Denmark, France, Italy, and Sweden, and the international MSBase registry
Milestones	• Anticipated start of data collection: Q1 2024 • Anticipated end of data collection: Q4 2032 • Annual interim reports start: Q2 2024 • Final study report: Q2 2033

Table 24: Ongoing and planned additional pharmacovigilance activities

Study name and description	Summary of objectives	Safety concerns addressed relevant for DRF	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***				
Planned studies				
An Observational Study Utilising Data From Big MS Data Registries to Evaluate the Long-Term Safety of Vumerity and Tecfidera (272MS403)	*Primary Objective:* • To estimate the incidence rate of SAEs, including but not limited to malignancies and serious and opportunistic infections, among patients with MS treated with Vumerity or Tecfidera.	• Long-term safety	Annual interim reports Final study report	Q2/2033

Study name and description	Summary of objectives	Safety concerns addressed relevant for DRF	Milestones	Due dates
Ongoing studies:				
Vumerity (diroximel fumarate) Pregnancy Exposure Registry (272MS401)	*Primary Objective:* To compare the maternal, foetal, and infant outcomes of women with MS exposed to DRF during pregnancy with 2 unexposed comparator populations.	Effects on pregnancy outcomes	Annual interim reports Final CSR	 Q1/2033

PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

Not applicable.

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 DRF.

In the postmarketing setting, routine risk minimisation measures are the SmPC and PL, which are the primary tools to communicate information about the risks and benefits associated with the use of DRF. 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 by safety concern are discussed in Table 25.

Table 25: 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 an ADR in SmPC Section 4.4 (*Special warnings and precautions for use*), SmPC Section 4.8 (*Undesirable effects*), PL Section 2 (*What you need to know before you take Vumerity*), *and* PL Section 4 (*Possible side effects*). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Recommendations on risk factors and the 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*); DRF should not be initiated in patients with severe lymphopenia (lymphocyte counts < 0.5×10^9/L). • Information regarding the clinical symptoms of PML are included in PL Section 4 (*Possible side effects*). • Contraindication in patients with suspected or confirmed PML as listed in SmPC Section 4.3 (*Contraindications*) and PL Section 2 (*What you need to know before you take Vumerity*). • Recommendations for treatment interruption/discontinuation are included in the SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you take Vumerity*). • Recommendations regarding the requirement for CBCs, including lymphocytes prior to the start of treatment and regularly during treatment (lymphocyte counts should be followed until recovery), are

Safety concern	Routine risk minimisation activities
	included in SmPC Section 4.4 (*Special warnings and precautions for use*), PL Section 2 (*What you need to know before you take Vumerity*), and PL Section 4 (*Possible side effects*). 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 DRF. • Enhanced vigilance recommendations in patients with lymphopenia and/or who are considered at increased risk of PML are described in the SmPC Section 4.4 (*Special warnings and precautions for use*). • Information regarding the risk factors of PML is included in PL Section 4 (*Possible side effects*). • Information in PL Section 2 (*What you need to know before you take Vumerity*) and PL Section 4 (*Possible side effects*) advises patients to contact their doctor immediately if they believe their MS is getting worse or if they notice any new symptoms. Patients are also advised to speak with their partner or caregivers and inform them about the treatment as symptoms might arise that they may be unaware of. ***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 nonclinical carcinogenicity studies is provided in SmPC Section 5.3 (*Preclinical safety data*). ***Other routine risk minimisation measures beyond the Product Information:*** Legal status: Medicinal product subject to restricted medical prescription.
Effects on pregnancy outcome	***Routine risk communication:*** • Information regarding the findings from nonclinical 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 DRF is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception is provided in SmPC Section 4.6 (*Fertility, pregnancy and lactation*) and PL Section 2 (*What you need to know before you take Vumerity*). ***Other routine risk minimisation activities beyond the Product Information:*** Legal status: Medicinal product subject to restricted medical prescription.
Missing information	
Long-term efficacy and safety	***Routine risk communication:***

Safety concern	Routine risk minimisation activities
	• Text in SmPC Section 4.8 (*Undesirable effects*) describes the safety profile, and text in SmPC Section 5.1 (*Pharmacodynamic properties*) describes clinical efficacy and safety. • Text in PL Section 1 (*What Vumerity is and what it is used for*) advises patients on what Vumerity is used for and how it works. Text in PL Section 4 *(Possible side effects)* advises patients on side effects and informing their HCP if they experience side effects. ***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 4.2 (*Posology and method of administration*), Section 4.4 (*Special warnings and precautions for use*), and Section 5.2 (*Pharmacokinetic properties*) advises caution when treating patients with severe renal impairment. • Text in PL Section 2 (*What you need to know before you take Vumerity*) advises patients to inform their HCP if they have an existing severe kidney disease. • Text in SmPC Section 4.4 (*Special warnings and precautions for use)* describes the paucity of data in participants with renal impairment and advises caution when treating such patients. ***Other routine risk minimisation measures beyond the Product Information:*** • Legal status: Medicinal product subject to restricted medical prescription.

V. 2 Additional risk minimisation measures

Routine risk minimisation activities (as described in Part V.1) are considered sufficient to manage the safety concerns of DRF.

V. 3 Summary of risk minimisation measures

Pharmacovigilance activities and risk minimisation activities are summarised in Table 26.

Table 26: 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:***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Sections 4.4, 4.8, and PL Section 4. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	Case reports of PML will be submitted with each PSUR and assessed using standardised criteria. Targeted follow-up questionnaire. ***Additional pharmacovigilance activities:*** None.
Important potential risks		
Malignancies	***Routine risk minimisation measures:*** SmPC Section 5.3 (*Preclinical Safety*) ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional 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:*** SmPC Sections 4.6, 5.3, and PL Section 2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Vumerity (Diroximel Fumarate) Prospective MS Pregnancy Exposure Registry (DRF Study 272MS401).
Areas of missing information		
Long-term efficacy and safety	***Routine risk minimisation measures:*** SmPC Sections 4.8 and 5.1. ***Other routine risk minimisation measure:***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	Observational registry-based safety study (Vumerity Study 272MS403)
Safety profile in patients with moderate-to-severe renal impairment	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. ***Other routine risk minimisation measure:*** Legal status: Prescription Only Medicine ***Additional risk minimisation measures:*** No additional risk minimisation measures.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None. ***Additional pharmacovigilance activities:*** Observational study (Tecfidera Study 109MS401).

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR VUMERITY™ (DIROXIMEL FUMARATE)

Summary of Risk Management Plan for Vumerity™ (diroximel fumarate)

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

Controlled pharmacokinetic studies have identified treatment regimens for Vumerity and Tecfidera that result in comparable exposure levels of the same active metabolite, monomethyl fumarate (MMF). Therefore, the established Tecfidera safety data relevant to Vumerity are used to further understand the risks associated with Vumerity.

The Vumerity Summary of Product Characteristics (SmPC) and Patient Leaflet (PL) give essential information to healthcare professionals and patients on how Vumerity should be used.

This summary of the RMP for Vumerity 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 (EPAR).

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

I. The medicine and what it is used for

Vumerity is indicated for the treatment of adults with relapsing-remitting multiple sclerosis (RRMS) [see SmPC for the full indication]. It contains diroximel fumarate (DRF) as the active substance, and it is given orally.

Further information about the evaluation of the benefits of Vumerity can be found in the EPAR for Vumerity, including in its plain-language summary, available on the European Medicines Agency (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 Vumerity, together with measures to minimise such risks and the proposed studies for learning more about Vumerity's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 the Periodic Safety Update Report assessment (after approval) 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 Vumerity is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vumerity are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Vumerity. 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 missing information	
Important identified risks	• Progressive multifocal leukoencephalopathy (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

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information. See Section II.C of this summary for an overview of the postauthorisation development plan.

Important identified risks	
PML	
Evidence for linking the risk to the medicine	Similar to Tecfidera, Vumerity has the potential to lower lymphocyte counts, and lymphopenia is a known risk factor for infections, including opportunistic infections. PML has occurred in the setting of lymphopenia (< 0.91×10^9/L) after Tecfidera administration. PML case definitions (which categorise cases into Level 1 to Level 5) allow classification of cases based on varying levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out cases (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). This adjudication process has been used to identify confirmed PML cases (Level 1) in association with Tecfidera use (and other products

Important identified risks	
	containing fumaric acid esters) in the setting of lymphopenia (< 0.91 × 10^9/L). Consequently, PML is an important identified risk for Vumerity and wording relating to the detection and management of PML is included in the Vumerity SmPC (Section 4.4 [*Special warnings and precautions for use*]).
Risk factors and risk groups	PML can only occur in the presence of a John Cunningham virus (JCV) infection, with studies indicating that approximately 60% to 70% of multiple sclerosis (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, those 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, some patient populations have a higher risk of developing PML, including those with human immunodeficiency virus (HIV); those with malignancies (including non-Hodgkin's lymphoma and chronic lymphocytic leukaemia [CLL]); those diagnosed with systemic lupus erythematosus (SLE), sarcoidosis, or autoimmune vasculitis; and those undergoing bone marrow transplantation. With regard to Tecfidera, the finding common to all confirmed cases of PML reported to date has been the presence of lymphopenia (< 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, in Tecfidera- and Vumerity-treated patients, lymphopenia is considered a risk factor. Information from studies evaluating lymphopenia associated with Tecfidera treatment have shown that absolute lymphocyte counts (ALC) was highly correlated with total, cluster of differentiation (CD)4+, 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 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 4.4 and 4.8, and PL Section 4. Legal status: Medicinal product subject to restricted medical prescription.

Important identified risks	
	Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	None
Important potential risks	
Malignancies	
Evidence for linking the risk to the medicine	In Study ALK8700-A301, there were 5 reported malignancies, and no malignancy was seen in greater than one participant. 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 non-clinical 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 those observed in the general population.
Risk factors and risk groups	None known
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 5.3. ***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	Reproductive toxicology studies conducted with Vumerity revealed no impairment of male and female fertility in rats, no teratogenicity in rats and rabbits, and no pre- and postnatal development toxicity in rats at MMF and 2-hydroxyethyl succinimide (HES) exposure area under the concentration-time curve (AUC) at least 2 times the recommended human dose (RHD) of Vumerity. At maternal toxic doses, the offspring of Tecfidera-treated pregnant animals exhibited skeletal variations in rats and skeletal variations/malformations in rabbits; these findings occurred at MMF AUC that was approximately 10 times the RHD of Vumerity in rats and ≥ 6 times that in rabbits. At a toxic dose to pregnant rats, with MMF exposure (AUC) that was approximately 10 times of that at the RHD of Vumerity, decreased birth weights and body weights/weight gains during the preweaning period were noted in the offspring. Except

Important identified risks	
	for skeletal malformations in rabbits, similar embryo-foetal developmental findings have been reported for Tecfidera. However, no adequate data exist on the developmental risk associated with the use of Vumerity in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. Ten pregnancies have been reported in the DRF clinical study programme (Study ALK8700-A110 and Study ALK8700-A301). The outcome in 60% was the delivery of healthy, full-term infants; 2 pregnancies resulted in spontaneous abortions; and 2 pregnancies were terminated by elective abortions. The impact of Vumerity on pregnancy outcomes is being evaluated in a prospective pregnancy registry (Study 272MS401). The effects of Vumerity on labour and delivery are unknown. Current data from clinical trials including the Biogen Multiple Sclerosis Pregnancy Exposure Registry (Study 109MS402) and the postmarketing setting do not suggest that Tecfidera, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. The observations from these studies are relevant to DRF given the shared common active metabolite, MMF, with Tecfidera.
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	Vumerity Pregnancy Exposure Registry.
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	Observational registry-based safety study (Vumerity Study 272MS403).

Important identified risks	
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 risk minimisation measures:*** No additional risk minimisation measures.
Additional pharmacovigilance activities	None

II.C Postauthorisation development plan

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

There are no studies that are conditions of the marketing authorisation or specific obligation of Vumerity.

II.C.2 Other studies in postauthorisation development plan

Other studies in the postauthorisation development plan are as follows:

- **Vumerity Pregnancy Exposure Registry Study 272MS401:**
  - *Purpose of the study:* To compare the maternal, foetal, and infant outcomes of women with MS exposed to Vumerity during pregnancy with 2 unexposed comparator populations.
- **Vumerity Observational Registry-Based Safety Study 272MS403:**
  - *Purpose of the study*: To estimate the incidence rate of SAEs, including but not limited to malignancies and serious and opportunistic infections, among patients with MS treated with Vumerity or Tecfidera.

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

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: _____

6) Provide details of all 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:					

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

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)

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 3 and 6 (Governed by DEV-SOP-836)	RD-FORM-2065 Version: 8.0 Page 3 of 6

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: #####

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 5 of 6

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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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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)

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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

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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)

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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).

Vumerity Breast Cancer

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

1. Specify the patient's type, stage, and grade of breast cancer.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (e.g., date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, then provide that information. Please include baseline values as well as reference ranges for any and all lab tests.
3. 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. Provide any social risk factors for breast cancer (e.g., smoking, alcohol consumption).
5. List the medications the patient has taken in the past 2 years.
6. 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, then provide the findings.
8. 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 HER-2/neu protein? If so, then provide test results. Please include baseline values as well as reference ranges for any and all lab tests.
10. Provide results from the physical exam.
11. If the patient was hospitalized, then provide discharge report.
12. Provide any treatments the patient received for the event.
13. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity Cervical Cancer

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

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

Vumerity Colon Cancer

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

1. Specify the patient's type, stage, and grade of colon cancer.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (e.g., date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, then provide that information. Please include baseline values as well as reference ranges for any and all lab tests.
3. Indicate if the patient has had any recent infections (e.g., bacterial, fungal, spirochetes, etc.).
4. 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. List all medications the patient has taken in the past 2 years.
6. 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, then provide the findings and the date it was performed.
8. If tumor marker(s) was/were analyzed, then provide the name of the marker(s) which was/were found and the date of the analysis.
9. Provide results and dates from all pathology or cytology studies.
10. Provide results from all imaging studies.
11. Provide results from physical examination.
12. If the patient was hospitalized, then provide discharge report.
13. Provide any treatments the patient received for the event.
14. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity Endometrial Cancer

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

1. Specify the patient's type, stage, and grade of endometrial cancer.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (e.g., date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, then provide that information. Please include baseline values as well as reference ranges for any and all lab tests.
3. 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. List the medications the patient has taken in the past 2 years.
5. Provide any concomitant medications the patient is taking, including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
6. Provide results from all pathology or cytology studies.
7. Provide results from all imaging studies.
8. Provide results from physical examination.
9. If the patient was hospitalized, then provide discharge report.
10. Provide any treatments the patient received for the event.
11. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity General Malignancy

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

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

Vumerity Lymphoma

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

1. Specify the patient's type and stage of lymphoma.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (e.g., date of lab test, absolute lymphocyte count). Provide lymphocyte subset data (CD4, CD8) if it was checked. Please include baseline values as well as reference ranges for any and all lab tests.
3. Indicate if the patient has had any recent infections (e.g., bacterial, fungal, spirochetes, etc.).
4. Indicate if the patient has a history of cancer.
5. Provide any medical history risk factors the patient had for lymphoma (e.g., family history, chromosomal abnormalities, transplantation, history of immune suppression, human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS], etc.).
6. List the medications the patient has taken in the past 2 years.
7. Provide any concomitant medications the patient is taking, including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
8. If a tissue biopsy was performed, then provide the findings.
9. Provide results from all imaging studies.
10. Provide results from physical examination.
11. Provide results from all laboratory tests. Please include baseline values as well as reference ranges for any and all lab tests.
12. If the patient was hospitalized, then provide discharge report.
13. Provide any treatments the patient received for the event.
14. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity Melanoma

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

1. Specify the patient's type, stage, and grade of melanoma.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (e.g., date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, then provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Indicate if the patient has had any recent infections (e.g., bacterial, fungal, spirochetes, etc.).
4. Indicate if the patient has a history of cancer.
5. Provide any medical history risk factors the patient had for melanoma (e.g., ultraviolet light exposure, family history of melanoma, pigmented lesions, etc.).
6. Indicate if the patient has a family history of melanoma skin cancer and describe the family history.
7. List all medications the patient has taken in the past 2 years.
8. 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, then provide the findings and the date it was performed.
10. If tumor marker(s) was/were analyzed, then provide the name of the marker(s) which were found and the date of the analysis.
11. Provide results from all imaging studies.
12. Provide results from physical examination.
13. If the patient was hospitalized, then provide discharge report.
14. Provide any treatments the patient received for the event.
15. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity Non-Melanoma Skin Cancer

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

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

Vumerity Non-Small Cell Lung Cancer

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

1. Specify the patient's type, stage, and grade of non-small cell lung cancer.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, then provide that information. Please include baseline values as well as reference ranges for any and all lab tests.
3. Indicate if the patient was exposed to tobacco smoke, how many packs per day they smoke(d), if they currently smoke, if they are exposed to second-hand smoke, or if they have a remote history of smoking.
4. 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. Indicate if the patient has any other lung diseases, such as chronic obstructive pulmonary disease (COPD), lung fibrosis, tuberculosis, etc.
6. Indicate if the patient has a family history of lung cancer and describe the family history.
7. List the medications the patient has taken in the past 2 years.
8. Provide any concomitant medications the patient is taking, including prescription medications, OTC, dietary supplements, vitamins, and herbs.
9. If a tissue biopsy was performed, then provide the findings and the date it was performed.
10. If tumor marker(s) was/were analyzed, then provide the name of the marker(s) which was/were found and the date of the analysis.
11. Provide results from all imaging studies.
12. Provide results from physical examination.
13. Provide the patient's pulmonary function test results and the date they were performed.
14. If the patient was hospitalized, then provide discharge report.
15. Provide any treatments the patient received for the event.
16. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity Prostate Cancer

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

1. Specify the patient's type, stage, and grade of prostate cancer.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (e.g., date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, then provide that information. Please include baseline values as well as reference ranges for any and all lab tests.
3. Indicate if the patient has had any recent infections (e.g., bacterial, fungal, spirochetes, etc.).
4. Indicate if the patient has a history of cancer.
5. Indicate if the patient has a history of right- or left-sided heart failure.
6. 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. List the medications the patient has taken in the past 2 years.
8. 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, then provide the findings.
10. Provide results from all imaging studies.
11. Provide results from physical examination.
12. 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 data.
13. If the patient was hospitalized, then provide discharge report.
14. Provide any treatments the patient received for the event.
15. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity Renal Cell Carcinoma

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

1. 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. Provide any available information on the histological type of cancer (e.g., clear cell vs. papillary).
3. List the medications the patient has taken in the past 2 years.
4. Provide any concomitant medications the patient is taking, including prescription medications, over the counter (OTC), dietary supplements, vitamins, and herbs.
5. Provide the clinical signs and symptoms of the patient and the date at which each sign or symptom began.
6. 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 (CrCl)
    f. Any other tests related to the diagnosis or management of renal cell carcinoma.
7. Provide results from urinalysis, or state that it was not performed.
8. If a tissue biopsy was performed, then provide the findings.
9. Provide results from all imaging studies.
10. Provide results from the physical exam.
11. If the patient was hospitalized, then provide discharge report.
12. Provide any treatments the patient received for the event.
13. Provide outcome for event and date of resolution, if applicable. If the patient recovered with sequelae, then describe the sequelae.

Vumerity Small Cell Lung Cancer

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

1. Specify the patient's type, stage, and grade of small cell lung cancer.
2. Did the patient develop lymphopenia while on Vumerity? Provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, then provide that information. Please include baseline values as well as reference ranges for any and all lab tests.
3. Indicate if the patient was exposed to tobacco smoke, how many packs per day they smoke(d), if they currently smoke, if they are exposed to second-hand smoke, or if they have a remote history of smoking.
4. 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. Indicate if the patient has any other lung diseases, such as chronic obstructive pulmonary disease (COPD), lung fibrosis, tuberculosis, etc.
6. Indicate if the patient has a family history of lung cancer and describe the family history.
7. List the medications the patient has taken in the past 2 years.
8. 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, then provide the findings and the date it was performed.
10. If sputum cytology was performed, then provide the findings and the date it was performed.
11. If tumor marker(s) was/were analyzed, then provide the name of the marker(s) which was/were found and the date of the analysis.
12. Provide results from all imaging studies.
13. Provide results from physical examination.
14. 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, then provide discharge report.
16. Provide any treatments the patient received for the event.
17. Provide outcome for event and date of resolution, if applicable. If the event recovered with sequelae, then describe the sequelae.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

None.