RISK MANAGEMENT PLAN
For
Dimethyl Fumarate
Version 1.0

RMP Version to be Assessed as Part of this Application:

RMP Version Number	1.0
Data Lock Point for this RMP	10-Jul-2023
Date of Final Sign Off	11-Mar-2024
Rationale for Submitting an Updated RMP	• RMP amended to reflect the final approved RMP version at the end of the initial marketing authorisation application
Summary of Significant Changes in this RMP	• RMP amended to reflect the final approved RMP version at the end of the initial marketing authorisation application

Other RMP Versions Under Evaluation:

RMP Version Number	0.2
Submitted On	03-Jan-2024
Procedure Number	EMEA/H/C/006397

Details of the Current RMP:

Version Number	Not applicable
Approved with Procedure	Not applicable
Date of Approval (Opinion Date)	Not applicable

Approver	Dr Eiko Soehlke, MD MPH, EEA QPPV
Signature	
E-mail address of contact person	[redacted]

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CP	Centralised Procedure
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
HCP	Healthcare Professional
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
PL	Package leaflet
PML	Progressive Multifocal Leukoencephalopathy
QPPV	Qualified Person for Pharmacovigilance
DLP	Data Lock Point
SPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Dimethyl fumarate
Pharmacotherapeutic Group(s) (ATC Code)	Immunosuppressants, other immunosuppressants (ATC code: L04AX07)
Marketing Authorisation Applicant	Mylan Ireland Limited
Medicinal Products to Which this RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)	Dimethyl Fumarate Mylan
Marketing Authorisation Procedure	Centralized (EMEA/H/C/006397)
Brief Description of the Product	Chemical class: Fumurate ester drug productcontaining the active ingredient DMF. Summary of mode of action: The mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood. Preclinical studies indicate that dimethyl fumarate pharmacodynamic responses appear to be primarily mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway. Dimethyl fumarate has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1]). If applicable, mention important information about its composition: Not applicable
Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier
Indication(s) in the EEA Current	Current: Dimethyl fumarate Mylan is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS). Proposed: Not applicable.

[redacted]

Dosage in the EEA **Current**	Current: Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis. Posology The starting dose is 120 mg twice a day. After 7 days, the dose should be increased to the recommended maintenance dose of 240 mg twice a day. Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended maintenance dose of 240 mg twice a day should be resumed. Proposed: Not applicable.
Pharmaceutical Form(s) and Strengths **Current**	Current: 120 mg and 240 mg gastro-resistant hard capsules. Proposed: Not applicable.
Will the Product Be Subject to Additional Monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Not applicable.

Part II: Module SII - Non-clinical Part of the Safety Specification

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Not applicable.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Not applicable.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Not applicable.

Part II: Module SV - Post-authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

This is a MAA for a generic medicine in which the safety concerns available in the RMP for the reference medicinal product (Tecfidera® EU RMP version 15.0 dated 19-Oct-2022) have been adopted by the Applicant.

[redacted]

Table 2: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	• PML • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury
Important Potential Risks	• Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Effects on pregnancy outcome • Interaction with nephrotoxic medications leading to renal toxicity
Missing Information	• Long term efficacy and safety • Safety profile in patients over the age of 55 years • Safety profile in patients with moderate to severe renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the initial RMP for dimethyl fumarate.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable as this RMP for dimethyl fumarate follows the same safety concerns as the safety concerns of the reference substance Tecfidera® RMP.

SVII.3.2. Presentation of the Missing Information

Not applicable as this RMP for dimethyl fumarate follows the same safety concerns as the safety concerns of the reference substance Tecfidera® RMP.

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: SVIII- Summary of safety concerns

Important Identified Risks	• PML • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury
Important Potential Risks	• Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Effects on pregnancy outcome • Interaction with nephrotoxic medications leading to renal toxicity
Missing Information	• Long term efficacy and safety • Safety profile in patients over the age of 55 years • Safety profile in patients with moderate to severe renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

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

The Pharmacovigilance System Master File contains details of the system and processes that the MAH/Applicant has in place to identify and/or characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities only.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for PML, drug-induced liver injury, serious and opportunistic infections (other than PML and herpes zoster), malignancies, moderate lymphopenia, and severe lymphopenia:

The forms are provided in Annex 4 - Specific Adverse Drug Reaction Follow-up Forms of the RMP.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES

The safety information in the proposed product information is aligned to the reference medicinal product (Tecfidera®, by Biogen Idec Ltd).

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Not applicable.

V.2 Additional Risk Minimisation Measures

Not applicable as routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary Table of Pharmacovigilance and Risk Minimisation Activities by Safety Concern

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Dimethyl fumarate Mylan (dimethyl fumarate)

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

Dimethyl fumarate Mylan's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Dimethyl fumarate Mylan should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Dimethyl fumarate Mylan's RMP.

I. The Medicine and What it is Used For

Dimethyl fumarate Mylan is authorised for treatment of relapsing remitting multiple sclerosis (RRMS) in adults and paediatric patients aged 13 years and older. It contains dimethyl fumarate as the active substance, and it is given by oral route.

Further information about the evaluation of Dimethyl fumarate Mylan’s benefits can be found in Dimethyl fumarate Mylan’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage (this line should be only edited by EMA): link to the EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Dimethyl fumarate Mylan, together with measures to minimise such risks are outlined below.

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 Dimethyl fumarate Mylan is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Dimethyl fumarate Mylan are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dimethyl fumarate Mylan. 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 is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.);

Table 4: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• PML • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury
Important Potential Risks	• Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Effects on pregnancy outcome • Interaction with nephrotoxic medications leading to renal toxicity
Missing Information	• Long term efficacy and safety • Safety profile in patients over the age of 55 years • Safety profile in patients with moderate to severe renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Dimethyl fumarate Mylan.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Dimethyl fumarate Mylan.

[redacted]

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Adverse event follow up forms will be distributed for potential/confirmed events of PML, drug- induced liver injury, serious and opportunistic infections (other than PML and herpes zoster), malignancies, moderate lymphopenia, and severe lymphopenia (see Part III [Pharmacovigilance Plan] of the EU RMP 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 Tools.
- Liver Disease Data Collection Tool.
- Serious Infections Data Collection Tool.
- Moderate Lymphopenia Data Collection Tool.
- Severe Lymphopenia Data Collection Tool.

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl Fumarate - Multiple Sclerosis Suspect Progressive Multifocal Leukoencephalopathy Data Collection Tool

I. Patients Details:

Patient Name: 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 □ Dimethyl fumarate □ Vumerity

□ Fampyra/Ampyra □ Plegridy □ Other:

Total exposure (months or doses): __

Date of last dose received: (DD/MMM/YYYY)

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:

TARGETED FOLLOW UP FORM
Case No.:

Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Dose	Frequency of Dosing	Number of Infusions (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 □ Dimethyl fumarate □ Vumerity

□ Fampyra/Ampyra □ Plegridy □ Other:

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 #

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

Since discontinuation of suspect product, is the patient being treated with any other MS therapy? □ Yes □ No If yes, specify:

VI. Multiple Sclerosis History

1) **MS diagnosis date:** _____ (DD/MMM/YYYY)
2) **Provide the MS therapies used prior to Primary Suspect Product:**

TARGETED FOLLOW UP FORM
Case No.:

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

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 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 signs 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 with onset dates that led to the evaluation for possible PML (even if identified in retrospect):

Symptoms	Date (DD/MMM/YYYY)

TARGETED FOLLOW UP FORM
Case No.:

3) **Provide copies of MRI reports. If not possible, provide detailed MRI results including lesion characteristics and location.**

a. MRI <u>at the time</u> 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:

(Provide copies of MRI images)[1,2]

4) **Provide details of lumbar puncture (LP) and CSF sample collection (please provide all tests, even if multiple assays are performed on a single puncture):**

(Provide copies of the CSF JCV DNA test results.)

	Test 1	**Test2**	**Test3**
Date of LP (DD/MMM/YYYY)			
LP performed Pre-PLEX (if applicable)	□Yes □No	□Yes □No	□Yes □No
CSFJCVDNA 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)

Please provide cell count: _____

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

TARGETED FOLLOW UP FORM
Case No.:

(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) **Has a brain biopsy been 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 ever lymphopenic within 12 months prior to PML suspicion?**

□ Yes □ No

Date (DD/MMM/YYYY)	WBC	Lymphocyte (%)	Absolute Lymphocyte Count	Lymphocyte Subset Analysis: (CD4, CDS, 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

TARGETED FOLLOW UP FORM
Case 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

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

Immunoadsorption (IA): □ Yes □ No

IA 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:

Reported Cause of Death: (DD/MMM/YYYY)

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 Status

On Primary Suspect Product prior to PML

TARGETED FOLLOW UP FORM
Case No.:

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[1] Definitions/Criteria		
Able to carry on normalactivity 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	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.

Karnofsky performance Status Scale Definitions/Criteria		
needed.		
Unable to care for self;requires equivalent of institutional or hospitalcare; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not
	20	Very sick; hospital admission necessary; active supportive treatment
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

XI. Rule Out PML

1) **Based on your evaluation, has PML been ruled out?** □ Yes □ No □ Still under investigation

2) **If PML has been 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?**

Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Additional Information:_____

_____

_____

[1] Additionally include copies of the radiology reports for 6 months prior to PML suspicion, if available.

[2] Kindly email to [redacted] for instructions on sending MRI images.

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate - Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 3 and 6

I. Patients Details:

Patient Name: 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 □ Avonex □ Dimethyl fumarate

□ Vumerity □ Fampyra/Ampyra □ Plegridy

IV. Functional Status post PML diagnosis: (please see table below)

a. EDSS: Date: (DD/MMM/YYYY)

b. Karnofsky score: Date: (DD/MMM/YYYY)

c. Modified ranking Score: Date: (DD/MMM/YYYY)

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

TARGETED FOLLOW UP FORM
Case No.:

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
	20	Very sick; hospital admission necessary; active supportive treatment
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

V. Test results Post-PML diagnosis: (provide a copy of test results):

Provide copies of MRI reports, including most recent MRI report, and MRI images, if not already provided[1,2]. If not possible, provide detailed MRI results including lesion characteristics and location:

Date of MRI: (DD/MMM/YYY)

Brief 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	Test2	Test3
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

TARGETED FOLLOW UP FORM
Case No.:

	Test 1	Test2	Test3
Quantitative (copies/mL)			
Laboratory Name and Limit of Detection			

Date (DD/MMM/ YYYY)	**WBC**	**Lymphocyte** (%)	**Absolute Lymphocyte Count**	**Lymphocyte Subset Analysis: (CD4, CDS, 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		

TARGETED FOLLOW UP FORM
Case No.:

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. Has the patient been diagnosed with PML-IRIS?

□ Yes; onset date (DD/MMM/YYYY): □ No

a) a. **Any new or worsening symptoms?** □ Yes □ No
If yes, specify the symptoms and onset:

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 <u>pre-PML_IRIS</u> onset? □ Yes □ No

b. Did the patient receive corticosteroids <u>post-PML-IRIS</u> onset? □ Yes □ No

Specify all treatments the patient has received for PML-IRIS: (*<u>including corticosteroid regimens</u>*)

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

TARGETED FOLLOW UP FORM
Case No.:

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 products?

□ Related □ Not Related □ Unknown

□ Tysabri □ Avonex □ Dimethyl fumarate □ Zinbryta

□ Fampyra/Ampyra

□ Plegridy

Reporter's Details:

Name: Sign

Occupation: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Additional Information:_____

_____

_____

[1] Additionally include copies of the radiology reports for 6 months prior to PML suspicion, if available.

[2] Kindly email to [redacted] for instructions on sending MRI images.

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl Fumarate - Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy Data Collection Tool for Months 12 and 24

I. Patients Details:

Patient Name: 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 anonymized copy of the autopsy report)

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

□ Yes □ No

□ Tysabri □ Avonex □ Dimethyl fumarate

□ Vumerity □ Fampyra/Ampyra □ Plegridy

IV. Current Functional Status/ Estimated Karnofsky Score (0-100): (please see table below)

a) EDSS (most recent): Date: (DD/MMM/YYYY)

b) Karnofsky (most recent): Date: (DD/MMM/YYYY)

c) Modified Rankin Score: Date: (DD/MMM/YYYY)

TARGETED FOLLOW UP FORM
Case No.:

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
	20	Very sick; hospital admission necessary; active supportive treatment
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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

Provide copies of MRI reports, including most recent MRI report, and the MRI images if not already provided[1,2]. If not possible, provide detailed MRI results including lesion characteristics and location.

Date of MRI: (DD/MMM/YYYY)

TARGETED FOLLOW UP FORM
Case No.:

Detailed description:

Date (DD/MMM/YYYY)	**WBC**	**Lymphocyte** (%)	**Absolute Lymphocyte Count**	**Lymphocyte Subset Analysis:(CD4, CDS, 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)

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 products?

□ Related □ Not Related □ Unknown

□ Tysabri □ Avonex □ Dimethyl fumarate

□ Vumerity □ Fampyra/Ampyra □ Plegridy

TARGETED FOLLOW UP FORM
Case No.:

Reporter's Details:

Name: Sign

Occupation: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Additional Information: _____

_____

_____

[1] Additionally include copies of the radiology reports for 6 months prior to PML suspicion, if available.

[2] Kindly to email [redacted] for instructions on sending MRI images.

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate - Malignancies Data Collection Tools

A. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

B. Please answer the general malignancy questionnaire and relevant questionnaire if applicable from the list in the table of contents below

Table of Contents

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate General Malignancy

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

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Breast Cancer

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

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Cervical Cancer

To provide consistency in our due diligence of Dimethyl fumarate cervical cancer reports, please ask thefollow-up questions below.

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Colon Cancer

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

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Endometrial Cancer

To provide consistency in our due diligence of Dimethyl fumarate endometrial cancer reports, please ask thefollow-up questions below.

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Lymphoma

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

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Melanoma

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

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Non-Melanoma

To provide consistency in our due diligence of Dimethyl fumarate non-melanoma reports, please ask thefollow-up questions below.

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Non-Small cell lung cancer

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

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Prostate cancer

To provide consistency in our due diligence of Dimethyl fumarate prostate cancer reports, please ask thefollow-up questions below.

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Renal cell carcinoma

To provide consistency in our due diligence of Dimethyl fumarate renal cell carcinoma reports, please ask thefollow-up questions below.

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

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate Small cell lung cancer

To provide consistency in our due diligence of Dimethyl fumarate small cell lung cancer reports, please askthe follow-up questions below.

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

TARGETED FOLLOW UP FORM
Case No.:

C. Do you believe there is a possibility that this adverse event was related to the drug used? ☐ Yes ☐ No ☐ Unknown

If yes, please confirm which drug: _____

D. Reporter's Details:

Name: Sign

Occupation: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Additional Information: _____

_____

_____

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate serious liver disease Data Collection Tool

A. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

B. To provide consistency in our due diligence of Dimethyl fumarate serious liver disease/ liver injury reports, please ask the follow-up questions below.

1.Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).

2.Please indicate if the patient has a history of right or left sided heart failure. Does patient have history of hypotension?

3.Please provide any medical history risk factors the patient had for liver disease / liver injury (e.g., alcohol intake, family history of liver disease or liver injury, history of nonalcoholic steatohepatitis (NASH), obesity, sexual promiscuity, etc.).

4.Please list all medications the patient has taken in the past 2 years.

5.Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins and herbs.

6.Please provide all signs and symptoms of liver disease / liver injury including dates of each event (e.g., jaundice, confusion, dark urine, severe abdominal pain, etc.).

7.Please provide the below laboratory results for the patient. Include reference ranges, baseline levels and levels for the treatment and management of the event.

a. Liver function tests

b. Renal function tests

c. Viral Hepatitis profile

d. Complete blood count with differential

e. Autoantibodies

f. Any other tests related to the diagnosis or management of liver disease/ liver injury.

8. Please provide results from all imaging studies.

9. Please provide results from the physical exam.

10. If the patient was hospitalized, please provide discharge report.

11. Please provide any treatments the patient received for the event.

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

C. Do you believe there is a possibility that this adverse event was related to the drug used? ☐ Yes ☐ No ☐ Unknown

If yes, please confirm which drug: _____

D. Reporter's Details:

Name: Sign

Occupation: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Additional Information: _____

_____

_____

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate- Serious Infections Data Collection Tool

A. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

B. To provide consistency in our due diligence of Dimethyl fumarate serious infection/ opportunistic infection reports, please ask the follow-up questions below.

1. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
2. Did the patient develop lymphopenia while on dimethyl fumarate ? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please provide any medical history risk factors the patient had for a serious or opportunistic infection (e.g., history of immunosuppression, human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS], transplant, chronic infectious disease, history of malignancy, or other autoimmune disorders).
4. Please provide details of above or any other relevant medical history or risk factors for infection (e.g., prior infections, background disease at site of infection such as chronic obstructive pulmonary disease [COPD] and pneumonia).
5. Please list all medications the patient has taken in the past 2 years.
6. Please provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins and herbs.
7. Please provide the below laboratory results for the patient. Include reference ranges, baseline levels and levels for the treatment and management of the event.
    a. Complete blood count with differential
    b. HIV panel
    c. Any other tests related to the diagnosis or management of serious / opportunistic infections (e.g., blood cultures, urinalysis, etc.)
8. Please provide results from all imaging studies.
9. Please provide results from the physical exam.
10. For central nervous system (CNS) infections, please provide results of a neurological assessment.
11. If the patient was hospitalized, please provide discharge report.
12. Please provide any treatments the patient received for the event.

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

C. Do you believe there is a possibility that this adverse event was related to the drug used? ☐ Yes ☐ No ☐ Unknown

If yes, please confirm which drug: _____

D. Reporter's Details:

Name: Sign

Occupation: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Additional Information: _____
_____
_____

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate - Moderate Lymphopenia Data Collection Tool

A. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

B. To provide consistency in our due diligence of Dimethyl fumarate moderate lymphopenia reports, please ask the follow-up questions below.

Moderate lymphopenia (500/µL < absolute lymphocyte < 800/µL)

Check action taken - if dose was not reduced or withdrawn ask for the following:

1. What was the action taken with Dimethyl fumarate therapy?
2. Please provide Absolute lymphocyte count from a recent date. Please include baseline values as well as reference ranges.
3. Please provide White blood cell count from a recent date. Please include baseline values as well as reference ranges.
4. Please provide Lymphocyte percentage from a recent date. Please include baseline values as well as reference ranges.
5. Please provide differential lymphocyte counts, if available, especially CD4+ and CD8+ counts from a recent date. Please include baseline values as well as reference ranges.
6. Please provide the outcome for lymphopenia and date of resolution, if applicable. If the patient recovered with sequelae, describe the sequelae.

C. Do you believe there is a possibility that this adverse event was related to the drug used? ☐ Yes ☐ No ☐ Unknown

If yes, please confirm which drug: _____

D. Reporter's Details:

Name: Sign

Occupation: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Additional Information:_____

_____

_____

TARGETED FOLLOW UP FORM
Case No.:

Dimethyl fumarate - Severe Lymphopenia Data Collection Tool

A. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

B. To provide consistency in our due diligence of Dimethyl fumarate severe lymphopenia reports, please ask the follow-up questions below.

Severe lymphopenia (absolute lymphocyte count less than 500/µL)

1. Please provide the outcome for lymphopenia and date of resolution, if applicable. If the patient recovered with sequelae, describe the sequelae.
2. Please provide Absolute lymphocyte count from a recent date. Please include baseline values as well as reference ranges.
3. Please provide White blood cell count from a recent date. Please include baseline values as well as reference ranges.
4. Please provide Lymphocyte percentage from a recent date. Please include baseline values as well as reference ranges.
5. Please provide differential lymphocyte counts, if available, especially CD4+ and CD8+ counts from a recent date. Please include baseline values as well as reference ranges.
6. What was the Action taken with Dimethyl fumarate? If discontinued, was Dimethyl fumarate restarted?

C. Do you believe there is a possibility that this adverse event was related to the drug used? ☐ Yes ☐ No ☐ Unknown

If yes, please confirm which drug: _____

D. Reporter's Details:

Name: Sign

Occupation: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Additional Information: _____

_____

_____

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.