EU Risk Management Plan

For

Dimethyl fumarate Accord 120 mg gastro-resistant hard capsules
Dimethyl fumarate Accord 240 mg gastro-resistant hard capsules
(Dimethyl fumarate)

RMP version to be assessed as part of this application:

RMP Version number	2.0
Data lock point for this RMP	08-Oct-2024
Date of final sign off	12-Nov-2024

Rationale for submitting an RMP: The RMP has been updated in line with the reference product Tecfidera (Dimethyl Fumarate) Risk management plan (version 17.0, dated 19-Aug-2024), published by EMA on 26-Sep-2024.

Summary of significant changes in this RMP: Significant changes have been made in the following sections of this RMP: Part II, Part III, Part VI and Part VII (Annex 4, Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

RMP Version number	Approved with procedure	Date of approval (opinion date)
1.0	EMEA/H/C/006471/0000	21-Mar-2024

QPPV Name: Dr. Arletta Werynska

QPPV Signature: [redacted]

[redacted]

TABLE OF CONTENT

[redacted]

LIST OF TABLES

Part I: Products Overview

Table 1: Product Overview

Active substance (INN or common name)	Dimethyl fumarate
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group(s):** Immunosuppressants, other immunosuppressants **ATC code:** L04AX07
Marketing Authorisation Holder	Accord Healthcare S.L.U, Spain
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)	Dimethyl fumarate Accord 120 mg gastro-resistant hard capsules Dimethyl fumarate Accord 240 mg gastro-resistant hard capsules
Marketing authorisation procedure	Centralised procedure (EMEA/H/C/006471/0000)
Brief description of the product	Chemical class: Dimethyl Fumarate is an orally bioavailable methyl ester of fumaric acid and activator of nuclear factor erythroid 2 [NF-E2]-related factor 2 (Nrf2, Nfe2l2), with potential neuroprotective, immunomodulating and radiosensitising activities.
	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]).
	Important information about its composition: *Dimethyl fumarate Accord 120 mg gastro-resistant hard capsules* Each gastro-resistant hard capsule contains 120 mg dimethyl fumarate *Dimethyl fumarate Accord 240 mg gastro-resistant hard capsules* Each gastro-resistant hard capsule contains 240 mg dimethyl fumarate
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC and PIL
Indication(s) in the EEA	***Current*** Dimethyl fumarate Accord is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).
Dosage in the EEA	***Current*** 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. If a patient misses a dose, a double dose should not be taken. The patient may take the missed dose only if they leave 4 hours between doses. Otherwise the patient should wait until the next scheduled dose. 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. Dimethyl fumarate Accord should be taken with food. For those patients who may experience flushing or gastrointestinal adverse reactions, taking Dimethyl fumarate Accord with food may improve tolerability Method of administration Dimethyl fumarate should be administered orally.
Pharmaceutical forms and strengths	***Current*** Gastro resistant hard capsules 120 mg and 240 mg
Is the product 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

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII - Identified and potential risks

The safety concerns for this Risk Management Plan (RMP) have been updated in-line with European Public Assessment Report (EPAR) - RMP of Tecfidera (Dimethyl fumarate) (version 17.0, dated 19-Aug-2024) published on EMA website on 26-Sep-2024. There is no change by MAH in safety concerns mentioned in Module SVIII.

Hence this section remains “Not applicable”.

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

Not applicable

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

Not applicable

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

Not applicable

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

SVII.3.2. Presentation of the missing information

Not Applicable

Part II: Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concern listed in module SVIII.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for following risks concerning use of dimethyl fumarate:

- Progressive Multifocal Leukoencephalopathy (PML)
- Malignancies

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

Targeted follow-up questionnaires and data collection forms are appended in Annex 4 of this RMP.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

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

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules (Dimethyl fumarate)

This is a summary of the risk management plan (RMP) for Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules. The RMP details important risks of Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules how these risks can be minimised, and how more information will be obtained about Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules's risks and uncertainties (missing information).

Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules's summary of product characteristics (SmPC) and package leaflets give essential information to healthcare professionals and patients on how Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules should be used.

This summary of the RMP for Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules should be read in the context of all this 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 Accord 120/240 mg gastro resistant hard capsules's RMP.

I. The medicine and what it is used for

Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

It contains dimethyl fumarate as the active substance and it is given by oral route.

Further information about the evaluation of Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules' benefits can be found in Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/dimethyl-fumarate-accord

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

Important risks of Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules, together with measures to minimise such risks and the proposed studies for learning more about Dimethyl fumarate Accord 120/ 240 mg gastro resistant hard capsules' 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 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, 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 Accord 120/240 mg gastro resistant hard capsules 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 Accord 120/240 mg gastro resistant hard capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Accord 120/240 mg gastro resistant hard capsules. 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).

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

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 Accord 120/240 mg gastro resistant hard capsules.

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

There are no studies required for Dimethyl fumarate Accord 120/240 mg gastro resistant hard capsules.

Annex 4 - Specific adverse drug reaction follow-up forms

MAH proposed specific adverse reaction targeted questionnaires for potential/confirmed events of PML, and malignancies.

The follow-up forms for distribution to healthcare professionals or patients post receipt of ICSR for relevant drug-event combination are provided in this annex below:

- Multiple Sclerosis Suspect PML Data Collection Tool
- Multiple Sclerosis Confirmed PML Data Collection Tool for Months 3 and 6
- Multiple Sclerosis Confirmed PML Data Collection Tool for Months 12 and 24
- Targeted Follow-Up Questionnaires for Malignancies:
    - Targeted Follow-Up Questionnaire for General Malignancy
    - Targeted Follow-Up Questionnaire for Breast Cancer
    - Targeted Follow-Up Questionnaire for Cervical Cancer
    - Targeted Follow-Up Questionnaire for Colon Cancer
    - Targeted Follow-Up Questionnaire for Endometrial Cancer
    - Targeted Follow-Up Questionnaire for Lymphoma
    - Targeted Follow-Up Questionnaire for Melanoma
    - Targeted Follow-Up Questionnaire for Non-Melanoma
    - Targeted Follow-Up Questionnaire for Non-Small Cell Lung Cancer
    - Targeted Follow-Up Questionnaire for Prostate Cancer
    - Targeted Follow-Up Questionnaire for Renal Cell Carcinoma
    - Targeted Follow-Up Questionnaire for Small Cell Lung Cancer

Multiple Sclerosis Suspect Progressive Multifocal Leukoencephalopathy (PML) Data Collection Tool

I. Patient Information

Patient Initials: ___ DOB: __/___/____ (DD/MMM/YYYY) Gender: _____

Height: _____ Weight: _____ BMI: _____

Il. 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:

☐ Dimethyl fumarate ☐ Other_____

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**	**Dose Frequency**	**Route of Administration**	**Lot/ Batch no.**

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:

☐ Dimethyl fumarate ☐ Other_____

Provide additional details on the dosing and frequency of the second suspect product, including information on the use of multiple regimens:

Start Date (DD/MMM/YYYY)	**Stop Date** (DD/MMM/YYYY)	**Dose**	**Dose frequency**	**Route of administration**	**Lot/ Batch no.**

In your assessment, is the suspected PML related to the secondary suspect product?

☐ Yes ☐ No

Since discontinuation of the suspect product, is 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:

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:

_____

_____

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 <u>signs and symptoms</u> that led to the evaluation for possible PML (even if identified in retrospect):

Symptoms	Date (DD/MMM/YYYY)

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 <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:

_____

_____

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 assay is performed 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 tests: ___/____/_____ (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 tests (positive, negative, pending)	Index value Available	Index value:	Laboratory Name:
	☐Positive	☐Yes ☐No		☐Focus/Quest

	☐Negative ☐Pending			☐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: ___/____/_____ (DD/MMM/YYYY)

Modified Rankin Score: Date: ___/____/_____ (DD/MMM/YYYY)

At the lime or PML suspicion:

EDSS: Date: ___/____/_____ (DD/MMM/YYYY)

Karnofsky score: Date: ___/____/_____ (DD/MMM/YYYY)

Modified Rankin Score: Date: _ _/__ _/__ __ (DD/MMM/YYYY)

EDSS (Expanded Disability Status Scale)	
Score	**Description**
0.0	No disability
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking

4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

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 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 <u>final</u> 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?**

Print name/title: _____

Signature: _____ Date: ___/____/_____

(DD/MMM/YYYY)

Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy (PML)

Data Collection Tool for 3 month and 6 months

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 dimethyl fumarate?

☐ Yes ☐ No

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)

EDSS (Expanded Disability Status Scale)	
Score	**Description**
0.0	No disability
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking

4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

Modified Rankin Score	
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.

2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

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

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

Provide copies of MRI reports, including most recent MRI report and a CD with the MRI images, if not already provided. 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	Test3
Date of LP (DD/MM/YYYY)			
LP performed pre-PLEX (if applicable)	☐Yes ☐ No	☐Yes ☐No	☐Yes ☐No
CSF JCV DNA Results	☐ Positive ☐ Negative ☐Inconclusive/Indeterminate	☐ Positive ☐ Negative ☐Inconclusive/Indeterminate	☐ Positive ☐ Negative ☐Inconclusive/Indeterminate
Quantitative (copies/ml)			
Laboratory Name and Limit of Detection			

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		

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-CRIS? ☐ 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

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 dimethyl fumarate?

☐ Related ☐ Not related ☐ Unknown

Print name/title: _____

Signature: _____ Date: _____

(DD/MMM/YYYY)

Multiple Sclerosis Confirmed Progressive Multifocal Leukoencephalopathy (PML) Data Collection Tool for 12 month and 24 months

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 dimethyl fumarate?

☐ Yes ☐ No

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)

EDSS (Expanded Disability Status Scale)	
Score	**Description**
0.0	No disability
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking

[redacted]

3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

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

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

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

Provide copies of MRI reports, including most recent MRI report and a CD with the MRI images, if not already provided. 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 tile 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 patients 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 dimethyl fumarate?

☐ Related ☐ Not related ☐ Unknown

Print name/title: _____

Signature: _____Date: _____

DD/MMM/YYYY

Targeted Follow-Up Questionnaire for General Malignancy

To provide consistency in our due diligence of Dimethyl fumarate general malignancy reports, please answer 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, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please indicate if the patient has had any recent infections (bacterial, fungal, spirochetes, etc.).
4. Please indicate if the patient has a history of cancer.
5. Please provide any medical history risk factors the patient had for a general malignancy (e.g family history of malignancies, radiation exposure, smoking, diabetes mellitus, etc.).
6. Please list all medications the patient has taken in the past 2 years.
7. Please, provide any concomitant medications the patient is taking including prescription medications, over the counter (OTC), dietary supplements, vitamins and herbs.
8. Please provide all signs and symptoms related to the malignancy.
9. If a tissue biopsy was performed, please provide the findings and the date it was performed.
10. Please provide results from all pathology or cytology studies.
11. Please provide results from all imaging studies.
12. Please provide results from physical examination.
13. If the patient was hospitalised, 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 Questionnaire for Breast Cancer

To provide consistency in our due diligence of Dimethyl fumarate breast cancer reports, please answer 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 hospitalised, 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 Questionnaire for Cervical Cancer

To provide consistency in our due diligence of Dimethyl fumarate cervical cancer reports, please answer the follow-up questions below:

1. Please specify the patient's type, stage, and grade of cervical cancer.
2. Did the patient develop lymphopenia while on 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 Questionnaire for Colon Cancer

To provide consistency in our due diligence of Dimethyl fumarate serious colon cancer reports, please answer 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 analysed, 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 hospitalised, 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 Questionnaire for Endometrial Cancer

To provide consistency in our due diligence of Dimethyl fumarate endometrial cancer reports, please answer the follow-up questions below:

1. Please specify the patient's type, stage, and grade of endometrial cancer.
2. Did the patient develop lymphopenia while on 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 fur 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 hospitalised, 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 Questionnaire for Lymphoma

To provide consistency in our due diligence of Dimethyl fumarate lymphoma reports, please answer 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 hospitalised, 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 sequalae, please describe the sequalae.

Targeted Follow-Up Questionnaire for Melanoma

To provide consistency in our due diligence of Dimethyl fumarate melanoma reports, please answer 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 analysed, 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 hospitalised, 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 Questionnaire for Non-Melanoma Skin Cancer

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

1. Please specify the patient's type, stage, and grade on non-melanoma skin cancer.
2. Did the patient develop lymphopenia while on 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 ionising 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 analysed, 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 hospitalised, 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 Questionnaire for Non-Small Cell Lung Cancer

To provide consistency in our due diligence of Dimethyl fumarate non-small cell lung cancer reports, please answer 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, halo ethers, 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 tumour markers were analysed, 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 hospitalised, 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 Questionnaires for Prostate Cancer

To provide consistency in our due diligence of Dimethyl fumarate prostate cancer reports, please answer the follow-up questions below:

1. Please specify the patient's type, stage, and grade of prostate cancer.
2. Did the patient develop lymphopenia while on 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 medication 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 patients prostate specific antigen (PSA) level and the date it was taken. Please include baseline values as well as reference range for any and all lab tests.
13. If the patient was hospitalised. 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 Questionnaire for Renal Cell Carcinoma

To provide consistency in our due diligence of Dimethyl fumarate renal cell carcinoma reports, please answer the follow-up questions below:

1. Please provide any medical history risk factors the patient had for renal cell carcinoma (e.g., family history, polycystic kidney disease, chronic haemodialysis, anaemia, 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 hospitalised, 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 Questionnaire for Small Cell Lung Cancer

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

1. Please specify the patient's type, stage, and grade of small cell lung cancer.
2. Did the patient develop lymphopenia while on 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-band 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, halo ether, 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 tumour markers were analysed, 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 hospitalised, 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