ANNEX 4 - SPECIFIC ADVERSE EVENT 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

Biogen Unique Case ID#: _____

I. Patient Information

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

Height: _____ Weight: _____ BMI: _____

II. Primary Neurologist:

Name: _____ Email: _____

Address: _____

Phone: _____ Fax: _____

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

Name: _____ Email: _____

Address: _____

Phone: _____ Fax: _____

IV. Primary Suspect Product

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

☐ Tysabri ☐ Avonex ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Other:

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

☐ Yes ☐ No

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

Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Dose	Frequency of Dosing	Number of Infusions (Tysabri)	Lot/ Batch #

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

☐ ***Yes*** ☐ ***No***

Biogen Unique Case ID#:_____

V. Secondary Suspect Product (if applicable)

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

☐ Tysabri ☐ Avonex ☐ Tecfidera ☐ 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 Biogen 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:**

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:

Biogen Unique Case ID#:_____

4) **Is this patient immunocompromised from any other cause?**

☐ Yes ☐ No

If yes, provide diagnosis:

5) **Has the patient ever been or currently is enrolled in a Biogen Clinical Trial?** ☐ Yes ☐ No

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

VII. PML Suspicion

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

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

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

2) **List earliest presenting <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. 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:

Biogen Unique Case ID#:_____

b. MRI prior to suspected PML diagnosis

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

Detailed description:

(Provide a CD of MRI DICOM images or direct upload to Biogen systems)[1,2]

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

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

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

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

Provide cell count: _____

Biogen Unique Case ID#: _____

6) Provide details of all serum anti-JCV antibody testing:

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

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

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

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

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

8) HIV status: ☐ Positive ☐ Negative ☐ Unknown

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

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

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

Biogen Unique Case ID#: _____

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:					

Biogen Unique Case ID#: _____

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

Biogen Unique Case ID#:_____

X. Functional Scores

Provide the patient's functional status scores

On Primary Suspect Product prior to PML

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

At the time of PML suspicion:

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

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

Biogen Case ID#: _____

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

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

Biogen Unique Case ID#:_____

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

[2] Mail the CD to: AESI Coordinator | 300 Binney Street | Cambridge, MA 02142 or your local Biogen representative. Biogen will incur the shipment cost of the CD. Alternatively, for faster MRI transfer, email AESI.coordinator@Biogen.com for instructions on uploading MRI images directly to Biogen's online platform.

Biogen Unique Case ID#:_____

I. Patient Demographics

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

II. Is the Patient alive? ☐ Yes ☐ No

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

☐ Hospital ☐ Home ☐ Nursing Home

☐ Intensive Care Unit ☐ Hospice ☐ Rehabilitation Facility

If no, provide the following information:

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

Reported Cause of Death: _____

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

III. In your assessment, was the patient's death related to one of the following products? ☐ Yes ☐ No

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex

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

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

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

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

Biogen Unique Case ID#: _____

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

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

Biogen Unique Case ID#:_____

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.[1,2] If not possible, provide detailed MRI results including lesion characteristics and location:

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

Detailed description: _____

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

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

Biogen Unique Case ID#: _____

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

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

If yes, what is the therapy?

Include start date and dosing regimen:

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

VII. PML Treatment:

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

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

Biogen Unique Case ID#: _____

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

VIII. PML Outcome:

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

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

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

IX. Was the patient diagnosed with PML-IRIS?

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

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

If yes, specify the symptoms:

Onset date of IRIS symptoms:

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

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

X. PML-IRIS Treatment:

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

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

Biogen Unique Case ID#: _____

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

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

XI. PML-IRIS Outcome:

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

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

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

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

☐ Related ☐ Not Related ☐ Unknown

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

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

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

[2] Mail the CD to: AESI Coordinator | 300 Binney Street | Cambridge, MA 02142 or your local Biogen representative. Biogen will incur the shipment cost of the CD. Alternatively, for faster MRI transfer, email AESI.coordinator@Biogen.com for instructions on uploading MRI images directly to Biogen's online platform.

Biogen Unique Case ID#:_____

I. Patient Information

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

II. Is the Patient alive? ☐ Yes ☐ No

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

☐ Hospital ☐ Home ☐ Nursing Home

☐ Intensive Care Unit ☐ Hospice ☐ Rehabilitation Facility

If no, provide the following information:

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

Reported Cause of Death: _____

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

III. In your assessment, was the patient's death related to one of the following products? ☐ Yes ☐ No

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex

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

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

Biogen Unique Case ID#: _____

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

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

Biogen Unique Case ID#: _____

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.[1,2] If not possible, provide detailed MRI results including lesion characteristics and location:

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

Detailed description: _____

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

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

If yes, what is the therapy?

Include start date and dosing regimen:

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

VII. PML Outcome:

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

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

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

Biogen Unique Case ID#: _____

VIII. PML-IRIS Outcome:

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

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

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

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

☐ Related ☐ Not Related ☐ Unknown

☐ Tysabri ☐ Tecfidera ☐ Vumerity

☐ Fampyra/Ampyra ☐ Plegridy ☐ Avonex

Print name/title: _____

Signature: _____ Date: _____
DD/MMM/YYYY

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

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

[2]Mail the CD to: AESI Coordinator | 300 Binney Street | Cambridge, MA 02142 or your local Biogen representative. Biogen will incur the shipment cost. Alternatively, for faster MRI transfer, email AESI.coordinator@Biogen.com for instructions on uploading MRI images directly to Biogen's online platform.

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Tecfidera General Malignancy

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

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

Tecfidera Breast Cancer

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

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

Tecfidera Cervical Cancer

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

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

Tecfidera Colon Cancer

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

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

Tecfidera Endometrial Cancer

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

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

Tecfidera Lymphoma

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

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

Tecfidera Melanoma

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

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

Tecfidera Non-Melanoma

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

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

Tecfidera Non-Small Cell Lung Cancer

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

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

Tecfidera Prostate Cancer

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

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

Tecfidera Renal Cell Carcinoma

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

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

Tecfidera Small Cell Lung Cancer

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

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

Tecfidera Liver Disease / Liver Injury

To provide consistency in our due diligence of Tecfidera 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.

Tecfidera Severe Lymphopenia

To provide consistency in our due diligence of 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 Tecfidera therapy? If discontinued, was Tecfidera restarted?

Tecfidera Moderate Lymphopenia

To provide consistency in our due diligence of moderate lymphopenia reports, please ask the follow-up question(s) 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 Tecfidera 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.

Tecfidera Serious Infection / Opportunistic Infection

To provide consistency in our due diligence of Tecfidera 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 Tecfidera? Please provide any available lymphocyte data (date of lab test, absolute lymphocyte count). If lymphocyte subset data (CD4, CD8) was checked, please provide. Please include baseline values as well as reference ranges for any and all lab tests.
3. Please provide any medical history risk factors the patient had for 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.