A Programme for Risk Assessment and Minimisation of Progressive Multifocal Leukoencephalopathy Developed for Vedolizumab Clinical Trials

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Electronic Supplementary Material 1

Table S1. RAMP-Defined Radiologic Probability Scores

Score	PML Probability	Criteria
5	Definite	Classic PML findings
4	Probable	Significant-size lesion with typical appearance but some aspect of imaging allows possibility of a differential diagnosis
3	Possible/equivocal	Insignificant-size lesion with typical appearance or significant-size lesion with atypical appearance
2	Unlikely	Insignificant-size lesion with atypical appearance
1	Highly unlikely	Unremarkable findings or explainable MRI lesion
0	Impossible	PML ruled out

Abbreviations: MRI, magnetic resonance imaging; PML, Progressive Multifocal Leukoencephalopathy.

Table S2. Summary of Findings from Patient Cases that required a Lumbar Puncture, Assessed by the IAC

Case	Past medical history	Event(s) and findings	Follow-up
1: 44 year old female	Ulcerative colitis Remote history of tobacco usage, resolved right pleural effusion, soft tissue sarcoma left arm treated with radiation, left upper extremity and face numbness (resolved), bronchitis, panic attacks with anxiety and depression, thalassemia, hydronephrosis with hydroureter	• Persistent problems with memory or thinking 8 days after 5th dose: o Clinical findings: normal • Severe, medically significant disabling events of joint/muscle fatigue, and weakness 16 days after 8th dose (had completed a course of antibiotics for pneumonia): o Clinical findings: unable to stand on one foot; weak upper arm strength bilaterally o MRI: inconclusive o CSF: negative for JC viral DNA	Discontinued vedolizumab
2: 39 year	Crohn's disease Complicated by fistulae,	• Floaters with impaired vision and repeated flashes 27 days after 8th dose. Events occurred 3 times, further described as sudden 'zigzag' type scotoma	Vedolizumab doses were withheld on

old female	abscesses, depression, Takayasu's arteritis, dyslipoproteinemia, bronchitis	in both eyes that intensified and then abated within 20 minutes ○ Clinical findings: normal ○ MRI: normal • Floaters recurred 49 days after 8th dose ○ CSF: negative for JC viral DNA	wk 30 and 34, however, resumed at wk 38. Later discontinued for lack of efficacy
3: 54 year old male	Crohn's disease With ileoconic resection, pyelonephritisduodenal ulcer, exertional dyspnoea, gastrectomy with vagotomy, hypertensive cardiomyopathy, lumbar osteoarthritis	• Numbness in legs 30 days after 12th dose ○ Clinical findings: sensory neuropathy ○ MRI: scattered nonspecific punctuate foci of T2 hyperintensity ○ CSF: negative for JC viral DNA	Discontinued vedolizumab
4: 43 year old male	Crohn's disease Ongoing tobacco use, memory changes, headaches,	• Numbness or loss of sensation (e.g. numbness daily episodic swelling, tingling in both feet) in his feet and weakness in his arms (e.g. arm tremors) 16 days after his first and only dose: persistent	Discontinued vedolizumab

	GERD, spondylosis of the back, tingling in fingers insomnia, weight loss, chronic cough, anxiety	○ Clinical findings: irregular tremor in his outstretched hand, brisker deep tendon reflexes in lower extremities, positive Romberg sign, impaired colour vision and urological complaints ○ MRI: 18x18x10 mm subependymoma versus ependymoma or central neurocytoma with 1.5 mm leftward deviation of the intraventricular septum ○ CSF: negative for JC viral DNA	
5: 37 year old male	Ulcerative colitis Vasectomy, motor vehicle accident with surgical repair of face and right elbow, remote smoker	• Hospitalised because of worsening bloody diarrhoea, diffuse myalgias, arthralgias, weakness in the lower extremities (difficulty walking), fever and cough after first and only dose in C13008: ○ Clinical findings: *Clostridium difficile* infection ○ MRI: poorly defined T2 FLAIR hyperintense signal in the deep white matter of the posterior right frontal lobe ○ CSF: negative for JC viral DNA	Discontinued vedolizumab

Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid attenuated inversion recovery; GERD, gastrooesophageal reflux disease; IAC, Independent Adjudication Committee;

MRI, magnetic resonance imaging; PCR, polymerase chain reaction

Electronic Supplementary Material 2

CONTENT

Methods

Studies and Patients:

- Text included in the Informed Consent Form

PML Checklists, PML Case Evaluation Algorithm, and serum JC virus assay:

- Identification of IAC experts, IAC charter describing roles and responsibilities, process flow, and scoring systems for case evaluation
- Detailed description of the RAMP algorithm and its individual steps

Supplementary Table

- Table S3. Patient Data Provided to IAC Members

Methods

Studies and Patients

Text included in the Informed Consent Form:

> *The study doctor will monitor you for signs and symptoms of a condition called progressive multifocal leukoencephalopathy, or PML. PML is a rare infection of the brain that is caused by JC virus. Signs and symptoms of PML include headaches, memory loss, changes in mental status, speech and vision difficulties, loss of strength, limb weakness, seizures, partial paralysis and loss of coordination. No cases of PML have been reported in patients receiving MLN0002*, however, PML has been seen in a few patients who were treated with a drug called natalizumab…. a monoclonal antibody with some similarities to MLN0002.*
>
> * Proprietary designation for vedolizumab during its drug development

PML Checklists, PML Case Evaluation Algorithm, and serum JC virus assay

Identification of IAC experts, IAC charter describing roles and responsibilities, process flow, and scoring systems for case evaluation

The Sponsor surveyed the medical literature to identify international experts in clinical diagnosis and management, radiological findings, and virology related to PML. From a short list of qualified candidates, experts able and willing to commit to certain requirements were enlisted to form the IAC. Its members held no financial ties to the Sponsor and were compensated solely for time initially spent in consultation on RAMP program design and thereafter for time spent in review of clinical cases. This committee initially comprised two neurologists, two neuroradiologists and a virologist experienced in JC virus. One of the two neurologists (senior author on this report) was appointed chairperson.

A charter defining roles and responsibilities, process flow, and scoring systems for case evaluation was co-authored by the Sponsor and the IAC members. Through ratification of the charter, committee members committed to facilitating real-time review of clinical, laboratory, and radiological data (see Electronic Supplementary Material 2, Table S3) in an effort to provide feedback to investigators as quickly as possible after confirmation of abnormal neurologic findings. All available data were anonymised and provided to IAC members by the Sponsor via email; anonymised MRI images were uploaded to a central server accessible via the Internet using individualised security credentials.

Description of the RAMP algorithm and its individual steps

All patients completed a Subjective PML Checklist (see Electronic Supplementary Material 6) to probe for alterations in vision, speech, gait, sensation, comprehension, coordination, and personality at screening, at each study visit, and whenever new neurologic symptoms presented over the course of the study. Any positive response on the subjective checklist prompted focused neurological testing using the corresponding Objective PML Checklist (see Electronic Supplementary Material 6) by the principal investigator at the study site; in addition, vedolizumab therapy was withheld. If this focused neurological testing revealed an objective unexplained new abnormality, the patient was referred to the local study neurologist for further evaluation. In several instances, patients without objective findings were referred for neurologist consultation outside of the algorithm directive. These data have been included in the final analysis presented in this report.

Detection of JC viral DNA in the setting of new neurological symptoms and a compatible lesion ordinarily confirms the diagnosis of PML [1]. MRIs were performed locally on an MR scanner with a field strength of at least 1.5 Tesla. The pulse sequences for MR imaging consisted of the following: Sagittal T1-weighted, axial fluid attenuated inversion recovery (FLAIR), coronal fast spin echo (FSE) T2-weighted, axial diffusion-weighted (DWI), axial gradient echo (GRE) susceptibility, contrast-enhanced axial T1-weighted and coronal T1-weighted MRI images. The imaging studies were transported by secure file transfer as high-resolution DICOM-compatible digital files. The imaging studies in cases of suspected PML were rapidly presented to the IAC to expedite preliminary review. The algorithm culminates in lumbar puncture with PCR testing of CSF for JC viral DNA. Lumbar punctures and CSF collection were to be performed according to the local

standard of care. Analysis of CSF by PCR for JC virus was conducted by a central laboratory (Viracor, Lee's Summit, Missouri, USA) with a Clinical Laboratory Improvement Amendments (CLIA) certified assay (limit of detection: 100 copies JC viral DNA per ml). Given known limitations in commercial assay sensitivity patients with continued clinical suspicion of PML and a negative CSF JC virus PCR result were to have their CSF reanalysed at the National Institutes of Health using a more sensitive research assay (Laboratory of Molecular Medicine and Neuroscience, Division of Neuroimmunology & Neurovirology, Bethesda, Maryland, USA; multiplex qPCR limit of detection: 10 copies JC viral DNA per ml), to minimise false negatives. If CSF studies were negative while symptoms or MR lesions progressed, the adjudication committee was prepared to request brain biopsy. Positive results from brain histopathology, currently rarely required for establishing PML diagnosis, were also to be considered as confirmed PML cases.

TABLES

Table S3. Patient Data Provided to IAC Members

Description	Time Point(s)	Data Description
Case history	All relevant study time points, with particular attention to the neurologic findings that prompted IAC referral	• Subject demographics • Past medical history • Prior therapies • Concomitant medications • Chief neurologic complaint under investigation • Temporal relationship of dosing to this complaint • Evolution of symptoms and signs (if any) since the time of initial presentation

Physical examination	All relevant study time points including baseline and any pre-enrolment examination results	• Available results of physical examination including detailed neurologic examination performed by a study neurologist
PML checklists	All relevant study time points including baseline	• PML subjective and objective checklists with documentation of positive responses
Laboratory test results	All relevant study time points including baseline and any pre-enrolment laboratory results	• Any available results of laboratory testing including o Cell counts and differentials o Lymphocyte subset analyses o Chemistries o Plasma JC virus testing
MRI findings	Any time points during the study when MRIs were performed, particularly as part of the PML case evaluation algorithm, and any incidental neuroimaging available from a previous date for comparison	• 1.5-Tesla or higher-field strength sagittal T1-weighted, axial FLAIR, coronal FSE T2-weighted, axial DWI, axial GRE susceptibility-weighted, contrast-enhanced axial T1-weighted and coronal T1weighted images • MRI images will be presented by SFTP or equivalent secure technology as highresolution DICOM-compatible digital files • Image sequences focused on any suspicious lesions noted by a local neuroradiologist at the study location may be presented to the IAC to expedite preliminary review
CSF analysis	Any available	• CSF cell count and differential • Total protein • Oligoclonal bands • Myelin basic protein
		• JC viral DNA copy number analysis by PCR • Any other studies performed
Biopsy	Any available	Any brain histopathology performed to confirm/exclude PML

Abbreviations: CSF, cerebrospinal fluid; DICOM, digital imaging and communications in medicine; DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; FSE, fast spin echo; GRE, gradient-echo; IAC, Independent Adjudication Committee; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, Progressive Multifocal Leukoencephalopathy; SFTP, secure file transfer protocol.

REFERENCES

1. Hammarin AL, Bogdanovic G, Svedhem V, Pirskanen R, Morfeldt L, Grandien M. Analysis of PCR as a tool for detection of JC virus DNA in cerebrospinal fluid for diagnosis of progressive multifocal leukoencephalopathy. *J Clin Microbiol.* 1996;34(12):2929-2932.

Electronic Supplementary Material 3

RAMP Subject Brochure

MLN0002 and Progressive Multifocal Leukoencephalopathy (PML)

A different drug called natalizumab (Tysabri®; Biogen Idec and Elan Pharmaceuticals, Inc.) which has been studied and is available in some countries for the treatment of Crohn's disease and Multiple Sclerosis, an inflammatory disorder of the brain, has been associated with PML. The chances of getting PML from Tysabri® are estimated to be between one in a thousand patients and two in a thousand patients. PML is a rare condition that usually causes death or severe disability. There is no proven treatment, prevention, or cure for PML.

PML is caused by a virus that infects the brain. PML usually occurs in people with decreased ability to fight infections because of a weakened immune system. Some medications used to treat ulcerative colitis, such as azathioprine, weaken the immune system. There are some similarities between the way Tysabri® and MLN0002 are believed to work in the body. Both decrease infection fighting in the digestive system, but Tysabri® is different from MLN0002 because it is believed to also decrease infection fighting in the brain.

It is not known if MLN0002 increases the risk of PML. There have been no reported cases of PML with MLN0002. However, there is not enough information to know if MLN0002 may increase the risk of PML.

The purpose of this brochure is to explain what we know about MLN0002 and PML. If you have any questions after reading the brochure, please talk to the study doctor or nurse. If you have any symptoms of PML during the study, contact your study doctor immediately. If you have any symptoms of PML after the study, contact your regular doctor immediately.

What is MLN0002?

MLN0002 is a biological medicine that is being tested for treating moderate to severe ulcerative colitis (UC) and Crohn's disease (CD) that has not responded adequately to other treatment.

UC and CD are a relatively common disease. Each disease affects about 150 to 200 people per 100,000 in developed countries. Significant percentages of the people who get UC or CD eventually do not respond to therapy and must have a surgery to remove diseased parts of the small bowel or colon. UC and CD also may lead to increased rates of colon cancer.

What is PML?

PML is a rare disease of the brain and nervous system caused by a common human virus, the JC virus. The virus damages the covering of the nerve cells (the myelin sheath). The virus is believed to infect most healthy individuals at an early age, but it does not have any noticeable effects in most people. However, in some people, especially those whose immune system does not work well, the JC virus may cause PML. The immune system fights and prevents infection in your body.

Most of the people who get PML are AIDS patients. Rare cases have also been reported in patients with other immune system diseases. PML usually causes death or severe disability. However, by watching out for symptoms of PML and stopping treatment with MLN0002 promptly, the progression of the disease may be stopped.

What are some of the symptoms of PML?

Symptoms of PML may include one or more of the following:

- Changes in **vision**, such as difficulty reading, blurred vision, double vision, or bumping into things because you do not see them
- Difficulty **speaking**, such as trouble forming words or people not understanding what you say
- **Muscle weakness**, such as weakness in an arm or a leg
- **Clumsiness**, such as difficulty handling small objects or difficulty with walking or writing
- **Confusion,** such as trouble understanding others or difficulty understanding ideas or directions you would have understood in the past
- Persistent **numbness** or other loss of sensation

During the study, if you notice any one or more of these symptoms, contact the study doctor immediately. After the study, tell your regular doctor if you notice any symptoms of PML.

What happens if I get symptoms of PML?

During the study, you will be questioned at study visits to see if you have symptoms of PML. If you notice these symptoms between study visits, call the study doctor immediately. If you report any symptoms, the nurse or study doctor will ask you to perform a task to see how you are affected. For example, if you report difficulty reading, the staff may ask you to read an eye chart. If your symptoms are not confirmed by the tests, you will be allowed to continue the study but the staff will call you a week later to check on your condition.

If your symptoms are confirmed, the study doctor may decide to stop further dosing of MLN0002 and may send you to a neurologist (a doctor who specializes in brain and nervous system diseases). The specialist may order a brain scan called an MRI (magnetic resonance imaging) scan and may perform a spinal tap to obtain cerebrospinal fluid for analysis. If you do not have PML, you may be able to resume treatment with MLN0002.

After you have finished your participation the study, you should continue to check for symptoms of PML and tell your regular doctor if you have any symptoms of PML. The study organizers will call you every 6 months for 2 years after you finish the study to ask a few questions about your health.

Does MLN0002 cause PML?

We do not know. A different drug called natalizumab (Tysabri®; Biogen Idec and Elan Pharmaceuticals, Inc.) which has been studied and is available in some countries for the treatment of Crohn's disease and Multiple Sclerosis, an inflammatory disorder of the brain, has been associated with PML. The chances of getting PML from Tysabri® are estimated to be between 1 in 1,000 patients and 2 in 1,000 patients.
Tysabri® and MLN0002 both decrease infection fighting in your digestive system, but Tysabri® is different from MLN0002 because it is believed to also decrease infection fighting in the brain.

There have been no cases of PML with MLN0002. However, there is not enough information to know whether MLN0002 may increase the risk of PML.

What if I notice symptoms of PML after the study?

After the study, you should continue to monitor your condition for symptoms of PML. If you notice symptoms, contact your regular doctor. Explain that you have been in this study.

The study organizers will call you every 6 months for 2 years after the study to ask you a few questions about your progress. In addition to some questions about your health, the study organizers will want to know if you have had symptoms of PML and if you have had a doctor examine these symptoms.

What if I have more questions?

If you have any questions about PML, MLN0002 or any aspect of this study, talk to your study doctor or nurse. They are in the best position to answer your questions or tell you where to go for more information.

The name, address, and contact information for the clinic will be inserted here.

Electronic Supplementary Material 4

RAMP Wallet Card

Study participants should be aware of progressive multifocal leukoencephalopathy (PML), a rare but often fatal condition. Symptoms of PML include:

- Changes in **vision**, such as difficulty reading, blurred vision, double vision, or bumping into things because you do not see them
- Difficulty **speaking**, such as trouble forming words or people not understanding what you say
- **Muscle weakness**, such as weakness in an arm or a leg
- **Clumsiness**, such as difficulty handling small objects or difficulty with walking or writing
- **Confusion**, such as trouble understanding others or difficulty understanding ideas or directions you would have understood in the past
- Persistent **numbness** or other loss of sensation

During the study, if you notice these symptoms, contact the study doctor immediately at [telephone number to be inserted here]. After the study, tell your regular doctor if you notice these symptoms.

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Electronic Supplementary Material 5

PML Risk Assessment and Minimization for PML (RAMP)

Staff Brochure

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This brochure is provided to each investigator conducting a clinical trial of the investigational drug MLN0002, as part of Millennium's Risk Assessment and Minimization Plan (RAMP). This brochure is not intended to be provided to subjects involved in MLN0002 studies, but is intended to provide supplemental information pertaining to risk minimization to the participating site staff. This brochure is to be read by each healthcare professional involved in the clinical trial before enrollment of the first subject.

After you have read this brochure, you are encouraged to contact Millennium to answer any questions you may have about PML and our RAMP program.

Progressive Multifocal Leukoencephalopathy (PML)

In the Investigator Brochure and Informed Consent Form for all MLN0002 clinical trials, it is stated that there may be a risk of developing a rare but serious condition known as PML (progressive multifocal leukoencephalopathy) following treatment with the investigational drug MLN0002. The purpose of this brochure is to explain PML so you are better prepared to recognize its occurrence and answer questions that your subjects may ask. In addition, this brochure will outline Millennium's Risk Assessment and Minimization Plan for managing the theoretical risk of PML.

What is PML?

Progressive Multifocal Leukoencephalopathy (PML) is caused by a common human polyomavirus, the JC virus. The JC virus is believed to infect approximately 80% of healthy individuals at an early age. In the overwhelming majority of individuals, JC virus remains dormant throughout life without causing any symptoms or disease. The ageadjusted death rate for PML is 3.3 per million persons in the general population. In significantly immunocompromised individuals, however, JC virus has an increased propensity to cause PML. In fact, this disease is most typically seen in the context of systemic immunosuppression (ie, post-chemotherapy, or patients with leukemia or AIDS) although cases have also been reported in persons with autoimmune disease following treatment with immunosuppressive medications. PML is characterized by demyelination or destruction of the myelin sheath that protects axons of neurons in the central nervous system (CNS). Clinical manifestations depend on the size and distribution of white matter lesions that develop as a result of the viral infection, demyelination, and glial cell lysis. There is no consistently effective prevention, treatment, or cure for PML.

How does MLN0002 work, how does MLN0002 differ from natalizumab (Tysabri®), and does MLN0002 cause PML?

MLN0002 is a monoclonal antibody directed against the D4E7 integrin, a subtype of D4 containing integrin. The primary role of D4E7 integrin is in modulating the trafficking of lymphocytes to the gut and gut-associated lymphoid tissues, and it appears to have insignificant roles outside the gut. Pharmacologic inhibition of D4E7 integrin represents a potential strategy for decreasing bowel inflammation in inflammatory bowel disease.

Use of natalizumab (Tysabri®; Elan Pharmaceuticals, Inc. and Biogen Idec Inc.), a monoclonal antibody directed against all D4 integrins, for the treatment of relapsing multiple sclerosis and Crohn's disease, resulted in cases of PML. The chances of getting PML from Tysabri are estimated to be between 1 in 1,000 patients and 2 in 1,000 patients.

Natalizumab (Tysabri®) inhibits the D4 integrin chain, which is present in all D4 integrins including D4E1 and D4E7. The D4E1 integrin has been shown to have a role in mediating lymphocyte trafficking to the CNS and various other organ systems. In contrast, MLN0002 specifically inhibits only the D4E7 integrin, a subtype of D4containing integrins, whose physiologic role appears to be restricted to the gastrointestinal tract.

The mechanisms by which natalizumab (Tysabri®) facilitated JC virus replication in the CNS are poorly understood. The working hypothesis of most experts is that natalizumab perturbs a critical CNS immunosurveillance function by virtue of its inhibitory effect on T-lymphocytes. As a consequence, the beneficial antiinflammatory effect that results in fewer lymphocytes entering the CNS in multiple sclerosis may simultaneously inhibit important defense mechanisms against pathogens such as JC virus, thereby permitting its local ingress and replication in the brain.

There have been no cases of PML reported in people treated with MLN0002. Over 1,800 people have participated or are participating in clinical trials of MLN0002. In completed studies, nearly 600 men and women are known to have received at least one dose of MLN0002, which includes over 300 people with ulcerative colitis or Crohn's disease.

Currently, there is not enough information to know whether MLN0002 may increase the risk of PML.

Has MLN0002 been included in regulatory action taken in relation to PML?

Yes. After the cases of PML associated with the use of natalizumab (Tysabri®) were reported to the US Food and Drug Administration (FDA), all clinical studies in the US with investigational drugs that target D4 integrins were suspended by order of the FDA (this is termed a "clinical hold"). MLN0002 was included in this action. The suspension was imposed because the relationship between the activities of each of these drugs and the risk of PML is unknown. Therefore, the FDA has required that each of the drugs' sponsors put in place a specific risk management program for PML before studies in the US are permitted to resume. This suspension of clinical studies does not indicate or imply that there is any specific evidence linking any of these drugs, other than Tysabri®, to an increased risk of PML. The FDA has reviewed the risk management program that is in place for MLN0002 and has removed MLN0002 from clinical hold and clinical studies with MLN0002 have resumed in the US.

Although regulatory authorities other than the US FDA have not instituted the same clinical hold policy toward this class of drugs, all of them are aware of the issue and have taken the steps they deem necessary to protect public health.

What is the RAMP Program?

The Risk Assessment and Minimization for PML (RAMP) program is Millennium's risk management plan for the minimization and assessment of the risks of MLN0002 in human subjects. The purpose of the plan is to minimize the risk of PML by focusing on early clinical detection and discontinuation of study treatment, if indicated. To accomplish these goals, the program will focus on:

- Education of health professionals and subjects participating in clinical trials involving MLN0002
- Systematic and thorough screening of subjects (both before and during the administration of MLN0002), as well as regular follow-up for a period of time after the trial
- Prompt discontinuation of MLN0002 in suspected cases
- Thorough evaluation of suspected cases until PML is excluded or confirmed

What are some possible symptoms of PML?

The most common symptoms of PML (as measured by a change from the subject's baseline examination) include the following:

- Changes in vision, such as difficulty reading, blurred vision, double vision, or bumping into things because of vision problems
- Difficulty speaking, such as trouble forming words or slurred speech ○ Weakness in an arm or a leg
- Clumsiness, such as difficulty handling small objects, difficulty walking, or difficulty writing
- Confusion, such as trouble understanding others or grasping ideas that the subject would ordinarily have easily understood
- Persistent numbness or other loss of sensation

Prior to the study, the study staff will administer a questionnaire to the subject (Subjective Checklist). Any subject who has a positive result on this checklist prior to receiving study treatment will be excluded from the study.

During the study, the site study staff will be asked to administer a questionnaire (Subjective Checklist) to assess the occurrence of PML symptoms on designated study visits. Subjects will also be instructed to contact the study doctor immediately if they notice these symptoms during the study. If the subject reports any symptoms, the objective checklist should be administered.

After the study is completed, subjects will be asked to continue to monitor for symptoms of PML. If they perceive any symptoms, they will be asked to contact their regular doctor.

Following the last dose of study treatment, each subject will be contacted every 6 months for 2 years to confirm that the subject has not been diagnosed with PML.

How do I check for PML symptoms?

At designated study visits, the PML Subjective Checklist will be administered to subjects. This checklist asks the subject to report the occurrence or worsening of common classes of symptoms associated with PML, as listed above. If the subject reports any symptoms

on this checklist, he/she will undergo objective testing using the PML Objective Checklist.

The purpose of the tests listed on the Objective Checklist is to help differentiate benign transient neurological symptoms, which all people experience from time to time (for example, headache or mild dizziness) from more serious symptoms that would indicate need for further evaluation for PML. While PML is a heterogeneous disease in terms of presentation, the symptoms are typically not subtle and, if present, tend to progress. For this reason, the Objective Checklist can be used to assess many of the characteristic signs of PML.

The PML Objective Test Demonstration Video has been provided to you in your study binder and demonstrates how to perform the basic tests of neurological function listed on the Objective Checklist.

What if the subject reports new or progressive neurologic symptoms (Subjective Checklist) but performance testing (Objective Checklist) of this new or progressing symptom does not reveal a new neurologic deficit?

If a subject reports a symptom or complaint but objective testing does not reveal a deficit, you may reassure the subject and instruct them that they may remain in the study, but that they will be carefully followed. The subject must be called in one week to confirm symptoms have not recurred or persisted. If the subject reports that symptoms have recurred or persisted, the subject should be asked to come to the clinic for further evaluation and evaluated using the PML Case Evaluation Algorithm (Appendix 1) beginning with the Subjective Checklist.

What if the subject reports new or progressive neurologic symptoms (Subjective Checklist) and performance testing (Objective Checklist) reveals a new neurologic deficit?

The PML Case Evaluation Algorithm is included in Appendix 1.

1. If a subject demonstrates a neurologic deficit related to PML upon administration of the specific test(s) on the Objective Checklist, no further doses of MLN0002 should be administered to that subject.

2. The subject should be referred to the Study Neurologist for further testing and Millennium must be notified of this action. The neurologist will examine the subject's symptoms, may order an MRI and may perform a lumbar puncture with

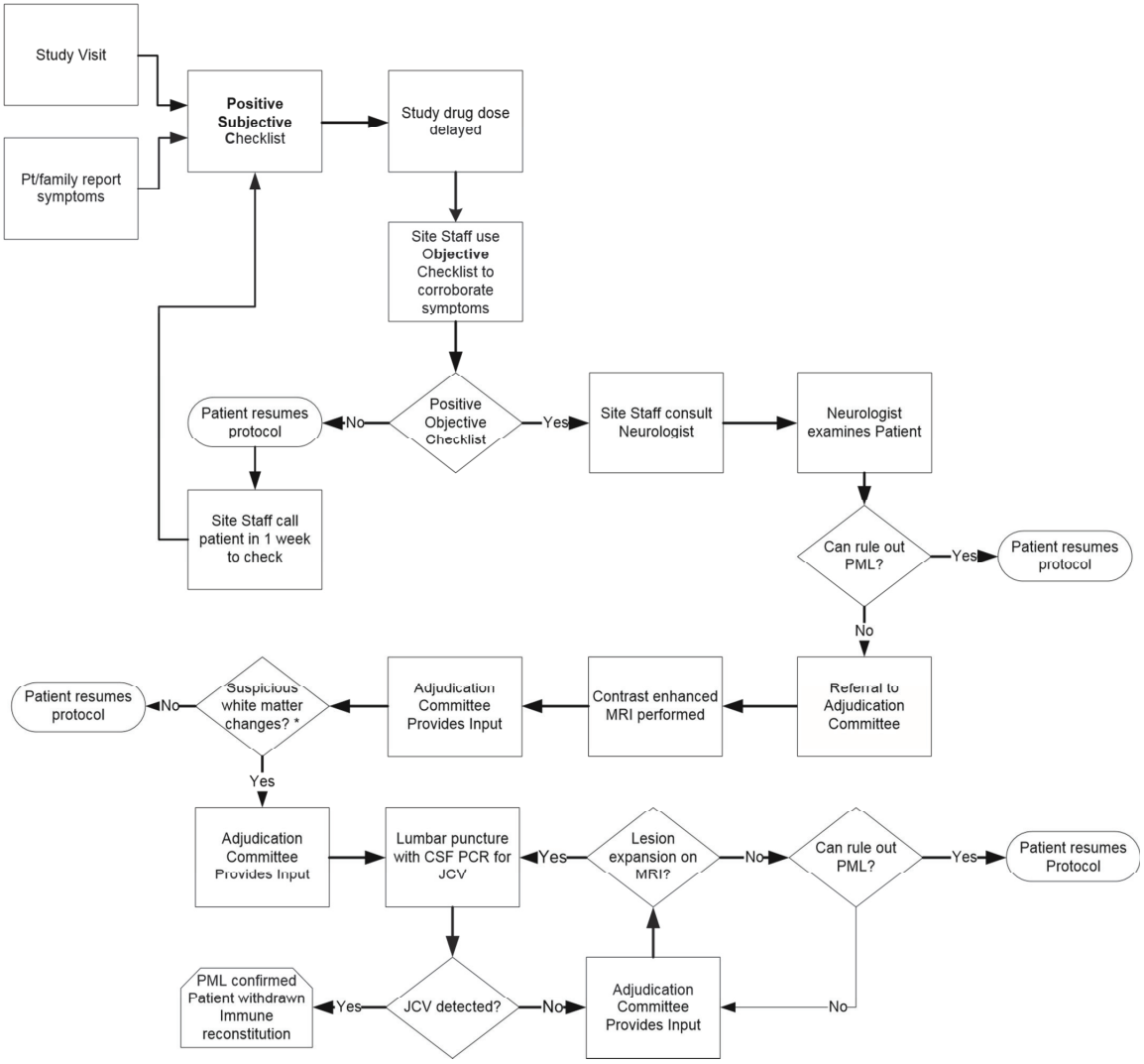
analysis of cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for JC virus. Any cases of suspected PML for which the Study Neurologist orders an MRI will be referred to Millennium's Independent Adjudication Committee (IAC) for PML. The IAC is a group of PML experts that will review subject data independently of Millennium and advise Millennium on a course of action that minimizes the risk to study subjects.

3. Millennium's Medical Monitor will report a summary of IAC assessment to the study site as soon as it is available. If subjects are found not to have PML, they may continue on the MLN0002 study.

What if I have more questions?

If you have any questions about PML, MLN0002 or any aspect of this study, talk to the Millennium Study Site Monitor associated with your trial site. You may also call Millennium and speak with the Medical Monitor at any time.

Appendix 1 - PML Case Evaluation Algorithm



The PML Case Evaluation Algorithm is shown in the figure above. As can be seen, performance testing with the tests listed on the Objective Checklist should follow subjective complaint(s) expressed by the subject in an effort to corroborate the symptom in question. If performance testing is judged to be completely unremarkable, the subject should be reassured, and may resume the protocol with follow-up by phone in 1 week as shown. Any positive finding on the Objective Checklist should result in referral to the Study Neurologist familiar with this study. Millennium should be notified of all

suspected PML cases that have been referred to the Study Neurologist for further evaluation. If the Study Neurologist excludes PML by exam, the subject may resume the protocol. In cases where PML cannot be excluded by the Study Neurologist's exam, the subject will undergo brain MRI. In such instances, the PML Independent Adjudication Committee (IAC) will be notified. The IAC will provide an independent assessment with regard to PML in order to advise Millennium on a course of action that minimizes risk to subjects participating in the trial. If PML can be excluded by the absence of positive MRI findings, the subject may resume the protocol. If changes potentially consistent with PML are detected on MRI, the MRI will be followed by lumbar puncture and polymerase chain reaction (PCR) analysis of CSF for JC virus.

If a case of PML is confirmed, MLN0002 will be stopped permanently. In cases where PML is suspected but not confirmed, the PML IAC will continue its assessment until it either excludes or confirms PML. If the IAC excludes PML, the subject may resume the protocol.

Center ID	Subject ID	Subject Initials
— — —	— — —	— — —

Electronic Supplementary Material 6

Subjective PML Checklist

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "Yes", obtain a description of the symptom(s) with examples.	Applicable Objective Test(s): Document results on PML Objective Checklist
	Yes	No		
1. Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble with reading?				Test visual fields and ocular motility.
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.
3. Have you been experiencing any persistent weakness in an arm or a leg?				Test for pronator drift (Barré maneuver) and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test symmetric muscle strength.
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				Ask for spontaneous writing sample and observe finger to nose, heel to shin, and tandem gait.
5. Have you regularly been experiencing difficulty understanding others?				Ability to follow serial commands (Close your eyes, stick out your tongue, and touch your left finger to your left ear)
6. Have you had persistent problems with your memory or thinking?				Recall of 3 objects over 1 minute with distraction; ability to follow commands.
7. Have you been experiencing any persistent numbness or other loss of sensation?				Test sensation side to side with pinprick.

_____ _____

Printed Name Date
Checklist Administrator

Signature Date
Checklist Administrator

Center ID	Subject ID	Subject Initials
__ __ __	__ __ __	__ __ __

Objective PML Checklist – To be completed for patients with positive subjective finding

Perform the objective test(s) that correspond to the subjective checklist finding

Positive Symptom(s)	Applicable Objective Test(s)	Test Result(s)		If test result is abnormal, briefly describe result
		Normal	Abnormal	
1. Difficulty with vision or reading	Test visual fields and ocular motility			
2. Difficulty with speaking	Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.			
3. Weakness in an arm or a leg	Test for pronator drift and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength.			
4. Bumping into things or difficulty writing	Ask for spontaneous written sample and observe finger to nose, heel to shin, and tandem gait			
5. Difficulty understanding others	Ability to follow serial commands (Close your eyes, stick out your tongue, and touch your left finger to your left ear)			
6. Problems with memory or thinking	Recall of 3 objects over 1 minute with distraction; ability to follow commands.			
7. Problems with numbness	Test sensation side to side with pinprick.			

x If the objective test corroborates the reported symptom, refer the subject for a Neurology consult. Otherwise, please follow-up with the subject one week after the objective checklist was administered to ensure symptoms are not recurring.

x Please notify your CRA and Millennium of any positive objective checklist findings

_____
Printed Name Date
Checklist Administrator

_____
Signature Date
Checklist Administrator

_____
PI Signature Date

Electronic Supplementary Material 7

MLN0002 Long Term Follow-up Questionnaire

Protocol C 1 3 | Subject ID | -- | Subject Initials

Interval since last dose of study drug: 6 months ☐ 12 months ☐ 18 months ☐ 24 months ☐

Was the questionnaire completed? Yes ☐ No ☐ Date ☐☐ ☐☐☐ ☐☐☐☐

THE FOLLOWING APPLIES TO PHONE CALLS AT ALL TIME POINTS DURING THE FOLLOW-UP:		
1. Since our last study contact, have you been diagnosed with dysplasia (a precancerous condition) of the colon or rectum, cancer of the colon or rectum, lymphoma, or any other type of cancer? **If Yes, please respond to the following** • Dysplasia of the colon or rectum YES / NO Date of diagnosis: • Cancer of the colon or rectum YES / NO Date of diagnosis: • Lymphoma YES / NO Date of diagnosis: • Other: (Specify) Date of diagnosis:	Yes ☐	No ☐
2. Since our last study contact, have you been diagnosed with progressive multifocal leukoencephalopathy (also known as PML)? **If Yes, please respond to the following** • Date of diagnosis:	Yes ☐	No ☐
3. Since our last study contact, have you had a colectomy or a bowel surgery (surgical removal of any part of your small or large intestine?) **If Yes, please respond to the following** • Colectomy YES / NO Date of diagnosis: • Bowel resection YES / NO Date of diagnosis:	Yes ☐	No ☐

ADDITIONAL QUESTIONS TO BE ASKED AT MONTH 6 ONLY:		
4. Since your last study contact / visit, have you been diagnosed with any infections that required hospitalization? **If Yes, please respond to the following** • Specify reason for hospitalization / diagnosis • Date of diagnosis	Yes ☐	No ☐
5. For females: Have you become pregnant since your last study visit? **If Yes, please respond to the following** • Pregnancy report must be completed • Specify expected delivery date	Yes ☐	No ☐
6. For males: Has a female partner become pregnant since your last study visit? **If Yes, please respond to the following** • Pregnancy report must be completed • Specify expected delivery date	Yes ☐	No ☐

Note:

- Consent will be requested to obtain a death report if applicable
- If a subject is not successfully contacted for a particular follow up (e.g. 12 months), efforts should still be made to contact the subject at the next scheduled follow up (e.g. 18 months).