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PROTOCOL NUMBER: 101JC402

PROTOCOL PHASE: 4

PROTOCOL TITLE: JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri®: STRATIFY-2

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Protocol 101JC402, Version 4, was approved by:

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[redacted] 3/7/2013

[redacted] MD, MRCPI, M Med Sci Date

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Biogen Idec Inc.

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1 SPONSOR INFORMATION

1.1 Coordinating Center

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2 LIST OF ABBREVIATIONS

CD	Crohn's disease
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ICF	Informed Consent Form
IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
IS	Immunosuppressant
JCV	JC Virus
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PBMC	Peripheral blood mononuclear cell
PLEX	Plasma exchange
PML	Progressive multifocal leukoencephalopathy
RNA	Ribonucleic acid
SAE	Serious adverse event
TOUCH	TYSABRI Outreach: United Commitment to Health
[redacted]	[redacted]
US	United States

3 SYNOPSIS

Protocol Number:	101JC402
Version Number:	4
Protocol Title:	JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri®: STRATIFY-2
Protocol Phase:	4
Study Design:	Observational, longitudinal cohort
Study Location:	United States (US)

Study Objectives:

Primary:

1. Demonstrate that the incidence of progressive multifocal leukoencephalopathy (PML) in Tysabri-treated patients who do not have detectable antibodies to JC virus (JCV) (antibody negative) is lower than in patients who have detectable antibodies to JCV (antibody positive)

Secondary:

1. Estimate the incidence of PML in Tysabri-treated patients who are anti-JCV antibody negative and anti-JCV antibody positive, based on a meta-analysis of data obtained from this study and other data sources
2. Define the prevalence of anti-JCV antibody in relapsing multiple sclerosis (MS) patients receiving Tysabri within the TYSABRI Outreach: United Commitment to Health (TOUCH) Prescribing Program
3. Determine changes in anti-JCV antibody status over time

Number of Planned Patients:	At least 8000 patients
Study Population:	Study population will consist of US patients with relapsing MS receiving commercial Tysabri. Patients may participate in other clinical studies sponsored by

Biogen Idec or Elan; however, if the anti-JCV antibody test is included in the other clinical study and that study is performing a longitudinal analysis of those samples, the patient should withdraw from STRATIFY-2.

Visit Schedule: There are no study-mandated visits.

Information Collected: After informed consent (or reconsent, if applicable) is obtained, serum samples will be collected at enrollment into the study and then every 6 months thereafter for up to 4 years. Samples will be sent to a central laboratory for analysis (presence of anti-JCV antibody), and remaining serum aliquots will be stored for future Tysabri and PML research.

Optional Procedures (Focused Sampling Group)

A study site is highly encouraged to offer optional procedures to patients who are anti-JCV antibody positive at any timepoint AND have received ≥12 infusions of Tysabri, whether or not they have a history of immunosuppressant (IS) use (hereafter referred to as the focused sampling group).

For patients who qualify for the focused sampling group and consent to participate, the collection of serum and the following biological samples will be performed, and samples will be stored for future Tysabri and PML research, including biomarker analysis.:

- Whole blood, serum, and plasma samples quarterly
- One whole blood sample every 6 months for the analysis of peripheral blood mononuclear cells
- Urine sample up to 2 times, preferably at an earlier timepoint in study participation
- One whole blood sample, preferably at an earlier timepoint in study participation, for pharmacogenomic analysis
- Other sample types in the event of suspected or confirmed PML (See Section 14, Appendix 1)

	Relevant patient data will be collected on the laboratory requisition form. **<u>Optional Procedures (Patients with Suspected or Confirmed PML)</u>** For patients who are suspected or confirmed to have PML and consent to sample collection, additional serum and biological samples (including a whole blood sample for pharmacogenomic analysis) will be collected (See Section 14, Appendix 1).
Assessments:	Serum will be tested for the presence of anti-JCV antibodies. Remaining serum aliquots and all other biological samples collected from all patients will be stored for future Tysabri and PML research.
Statistical Analysis:	The primary objective of this study is to determine if the incidence of PML in Tysabri-treated patients who are anti-JCV antibody negative is lower than in patients who are anti-JCV antibody positive. The incidence of PML in patients testing anti-JCV antibody positive and in those testing negative will be presented separately and compared using a 1-sided Fisher's Exact Test. One of the secondary objectives in this study is to estimate the incidence of PML in anti-JCV antibody negative patients and in anti-JCV antibody positive patients. Because PML is a relatively rare adverse event in Tysabri-treated patients, in order to have a sufficient number of PML cases for estimating the incidence of PML in anti-JCV antibody negative patients and anti-JCV antibody positive patients, it will be necessary to combine PML cases from multiple sources (e.g., other Biogen Idec studies, registries, and the post-marketing setting, worldwide) as well as previously reported cases of PML.

4 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Procedures and Assessments	Enrollment	Quarterly	Every 6 Months
Informed Consent[1]	X		
Information on Laboratory Requisition Form[2]	X	X[4]	X
Obtain History of IS Use[3]	X		
Serum Sample for anti-JCV Antibody Analysis and Storage	X		X
Whole Blood, Serum, and Plasma Samples for Future Tysabri and PML Research[4]		X	
Whole Blood Sample for PBMC Analysis[4]			X
Urine Sample for Future Tysabri and PML Research[4]	Up to 2 times, preferably at an earlier timepoint in study participation		
Whole Blood Sample for DNA Analysis[5]	1 time, preferably at an earlier timepoint in study participation		
Sampling and Data Collection in the Event of Suspected or Confirmed PML[6]	See Section 14, Appendix 1 for timing and frequency of samples		
Serious Adverse Events	Only SAEs related to the venipunctures/blood draws will be collected during this study and optional procedures, if applicable (see Section 9).		

Abbreviations: DNA = Deoxyribonucleic acid; ECGs = Electrocardiograms; IS = Immunosuppressants; JCV = JC virus; MRI = Magnetic resonance imaging; PBMC = Peripheral blood mononuclear cell; PML = Progressive multifocal leukoencephalopathy; SAE = Serious adverse event; TOUCH ID = TYSABRI Outreach: United Commitment to Health identification.

1 For all patients who are already enrolled, reconsent for study participation in accordance with the protocol amendment is required. Informed consent for participation in the focused sampling group or in PML sampling will be documented by the Investigator; patients will be provided with the option to decline genetic testing without affecting their ability to participate in other study procedures, as required by local laws and regulations.

2 Information to be collected on laboratory requisition form includes: date and time of sample collection, patient information (initials, date of birth, gender, patient TOUCH ID), prescriber name, site number, and date informed consent (or reconsent, if applicable) was obtained.

3 Study personnel are required to obtain the history of IS use at the time of reconsent in accordance with the protocol amendment. Information is to be collected on the laboratory requisition form.

4 Only for patients who qualify (patients who are anti-JCV antibody positive at any timepoint AND have received ≥12 infusions of Tysabri, whether or not they have a history of IS use) and consent to participate in the focused sampling group.

5 Only for patients who qualify for the focused sampling group OR have suspected or confirmed PML and consent to participate.

6 For patients who are suspected or confirmed to have PML, in addition to the sampling schedule in Section 14, Appendix 1, Biogen Idec requests consent to collect copies of MRI scans, ECGs, relevant additional elements of the patient's clinical history, and any pre-PML biological samples or biological samples collected outside the recommended study assessments that may be available from the participating patient for research purposes.

5 INTRODUCTION

Tysabri (natalizumab) is approved in the United States (US), the European Union, and multiple other countries in the rest of the world for the treatment of multiple sclerosis (MS). Tysabri is also approved in the US for the treatment of moderate-to-severe Crohn's Disease (CD).

The use of Tysabri has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare brain infection that usually causes death or severe disability, often rapidly after diagnosis. PML is caused by a polyomavirus called the JC virus (JCV) that results in asymptomatic infection in approximately 50% to 60% of the population (Stolt et al, 2003; Knowles et al, 2003; Egli et al, 2009; Kean et al, 2009). The virus normally only reactivates and progresses to PML in individuals who are immunocompromised (Chesters et al, 1983; Cinque et al, 2003). PML is likely caused by a convergence of multiple factors. Currently there are no established prognostic markers of PML or proven treatments for clinical management of PML.

Biogen Idec Inc. (Biogen Idec) and Elan Corporation (Elan) are committed to providing access to the anti-JCV antibody assay to all MS patients. Because JCV infection is a necessary step for PML development, an assay to detect JCV exposure in patients was thought to be a potentially useful tool to assist in stratifying Tysabri-treated patients for PML risk (i.e., identifying patients who may be at lower or higher risk of PML).

The anti-JCV antibody assay is commercially available through Quest Diagnostics Laboratory. In addition, the presence of anti-JCV antibodies has been determined to be a risk factor for PML, based on global post-marketing PML cases in Tysabri-treated patients who had available sera collected and archived prior to PML diagnosis and tested for anti-JCV antibody status. Patients who are anti-JCV antibody negative may still be at risk for PML for reasons such as a new JCV infection, fluctuating antibody status, or a false negative test result. Although the presence of anti-JCV antibodies is now recognized as a risk factor for PML, continued sample collection through the current protocol is strongly encouraged in order to (1) further demonstrate in a prospective cohort that the risk of PML in anti-JCV antibody-positive patients is higher than that in antibody-negative patients, (2) enable longitudinal analysis of anti-JCV antibody data, and (3) provide samples that can potentially be used for further Tysabri and PML research, including the possible identification of additional biomarkers for PML.

6 RATIONALE

Biogen Idec has developed an enzyme-linked immunosorbent assay to detect the presence of anti-JCV antibodies in serum as an indicator of exposure to JCV. Using this assay, Biogen Idec tested sera from approximately 900 MS patients treated with Tysabri in a global safety extension study (STRATA: An Open-Label, Multicenter, Extension Study to Evaluate the Safety and Tolerability of Natalizumab Following Re-Initiation of Dosing in Multiple Sclerosis Subjects Who Have Completed Study C-1801 or C-1802 and a Dosing Suspension Safety Evaluation) and have demonstrated that the prevalence of anti-JCV antibodies in Tysabri-treated MS patients is 54%. This is similar to the

prevalence reported in healthy subjects in the literature, using similar methodologies (Stolt et al, 2003; Knowles et al, 2003; Egli et al, 2009; Kean et al, 2009).

As of January 2010, in 11 patients who developed PML while on Tysabri treatment and in whom serum samples were available at least 12 months prior to the onset of PML, all 11 patients tested positive for the presence of serum anti-JCV antibody using Biogen Idec's assay. This included 3 patients from the original clinical trials (2 MS patients and 1 CD patient) and 8 MS patients since the re-marketing of Tysabri (of which 3 were from the STRATA study, 2 from the Swedish Registry, and 3 were from the post-marketing setting in Europe [n=2] and the US [n=1]). Assuming a prevalence of anti-JCV antibody of approximately 50% in MS patients, it would have been predicted that only half of these PML patients would be seropositive, suggesting that seronegativity may be associated with a reduced risk of PML.

Biogen Idec has demonstrated that the false negative rate of the assay is 2% to 3% and the seroconversion rate (i.e., change from anti-JCV antibody negative status to anti-JCV antibody positive status) in MS patients over time is approximately 2% to 3% annually (Bozic et al, 2011; Gorelik et al, 2010).

Overall, these data suggest that patients who are anti-JCV antibody negative may have a lower risk of developing PML relative to patients who are anti-JCV antibody positive. Although anti-JCV antibody status has now been recognized as a risk factor for PML, there is still a need to demonstrate the clinical utility of the anti-JCV antibody assay and further analyze longitudinal JCV data within a prospective study.

The purpose of this study is to demonstrate that the risk of PML in Tysabri-treated patients who are anti-JCV antibody negative is lower than in patients who are anti-JCV antibody positive. In addition, through a meta-analysis approach utilizing data collected from this study and other sources (e.g., other Biogen Idec studies, registries, and the post-marketing setting, worldwide) the incidence of PML in Tysabri-treated patients who are anti-JCV antibody negative and anti-JCV antibody positive will be estimated. In order to perform more meaningful assessments of these data, the duration of the study has been increased to up to 4 years. More importantly, the longer study duration will provide longitudinal data on the anti-JCV antibody assay, ensuring that the endpoints are met.

Optional Procedures

An option to collect biological samples from patients who are anti-JCV antibody positive at any timepoint within this study AND have received ≥12 infusions of Tysabri, whether or not they have a history of IS use, (hereafter referred to as the focused sampling group) is offered as a part of this study to enable future Tysabri and PML research, including biomarker and exploratory pharmacogenomic analyses. Study sites are highly encouraged to offer this option to their study patients. These additional study procedures will only be conducted at study sites that agree to participate in these activities and in patients that consent to participate in the focused sampling group.

Biomarkers offer the potential to discover predictive signals that may be associated with an increased risk of PML development. Characterization of how these markers change as

the disease process evolves may contribute to an enhanced understanding of the disease and its development.

Similarly, an exploratory pharmacogenomic analysis may improve disease comprehension by seeking host genetic mutations that may render individual patients more susceptible (or resistant) to developing PML. The pharmacogenomic analysis will identify specific genetic polymorphisms associated with study treatment response. Experience with treatment in MS shows that there is heterogeneity in clinical response, and some of the heterogeneity may be associated with genetic variation in patients. The results of these assays may guide the weighting of analysis of genes when the genome sequences are analyzed. This approach has been used to identify defective pathways in primary immune deficiencies and has led to the discovery of mutations in the TLR3 pathway, conferring susceptibility to herpes simplex virus encephalitis [Casrouge et al, 2006].

To enable future Tysabri and PML research (including biomarker analysis), whole blood, serum, and plasma samples will be collected quarterly from patients who meet the criteria and consent to participate in the focused sampling group. An additional whole blood sample will be collected every 6 months from these patients for peripheral blood mononuclear cell (PBMC) analysis. Additionally, urine will be collected from these patients up to 2 times, preferably at an earlier timepoint in their study participation.

To enable exploratory pharmacogenomic analysis, patients in the focused sampling group and patients with suspected or confirmed PML will be asked to provide a deoxyribonucleic acid (DNA) sample from whole blood once, preferably at an earlier timepoint in their study participation. DNA may be used for genome-wide or candidate gene single nucleotide polymorphism analyses. Samples will be coded for anonymity, and no genetic testing will be performed on any samples other than those collected for this purpose. Patients will be provided with the option to decline genetic testing without affecting their ability to participate in other study procedures, as required by local laws and regulations.

To enable exploration and discovery of potential biomarkers for risk and early detection of PML, it is necessary to obtain biological samples from patients confirmed to have PML or who are suspected of having it as early as possible and at particular timepoints during their course of treatment. Patients for whom PML is suspected or confirmed will be asked to provide additional information (if available; see Section 14, Appendix 1) to explore predictive signals that may be associated with an increased risk of PML development.

7 OBJECTIVES

Primary:

1. Demonstrate that the incidence of PML in Tysabri-treated patients who do not have detectable antibodies to JC virus (JCV) (antibody negative) is lower than in patients who have detectable antibodies to JCV (antibody positive)

Secondary:

1. Estimate the incidence of PML in Tysabri-treated patients who are anti-JCV antibody negative and anti-JCV antibody positive, based on a meta-analysis of data obtained from this study and other data sources
2. Define the prevalence of anti-JCV antibody in relapsing MS patients receiving Tysabri within the TYSABRI Outreach: United Commitment to Health (TOUCH) Prescribing Program
3. Determine changes in anti-JCV antibody status over time

8 STUDY DESIGN

8.1 Enrollment

This is an observational, longitudinal cohort study. All patients with relapsing MS treated with Tysabri are eligible to participate.

Patients who are receiving Tysabri at the time of enrollment into STRATIFY-2 and their prescribers must be enrolled in the TOUCH Prescribing Program before enrollment into this study.

Patients with suspected or confirmed PML who are at or referred to a participating STRATIFY-2 site may enroll into STRATIFY-2 for purposes of PML sample collection.

Patients may participate in other clinical studies sponsored by Biogen Idec or Elan; however, if the anti-JCV antibody test is included in the other clinical study and that study is performing a longitudinal analysis of those samples, the patient should withdraw from STRATIFY-2.

Site personnel will administer informed consent to eligible patients prior to any study procedures taking place. The original Informed Consent Forms (ICF) and documentation of the consent process will be retained in the patient record at the Investigator's site. A copy is to be sent to the Prescribing Physician.

8.2 Sample Collection Process

After the patient has provided written informed consent, a serum sample will be collected to be tested for the presence of anti-JCV antibodies. A serum sample will then be collected every 6 months for up to 4 years.

Samples will be sent to a central laboratory. Results of the serum anti-JCV antibody tests (positive/negative) will be provided to the Investigator/Prescribing Physician. If the Investigator is not the Prescribing Physician, the Investigator will be responsible for providing the results to the Prescribing Physician(s). Remaining serum aliquots from both anti-JCVantibody negative and positive patients will be stored for future Tysabri and PML research. If a sample collection is not received approximately every 6 months after enrollment, a reminder will be sent to the Investigator.

Relevant patient data (see Sections 8.3 to 8.6) will be collected using provided laboratory requisition forms. Copies of the laboratory requisition forms are to be kept at the Investigator's site in the patient record.

There are no study-mandated visits. Samples will be collected during routine patient care or follow-up visits for up to 4 years after the initial sample collection at enrollment. Additional samples will be collected at participating sites from patients who qualify and consent to participate in focused sampling, as described in Sections 8.5 and 8.6.

No treatment is provided in this study. Any patients, including patients in the focused sampling group, may withdraw from any study procedures, at any time, for any reason. If a patient discontinues Tysabri or disenrolls from TOUCH, the patient should remain in STRATIFY-2 until their next scheduled 6-month serum sample is collected and then should be withdrawn from this study.

8.3 Samples and Information Collected at Enrollment/Reconsent

The Investigator will collect the following samples and information at enrollment:

- Informed consent for participation in the study
- For all patients who are already enrolled, reconsent for study participation in accordance with the protocol amendment
- Optional consent for participation in the focused sampling group (and an option to decline genetic testing), if applicable
- Optional consent for PML sample collection in the event a patient is suspected or confirmed to have PML
- Serum collection for anti-JCV antibody testing and storage for future Tysabri and PML research
- Information on laboratory requisition form: date and time of sample collection, patient information (initials, date of birth, gender, patient TOUCH ID), prescriber name, site number, and date informed consent (or reconsent, if applicable) was obtained

- History of IS use

8.4 Samples and Information Collected Every 6 Months for up to 4 Years From Enrollment (All Patients)

The Investigator will collect the following samples and information every 6 months after enrollment:

- Serum collection for anti-JCV antibody testing and storage for future Tysabri and PML research
- Information on laboratory requisition form: date and time of sample collection, patient information (initials, date of birth, gender, patient TOUCH ID), prescriber name, site number, and date informed consent (or reconsent, if applicable) was obtained

8.5 Samples and Information Collected for up to 4 Years From Enrollment for Patients Enrolled in the Focused Sampling Group

Quarterly

The Investigator will collect the following samples and information quarterly from patients in the focused sampling group:

- Whole blood, serum, and plasma collection for storage for future Tysabri and PML research
- Information on laboratory requisition form: date and time of sample collection, patient information (initials, date of birth, gender, patient TOUCH ID), prescriber name, site number, date informed consent (or reconsent, if applicable) was obtained, and whether the patient consented to participate in the focused sampling group

Every 6 Months

The Investigator will collect the following samples and information every 6 months from patients in the focused sampling group:

- One whole blood sample for PBMC analysis
- Information on laboratory requisition form: date and time of sample collection, patient information (initials, date of birth, gender, patient TOUCH ID), prescriber name, site number, date informed consent (or reconsent, if applicable) was obtained, and whether the patient consented to participate in the focused sampling group

8.6 Samples and Information Collected at Unspecified Timepoints (Focused Sampling Group and Patients With Suspected or Confirmed PML Only)

The Investigator will collect the following samples and information from patients in the focused sampling group and from patients with suspected or confirmed PML (as indicated) at an appropriate time:

- Urine sample collection up to 2 times, preferably at an earlier timepoint in study participation for future Tysabri and PML research (focused sampling group only)
- One whole blood sample collection, preferably at an earlier timepoint in study participation for future pharmacogenomic analysis (i.e., viral DNA testing and genomic testing)
- If at any time during the course of the study, a patient is suspected or confirmed to have PML, blood, urine, and cerebrospinal fluid (CSF) samples (where available) should be collected as soon as possible and whenever possible, prior to initiation of plasma exchange (PLEX) therapy. See Section 14, Appendix 1 for the recommended sampling schedule.
- In addition to the sampling schedule in Section 14, Appendix 1, for patients in whom PML is suspected or confirmed, Biogen Idec requests consent to collect copies of magnetic resonance imaging (MRI) scans, electrocardiograms (ECGs), relevant additional elements of the patient's clinical history, and any pre-PML biological samples or biological samples collected outside the recommended study assessments that may be available from the participating patient for research purposes.
- Information on laboratory requisition form: date and time of sample collection, patient information (initials, date of birth, gender, patient TOUCH ID), prescriber name, site number, date informed consent (or reconsent, if applicable) was obtained, and whether the patient consented to participate in the focused sampling group, PML sampling, and genetic testing (if applicable).

8.7 Sample Banking

Samples, including remaining aliquots from other analyses, will be archived and may be studied to characterize potential biomarkers (for example, ribonucleic acid [RNA] and proteomic analysis, associated with the effects of Tysabri treatment, including immune function and possible risk factors related to JCV and development of PML).

Samples may be stored for analyses for up to 15 years after completion of the study.

9 SERIOUS ADVERSE EVENTS

Information on serious adverse events (SAEs) **related to the venipunctures/blood draws** will be collected in this study and in the optional study procedures, if applicable. If your patient experiences an SAE related to the venipuncture/blood draw based on the definition below, you must call [redacted] at:

[redacted]

[redacted]

An SAE is any event which:

- results in death,
- is an immediate threat to life,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly or birth defect, or
- any other event which requires intervention to prevent death or hospitalization.

If a patient has an SAE related to the venipunctures/blood draws, this must be reported to [redacted]. Other adverse events in patients treated with Tysabri will be collected according to the requirements set forth by the TOUCH Prescribing Program and do not need to be reported to [redacted] under this protocol.

Biogen Idec will notify regulatory authorities of SAEs, as necessary, according to local regulations.

10 STATISTICAL CONSIDERATIONS

Prior to data analysis, detailed statistical methods will be included in a separate Statistical Analysis Plan.

10.1 Sample Size

The objective of this study is to demonstrate that the incidence of PML in Tysabri-treated patients who have tested negative for anti-JCV antibody is lower than that in those who have tested positive for anti-JCV antibody. As of January 2010, the incidence of PML in patients with at least 2 years of Tysabri treatment is approximately 1.3 cases per 1000 patients (95% confidence interval: 0.8 to 1.9 cases per 1000 patients).

Assuming that the prevalence of anti-JCV antibodies in Tysabri-treated patients is 54% and that the anti-JCV antibody assay has a false negative rate of 2%, an overall PML incidence in patients treated for at least 2 years of approximately 1.3 cases per 1000 patients implies that the incidence for patients who tested positive for anti-JCV antibody is 2.4 (= 1.3/ (0.54+0.46×0.02)) per 1000 patients, and for patients who tested negative

for anti-JCV antibody is 0.05 (= 2.37×0.02) per 1000 patients. This calculation assumes that PML will not occur in patients who are truly anti-JCV antibody negative, and that patients who tested anti-JCV antibody positive are truly antibody positive (i.e., no false positives). With the PML incidence of 1.3 cases per 1000 patients among patients with at least 2 years of Tysabri treatment, a sample size of approximately 6000 patients will be required to detect a difference in the incidence of PML between anti-JCV antibody positive and antibody negative patients with 83% power, based on a 1-sided Fisher's Exact Test at 0.05-level of significance. Assuming that the annual drop-out rate from this study is approximately 10%, at least 8000 patients will be enrolled into this study.

Based on the assumptions above, 8 cases of PML in patients who are anti-JCV antibody positive are required in order to have adequate power to confirm the primary objective. Patients enrolling in this study will have varying durations of Tysabri treatment at the time of enrollment (ranging from 0 to >3 years of treatment). Because the rate of PML increases with duration of treatment, the distribution of Tysabri exposure among the enrolled patients will influence the actual observed incidence of PML and hence, the sample size needed to confirm the primary objective. Biogen Idec will monitor the assumptions in the enrolled patients, including the distribution of Tysabri exposure, the incidence of PML, the prevalence of positive anti-JCV antibody, and the false negative rate for the anti-JCV antibody assay, and may need to re-assess the sample size during the conduct of this study.

In order to explore the correlation between anti-JCV antibody index values and PML risk, a sample size of at least 5000 patients will be needed.

10.2 Patient Population

All patients who are enrolled and have provided at least one serum sample will be included in the analysis.

10.3 Statistical Methods

All appropriate background data will be summarized by presenting frequency distribution and/or basic summary statistics.

The primary objective of this study is to determine if the incidence of PML in Tysabri-treated patients who are anti-JCV antibody negative is lower than that in patients who are anti-JCV antibody positive. The incidence of PML in patients testing anti-JCV antibody positive and in those testing negative will be presented separately and compared using a 1-sided Fisher's Exact Test.

The secondary objectives of this study are to define the prevalence of anti-JCV antibody and to determine the changes in anti-JCV antibody status over time. The percentage of patients who have tested anti-JCV antibody positive will be presented for those receiving Tysabri in the TOUCH Prescribing Program and for those who are interested in or are considering beginning Tysabri treatment. In addition, the percentage of patients who have anti-JCV antibody status changes from negative to positive over time will be presented.

The data from this study will be analyzed separately and in combination with the data from the STRATIFY-1 study (Biogen Idec study 101JC401).

Meta-Analysis to Estimate the Incidence of PML Based on Anti-JCV Antibody Status

Since PML is a relatively rare adverse event in Tysabri-treated patients, in order to have a sufficient number of PML cases for estimating the incidence of PML in anti-JCV antibody negative patients and anti-JCV antibody positive patients, it will be necessary to combine PML cases from multiple sources, including STRATIFY-1. Biogen Idec will continue to evaluate cases of PML in patients on Tysabri from worldwide sources in whom there are serum samples available prior to the onset of PML, in order to determine their anti-JCV antibody status. Based on an accumulating number of such Tysabri-PML cases, Biogen Idec will calculate an estimated risk of PML in patients who are anti-JCV antibody negative compared to patients who are anti-JCV antibody positive.

10.4 Interim Analyses

The objectives will be assessed on an ongoing basis.

11 ETHICAL, REGULATORY, AND ADMINISTRATIVE REQUIREMENTS

The sponsor (Biogen Idec) [redacted] agree to comply with this protocol and to conduct the study according to local law and regulations.

11.1 Informed Consent and Confidentiality

Prior to any data collection under this protocol amendment, written informed consent must be provided by the participating patient. The Investigator, or their qualified designee, is required to discuss the rationale of STRATIFY-2 and the assessment schedule with the patient. A copy of the completed ICF, signed and dated by the patient and the administrator of the informed consent, must be given to the patient. The informed consent process as well as a copy of the signed ICF must be documented in the patient's medical records prior to any data collection under this protocol amendment. The ICF must not be altered without the prior agreement of the relevant Institutional Review Board (IRB) and Biogen Idec.

Investigator agreement with the study duration up to 4 years and participation in the optional study procedures for the focused sampling group or PML sampling are strongly encouraged and will be contingent upon approval of his/her IRB. All enrolled patients must be reconsented to study participation in accordance with the changes made to the protocol. For eligible patients, consent to the option to participate in the focused sampling group or in PML sampling will be documented by the Investigator and recorded on the laboratory requisition forms. Patients who qualify and consent to participate in the focused sampling group or in PML sampling will also be provided with the option to decline genetic testing as required by local laws and regulations, without affecting their ability to participate in the other study procedures. If the Investigator is not participating in the optional study procedures or if the optional study procedures are not approved by

his/her IRB, the section(s) of the protocol referring to the optional study procedures and focused sampling group will not be applicable to his/her site.

In order to ensure patient confidentiality, patients will be tracked using their TOUCH ID or patient initials, date of birth, and gender.

In any presentations or in publications of the results, the patients' identities will remain anonymous and confidential. Biogen Idec, its designee(s), and various government health agencies may inspect the records of physicians participating. Every effort will be made to keep the patients' personal medical data confidential.

11.2 Institutional Review Board

Approval of this protocol and the patient ICF must be obtained by each site from an IRB prior to the start of the study. A copy of the IRB approval letter, a roster of IRB committee members, and the IRB approved ICF must be kept by each Investigator in their files. The study enrollment materials will be supplied to the Investigator upon IRB committee approval.

11.3 Changes to the Final Study

All changes to the study must be submitted to the IRB and Regulatory Authorities as required by law.

11.4 Internal Committees

11.4.1 Internal Safety Review

Safety and Benefit-Risk Management and other applicable personnel at Biogen Idec will review SAEs related to venipuncture/blood draw collected in this protocol on a periodic basis.

11.5 Record Retention

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen Idec in writing and receive written authorization from Biogen Idec to destroy study records. In addition, the Investigator must notify Biogen Idec of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

12 GENERAL INFORMATION

12.1 External Contract Organizations

Biogen Idec has chosen [redacted] to manage this study.

12.2 Central Laboratories of Laboratory Assessments

[redacted] has been selected by Biogen Idec to manage the sample collection process.

Focus Laboratories has been selected by Biogen Idec to perform anti-JCV antibody testing for this study. Other qualified laboratories may also be considered by Biogen Idec for this purpose.

13 REFERENCES

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14 APPENDIX 1

Sampling in the Event That PML is Suspected or Confirmed

Progressive multifocal leukoencephalopathy (PML) is a progressive, demyelinating disease of the central nervous system that is debilitating and often fatal. Currently, there is an acute lack of preventative, early diagnostic, and therapeutic options, and a significant unmet medical need exists for methods that facilitate early detection and diagnosis of PML and immune reconstitution inflammatory syndrome (IRIS) associated with PML. This is particularly important for patients who are treated with Tysabri, which has been associated with the infrequent occurrence of PML.

To enable exploration and discovery of potential biomarkers for risk and early detection of PML, it is essential to obtain biological samples from patients with PML at particular timepoints starting as early as possible during the course of this rapidly progressing disease. Biological samples will be collected serially from patients when PML is suspected, so that Biogen Idec can discover predictive biomarkers that may signal increased risk of PML development in certain patients. Samples collected under this initiative will enable critical research that may lead to improved outcomes in future PML patients.

The objective is to collect critical biological samples from Tysabri-treated patients, starting as soon as possible after PML is suspected based on clinical or magnetic resonance imaging (MRI) findings, or diagnosed by detection of JC virus in cerebrospinal fluid or a brain biopsy. The collection of samples coincident with, or preferably prior to, early treatment intervention is critical for therapeutic research involving the discovery and validation of biomarkers for PML risk stratification, early diagnosis, and disease monitoring. These early samples will represent the baseline assessments, taken in the absence of any disease-specific therapeutic intervention, to which all follow-up samples can be compared.

Suggested Sample Collection Schedule:

Whenever possible, sample collections should be completed during regularly scheduled clinic visits or during hospitalization, and while patients are undergoing blood draws or providing urine for treatment of PML and/or IRIS. Participating patients may choose to provide some or all of the samples specified below, and they may withdraw consent or request that any remaining biological samples in storage be destroyed at any time. Biogen Idec will provide collection kits for the samples. All samples are to be returned to the Central Laboratory on the day of collection via express courier.

Activities and Sample Collection	Prior to PLEX	Within 24 Hours Post Final PLEX	Prior to First Corticosteroid Dose for IRIS (or Within 1 to 2 Weeks Post Final PLEX Cycle)[2]	1 to 2 Months Post Last Dose of Corticosteroids for IRIS (or 2 to 3 Months Post Final PLEX if no Corticosteroid Treatment)[3]
Lumbar Puncture (CSF)	X[1]		X	X
Plasma	X	X	X	X
Serum	X	X	X	X
PBMC	X		X	X
Urine	X	X	X	X
RNA (where allowed)	X		X	X

Abbreviations: CSF = Cerebrospinal fluid; IRIS = Immune reconstitution inflammatory syndrome; PBMC = Peripheral Blood Mononuclear Cell; PLEX = Plasma exchange; RNA = Ribonucleic acid.

1 Excess CSF available from lumbar punctures used to assess viral load for the purpose of PML diagnosis; an aliquot of ≥3 mL is to be provided, if available.

2 Prior to first corticosteroid dose for IRIS is the preferred collection timepoint.

3 1 to 2 months post last dose of corticosteroids for IRIS is the preferred collection timepoint.

In addition to the sampling schedule above, Biogen Idec requests copies of MRI scans, electrocardiograms, relevant additional elements of the patient's clinical history, and any pre-PML biological samples or biological samples collected outside the recommended study assessments that may be available from the participating patient for research purposes.