MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 6, 2006

TO: Russell Katz, M.D., Director
Division of Neurology Products, HFD-120

THROUGH: Gerald Dal Pan, M.D., Director
(Jonca Bull, M.D. for Dr. Dal Pan 02/06/06)
Office of Drug Safety

FROM: ODS Natalizumab RiskMAP Review Team

DRUG: Tysabri® (Natalizumab); STN 125104/15

APPLICANTS: Biogen Idec and Elan Pharmaceuticals, Florida

SUBJECT: Risk Management Program, submitted September 26, 2005

PID: D050552

1 EXECUTIVE SUMMARY/INTRODUCTION

The purpose of this memorandum is to provide the Office of Drug Safety's view on the risk management issues posed by this application and to provide a framework for discussing the Risk Minimization Action Plan (RiskMAP) and Risk Assessment Plan submitted by the sponsor in preparation for the upcoming Peripheral and Central Nervous System Advisory Committee. Given the known risks associated with this product and the absence of tools with documented effectiveness to manage these risks we believe that the RiskMAP proposed by the sponsor should be discussed openly before the advisory committee.

Natalizumab is an alpha-4 integrin-specific humanized monoclonal antibody approved in the United States on November 23, 2004 for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations. Its marketing was voluntarily suspended on February 28, 2005 based on reports of progressive multifocal leukoencephalopathy (PML) in clinical trial patients treated with Tysabri. Of approximately 3,000 patients treated with Tysabri in clinical trials, 3 patients developed PML (2 in clinical trials for MS and one in a clinical trial for Crohn's disease), a rare, serious, and often fatal disease. Two of the 3 patients died.

The sponsor of Tysabri is proposing a reintroduction of the product into the U.S. market with a RiskMAP, Tysabri Outreach Unified Commitment to Health (TOUCH) "to strike a balance between maximizing the benefits of Tysabri and minimizing the risks of PML without placing unnecessary burdens on MS patients and physicians." It is the opinion of ODS that the RiskMAP in its current form does not adequately address the risk of PML.

This document provides a summary of the RiskMAP as well as considerations for RiskMAP options. We would encourage the AC to discuss what essential features would be necessary for an acceptable RiskMAP such as mandatory versus voluntary enrollments, restriction to more severe forms of MS, restriction in distribution to infusion centers and other options addressed in this document.

2 BACKGROUND

Tysabri™ (natalizumab) is a recombinant humanized monoclonal antibody that was approved by FDA on November 23, 2004, for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations. Its mechanism of action is inhibition of the alpha-4 mediated transmigration of leukocytes into inflamed brain parenchyma. The recommended dose of Tysabri is 300mg IV infusion administered every 4 weeks.

Tysabri was voluntarily suspended from the market on February 28, 2005 after two patients enrolled in a long-term clinical trial developed progressive multifocal leukoencephalopathy (PML). Both patients had been treated with natalizumab for MS for more than two years. A third case of fatal PML, originally diagnosed as astrocytoma, was discovered in a patient with Crohn's disease who had also been in a clinical trial of Tysabri. Thus, there have been a total of 3 confirmed cases identified from clinical trials involving approximately 3000 patients.

PML is a serious and often fatal disease of the brain white matter, characterized by dementia and progressive motor deterioration. It is caused by the JC virus and often occurs in immunodeficient individuals such as those with AIDS and organ transplant recipients or cancer patients who have received immunosuppressive medications. JC virus antibodies are present in a large percentage of the adult population in the United States and the disease is thought to be caused by reactivation of latent JC infection.

The risk of acquiring PML in patients treated with natalizumab is unknown, therefore the natalizumab IND was placed on clinical hold and the Sponsor was instructed to re-evaluate patients who had received natalizumab to determine if any other cases of PML could be identified. To date, they have found no additional cases of PML in patients enrolled in clinical trials. There have also been no additional cases reported to the Adverse Event Reporting System at FDA.

The Sponsor is proposing a reintroduction of the product into the U.S. market with a RiskMAP to address the risk of PML associated with natalizumab. This document

summarizes recommendations on the RiskMAP of the entire Office of Drug Safety Tysabri team.

3 SUMMARY OF THE SPONSOR'S PROPOSED RISK MINMIZATION ACTION PLAN

3.1 GOALS AND OBJECTIVES

The goals and objectives of the Tysabri RiskMAP as stated by the Sponsor are the following:

a) To promote informed risk-benefit decisions regarding Tysabri use in the treatment of MS patients
   - Prescribing physicians, and consequently their patients know that Tysabri is associated with an increased risk of PML.
   - Physicians prescribe Tysabri only for treatment of MS

b) To minimize the health consequences of PML (e.g., death disability)
   - Prescribing physicians know how to diagnose PML and know to suspend Tysabri dosing immediately at the first signs or symptoms suggestive of PML.
   - Patients should know to promptly report to their physician any continuously worsening symptoms lasting over several days.

c) To minimize the risk of PML
   - Prescribing physicians know that Tysabri is contraindicated in patients who are immunocompromised.

3.2 TOOLS

The sponsor proposes a program entitled the TOUCH (Tysabri Outreach: Unified Commitment to Health) System. The program includes what the company has described as the "prescribing and enrollment process" and the "dispensing process". Both are means to deliver education to healthcare providers and patients regarding the use of Tysabri and associated risks. The "prescribing and enrollment process" supports the delivery and use of the patient information leaflet and the Patient-Physician Acknowledgement form. The "dispensing process" supports delivery of the patient checklist and the patient information leaflet. These are described in more detail below.

3.2.1 Education and Reminder Tools

The Sponsor has proposed the following educational materials for patients and health care professionals (HCPs):

Patients
- Patient information leaflet
- Dear Patient Letter
- Patient-Physician Acknowledgment

HCPs
- Revised labeling
- Dear HCP Letter
- Targeted education and sales force

form	detailing directed at neurologists and infusion nurses. • Patient Checklist • Patient-Physician Acknowledgment form • Toll free helpline • Specialized website

The Sponsor has provided the proposed Patient-Physician Acknowledgement and the Patient Checklist for review.

Additionally, Biogen Idec and Elan's field force will detail Tysabri only to neurologists and other HCPs involved in the care of MS patients. They believe this will facilitate compliance with the recommendation that Tysabri be prescribed only for the treatment of MS.

3.2.1.1 Prescribing and Enrollment Process

The *prescribing and enrollment process* supports the delivery of two reminder and educational tools, the Patient-Physician Acknowledgement and the Patient Information leaflet. At the first patient-physician visit, [during the *prescribing and enrollment process*] the physician reviews the label and reviews the Patient Leaflet with the patient. Patients who want to start treatment with Tysabri will complete an enrollment form (called a Start Form) that includes a Patient-Physician Acknowledgment documenting that the physician is prescribing Tysabri for MS and that the patient and physician have discussed Tysabri benefits and risks, including the risk of PML. The signed Start Form/Patient-Physician Acknowledgement is sent to Biogen Idec. The data from this form are entered into a Biogen Idec database.

Patient and Physician enrollment is voluntary, meaning that physicians will not be required to enroll themselves or their patients in order to prescribe or administer natalizumab. The purpose of the *prescribing and enrollment process* appears to be data collection and a means to provide educational materials for physicians to provide to their patients.

3.2.1.2 Dispensing Process

The *dispensing process* tracks product to all infusion sites or physicians offices, allowing the delivery of the Patient Information leaflet and the Patient Checklist to the infusion site and office staff. The Sponsor will be able to track product because they plan distribution of Tysabri from a single distribution point. The Sponsor does not believe that a performance-linked access system (e.g., restricted distribution) is necessary "due to the unique way in which this product is administered." Distribution of Tysabri is as described below:

- All Tysabri vials are shipped directly to the point of infusion from a central distribution point.
- Biogen Idec and Elan plan to track the number of Tysabri vials shipped to each infusion site.
- Education and reminder materials will be delivered to infusion sites
- The Sponsors will make personal educational visits to the infusion centers.

The infusion nurses will be expected to complete a Patient Checklist for each patient prior to infusion to "confirm" that, among other things, the patient is not known to be immunocompromised or experiencing "any continuously worsening symptoms lasting over several days." This checklist is to be completed prior to each infusion and should be kept in the patient's medical chart.

The key features of the program are briefly described below.

1 Voluntary enrollment of physician prescribers and patients (Prescribers may be neurologists and other HCPs; sales force will detail Tysabri to neurologists and other HCPs involved in care of MS patients)
2 During the enrollment process, the physician will provide the patient with the Patient Information Leaflet.
3 Patients who wish to start Tysabri will be invited but not required to complete a Start form (enrollment form) that includes a Patient-Physician Acknowledgment Form (similar to informed consent), which is sent to Biogen Idec.
4 Biogen Idec enters the patient and physician information into a database and delivers educational information to physicians on an ongoing basis (via mailings, website, toll-free helpline, and CME programs)
5 Product shipment information from the centralized distribution point will be compared to physicians' names in the Biogen Idec database to identify physicians who haven't enrolled their patients (but apparently who have already received the drug). Biogen Idec will contact the physician to urge him/her to complete the Start form and of the risks associated with the use of Tysabri, including the risk of PML. The physician will be expected to inform the patient of the risks of Tysabri (using the Patient Information Leaflet and Patient-Physician Acknowledgment form).
6 Tysabri will be administered in infusion centers or physicians offices under the supervision of infusion nurses on a monthly basis.
7 Infusion center nurses will [voluntarily] complete a Patient Checklist for each patient to confirm that the patient has MS, is not known to be immunocompromised, has read the Patient Information Leaflet, and that the patient has not experienced any continuously worsening symptoms lasting over several days.
8 Neurologists and other HCPs can obtain Tysabri from a central distribution point. The start form includes an option for the doctor to administer Tysabri or refer the patient to another site for administration. The intent is for its administration to occur in an infusion center or possibly a physician's office; however there do not appear restrictions in distribution that would limit its use outside of these settings.

3.3 EVALUATION PLAN

The Sponsor plans to evaluate the performance of the RiskMAP by measuring physician and nurse knowledge about Tysabri's PML risk and appropriate-use conditions. They plan to send surveys to physicians and infusion nurses, make infusion site visits, and determine the proportion of non-use of the enrollment form. Specifically, the sponsor has proposed the following as part of the evaluation of the risk management program:

- Start form (enrollment form) analysis – sponsor will track the percentage of start forms that include the Patient-Physician Acknowledgement Form
- Surveys of Neurologists and infusion nurses will evaluate knowledge about PML risk and risk minimization initiatives

It is unclear whether the Sponsor will survey all or a sample of physicians and nurses and whether those physicians sampled will be limited to those physicians who have sent in a Start Form.

4 SUMMARY OF THE SPONSOR'S RISK ASSESSMENT PROGRAMS AND STUDIES

The sponsor has proposed the following risk assessment programs:

4.1 TYSABRI SURVEILLANCE PROGRAM

The Tysabri Surveillance Program is a reporting and data collection system for any PML event that occurs in Tysabri-treated patients. The purpose is to identify risk factors for PML. On the patient enrollment form (Start Form), physicians are asked if they have had any Tysabri–treated patients develop PML and if the cases have been reported to Biogen Idec. If a physician does not complete any additional start forms for 6 months, Biogen Idec will mail the physician a card to determine if the physician has had any cases of PML. If there is no response to the mailed card, Biogen Idec will contact the physician by phone. To identify risk factors, a qualitative analysis of the cases will be performed.

4.2 EPIDEMIOLOGICAL STUDIES

4.2.1 Tysabri Registry

The Sponsor will enroll 5,000 Tysabri-treated MS patients after its reintroduction into the U.S. market and introduction into the European market and follow the patients for up to 5 years. Patients will remain in the study 5 years after the enrollment date or until 3 months after their last dose of Tysabri, whichever is shorter. It is not clear whether those patients who only receive one dose would be followed for only 3 months. We suggest that all patients regardless of the length of therapy be followed for a minimum of 5 years from the date of last dose of Tysabri.

4.2.2 Pregnancy Registry

A pregnancy registry will be established in the US to determine the safety of natalizumab in pregnant patients. The primary objective of the study will be to evaluate any pattern or increase in birth defects in children of women with MS who were exposed to natalizumab. The secondary objectives will be to evaluate the following outcomes in pregnant women exposed to natalizumab: live born infants, fetal loss, and gestational age, body weight, gender, head circumference, and length of child.

4.2.3 Epidemiological Study of PML in Insurance Claims Database

The company plans to study the incidence of and risk factors for PML in a claims database and in a large Midwestern health plan. The primary goal is to quantify the incidence of PML in the general population, as well as in MS and other autoimmune diseases and to assess the impact of selected characteristics, risk factors, and other variables on the risk of developing PML.

4.3 CLINICAL STUDIES

The companies plan to conduct the following clinical studies:

4.3.1 Tysabri Re-dosing studies

The Sponsor is planning two worldwide, multi-center, open-label, single arm re-dosing studies. Approximately 1500 MS patients who were previously exposed to Tysabri in clinical trials will participate in these studies. The primary objective will be to further evaluate the safety of Tysabri monotherapy and the safety of switching from other therapies to Tysabri. Additional objectives will be to explore whether serial blood testing can be used to monitor for the presence of JC virus in the MS population and to explore a methodology of testing for persistent anti-natalizumab antibody positivity.

4.3.2 Immune function/vaccine study

As part of the original approval of natalizumab, Biogen Idec committed to this single-center, randomized, multiple-dose study of 40 MS patients to determine the effect of natalizumab on humoral and cellular immunity. The study will examine the effects of natalizumab administered for 6 months compared to no treatment on cellular and humoral responses to vaccines and in lymphocytes subsets.

4.4 NON-CLINICAL STUDIES

The Sponsor proposes to initiate specific *in vitro* studies to directly address the effects of natalizumab interaction with specific cellular targets and functions with respect to JC virus infection and replication. They also plan to study the effects of short term alpha-4 integrin inhibition on rodent and guinea pig experimental autoimmune encephalomyelitis with respect to effects on immune function. The purpose of these studies is to gain

insights into the potential immunological risk factors for PML development with natalizumab therapy.

5 CONSIDERATIONS IN RISK MINIMIZATION OF NATULIZAMAB

The company is proposing a RiskMAP consisting primarily of education and reminders for nurses, prescribers and patients. The Sponsor does not believe that a performance-linked access system is necessary due to the unique way in which this product is administered. The Office of Drug Safety recommends the following risk management tools or interventions might be considered if the product is reintroduced into the U.S. market.

5.1 RESTRICTIONS IN PRESCRIBING, DISPENSING, AND USE

Restricted distribution systems (also referred to as performance-linked access systems or PLAS) link drug product access to compliance with RiskMAP elements.[1] Restricted distribution systems may:

- Limit prescribing and dispensing to selected prescribers and pharmacists
- Require documentation of safe use conditions or require that the severity criteria associated with the indication have been met before dispensing the product to patients.

Restricted distribution systems have been applied to date for products where there are limited therapeutic alternatives and significant risks associated with the product. In these instances, the user populations have been typically small. Restricted distribution systems may have the unintended consequence of leading to substitution of alternative drug products that haven't been studied or that may themselves impose other risks.

5.1.1 Restrictions in Prescribing

The Sponsor plans to detail natalizumab only to neurologists and other HCPs involved in the treatment of MS, but use by other prescribers could be considerable given that it is currently being studied for use in various other diseases including Crohn's disease.

One approach is to limit the prescribing and/or administration of natalizumab to those physicians who meet certain qualifications or agree to certain conditions including:

- Prescribing only to patients with relapsing MS who meet the conditions stated in the labeled indication.
- Prescribing only by physicians enrolled in the RiskMAP:
  - who attest to having the ability to manage MS
  - who attest to having an understanding of the risks and benefits of natalizumab

[1] The RiskMAP for clozapine requires presentation of a WBC prior to dispensing of the drug. This led to the development of the coined phrase "no blood, no drug."

- who attest to the ability to diagnose and treat PML
- who have the staff to query the patient and infuse and monitor him/her following the infusion (for those HCPs who will administer the product in their office).

5.1.2 Restrictions in Dispensing

Although the Sponsor is proposing a centralized distribution system, which eliminates wholesalers and retailers, there does not appear to be any restrictions in ordering, nor is there a system of dispensing or administering product to only those physicians and patients who have enrolled. It is also not clear if retail or hospital pharmacies would be able to order natalizumab under the current proposal. Likewise, there appears to be potential ways to prescribe and obtain Tysabri outside of the RiskMAP. Also, if patients change their minds between the time of enrollment and infusion, the drug could be stockpiled and used in the future for unenrolled patients.

We suggest the Sponsor identify and close all possible mechanisms for obtaining the drug outside of the program.

- One possibility is to only allow shipment of product to physicians enrolled in the program. The enrolled physicians should be required to enroll or register all patients they plan to treat with natalizumab.
- If pharmacies are to be allowed to dispense, one approach is to limit dispensing this product to those pharmacies who enroll in the RiskMAP and agree to certain conditions, such as ensuring that prescribing physicians and/or patients are also enrolled in the RiskMAP.

5.1.3 Restrictions in Patient Use

5.1.3.1 Use in Certain Patient Populations

The current RiskMAP proposal does not restrict use of natalizumab to the indicated population. The lack of such a restriction could lead to its use in patients with less severe forms of the disease or in disease states (such as Crohn's disease) where the potential clinical benefits have not been demonstrated to justify the potential risks of PML.

The Advisory Committee should discuss whether the use of this nataluzimab should be limited to the following patient populations:

- To patients with relapsing MS who meet the conditions stated in the labeled indications
- Those patients that have failed other available therapies
- To patients who are not immunosuppressed
- To patients not being treated with concomitant immunosuppressants that might contribute to systemic immunosuppression, such as beta-interferon and other immunosuppressants.
- Only to those patients enrolled by their physicians in the RiskMAP

5.1.3.2 Mandatory Patient-Based Registry

Establishment of a mandatory, patient-based registry (maintained by Sponsor) should be considered for several reasons:

- A patient-based registry would also aid in the detection and determination of the rate of rare and serious adverse events, such as PML. Close monitoring of all patients receiving Tysabri may also aid in identifying possible patient risk factors associated with PML. Identification of such risk factors would help inform appropriate use for the prescriber and help to advance the safest use of the product in those patients with MS whose alternate treatment options are few or non-existent. The numbers of patients in the registry would also provide an exact denominator for risk estimates.
- A patient-based registry would be required to provide information on the indications for which Tysabri is being prescribed. Although the Agency has access to prescribing data from physician's offices, the numbers of users of Tysabri would likely be too small to detect in such available systems. Only a mandatory, patient-based registry would provide the critical information that could monitor the range of uses, including off-label use.
- Drug utilization data for products such as Tysabri are difficult to track, due to their venue of administration and the relatively small population of users. The product is administered to patients in doctor's offices, or infusion centers, rather than dispensed in pharmacies. In the past, we have attempted to trace the channels of distribution for drugs administered in this manner but have been unable to gain necessary information about the numbers and types of patients receiving the drug and the quantity administered.

5.2 ADDITIONAL RISK MINIMIZATION OPTIONS

5.2.1 Medication Guide

Mandatory FDA Approved Patient labeling in the form of a Medication Guide (MG) should be considered. This would be provided to the patient in lieu of the currently proposed patient leaflet. The advantages of a MG over a patient leaflet are:

- MGs are required to be dispensed with medications to patients. MGs are generally utilized for outpatient medications and although this product would be administered in an infusion center or a physician's office, the MG could be utilized, along with the Patient-Physician Agreement form, as a counseling tool.
- Changes to the MG would require review and approval of the FDA, because MGs are part of approved labeling.
- MGs are covered under CFR 208.20 which specifies content areas and format, including font size

The primary condition for a MG appears to be met, because the risk of PML can be viewed as a serious and significant public health concern. Further, the risk of PML associated with natalizumab appears to meet the requirement of filling at least one of 3 possible criteria for a MG that serious risks exist which could affect a patient's decision to use the product (CFR 208.1(c)(1)).

5.2.2 Educational Program

- The education program for natalizumab may not be specific enough with regard to the concomitant use of immunosuppressants and symptoms of PML. For instance, infusion nurses will be expected to complete a Patient Checklist for each patient prior to infusion to "confirm" that, among other things, the patient has not experienced "any continuously worsening symptoms lasting over several days." Because many of the symptoms of PML are also symptoms of MS, it will be difficult to differentiate the two and mistakes about administration may potentially to be made.

  For these reasons, we suggest the Sponsor be as specific as possible about which symptoms are of concern. In addition, the Sponsor should provide some guidelines for differentiation of MS symptoms from PML symptoms. Nurses who receive positive answers to questions concerning these symptoms should know what further questions to ask to determine if the drug should be administered. In cases of indecision concerning natalizumab administration, nurses should be instructed to direct questions to the patient's physician for a decision. Individuals with symptoms suggestive of PML should be promptly referred for additional testing in an attempt to achieve early diagnosis and treatment of PML

- The education materials do not include sufficient information regarding PML including:
    - the numerical risk of PML
    - the symptoms of PML (see above)
    - the time from diagnosis of PML to death may be only a few months.

  We suggest the Sponsor design an information guide for prospective prescribers and other healthcare provider. The information guide should include the following: quantitative risk data for PML based on Tysabri clinical trial data, symptoms of PML, methods of diagnosis, PML progression and course (including the possibility of a short course preceding death), and PML treatments.

  Other risks (e.g., hypersensitivity/anaphylaxis reactions and infections) also should be included. The information guide should clearly state the labeled indication for Tysabri, and distinguish it from non-labeled forms of MS. This information should mirror the MG (if implemented).

5.2.3 Miscellaneous Recommendations

- The Sponsor did not provide the number and location of licensed infusion centers throughout the country. If licensed infusion centers are not in convenient locations, this could be a disincentive for patients because of logistical problems, cost, and time involved in traveling to the center. We recommend the Sponsor provide a listing of licensed infusion centers and their locations throughout the country to HCPs and patients.
- The list of medications and treatments on the patient checklist that might indicate that the patient is immunocompromised is not complete. The checklist for nurses should include a list of all immunoosuppressive agents whose effects would potentially interact with that of Tysabri to produce PML.
- The Sponsor's plans for re-introduction of Tysabri should account for the potential role of concomitant immunosuppressants. We note that all 3 Tysabri-treated patients who developed PML were taking concomitant immunosuppressants suggesting the co-administration of other immunosuppressants with Tysabri is a risk factor for Tysabri-associated PML. We suggest that if the Sponsor contemplates administration of Tysabri with other immunosuppressant, the Sponsor should first study such use. For now, the concomitant use of Tysabri with immunosuppressant agents such as beta-interferon should be contraindicated, though we suggest the AC address this point.

5.2.4 Evaluation Plan

We note that the evaluation plan does not include a plan to measure the outcomes of interest, namely to determine whether the RiskMAP minimizes the risk of PML or minimizes the health consequences of PML. Whatever tools are selected for appropriate risk management for this product, it is essential that the sponsor develop a comprehensive evaluation plan to determine the effectiveness of the overall program as well as the effectiveness of the tools in achieving the stated goals. The evaluation plan should also include plans of action if stated goals are not met.

With regard to what the Sponsor has already proposed, we suggest they provide more details about this evaluation plan to include the survey methodology and analysis to determine if the information collected will be scientifically valid. The evaluation plan should additionally provide more detail about the infusion site visits (e.g., number and periodicity).

5.3 RECOMMENDATIONS ON PHARMACOVIGLIANCE, EPIDEMIOLOGIC STUDIES, AND OTHER STUDIES

- We recommend the Sponsor submit all cases of confirmed and suspected PML to FDA on an expedited basis.
- The Sponsor proposes a qualitative analysis of cases reported to the Tysabri Surveillance Program to identify risk factors. However, to identify risk factors, a comparison group is needed. We suggest Biogen Idec compare the frequency of the potential risk factors in MS patients who receive the drug and develop the disease versus the frequency of the risk factors in those who receive the drug and do not

develop the disease. To obtain these data, a mandatory enrollment program would be necessary. We note that the number of Tysabri-treated patients who develop PML may be small, and formal statistical analysis may not be possible. The Sponsor proposed a Tysabri Registry protocol but does not provide details about how patients will be enrolled in the registry, whether it will be a complete registry of patients or a partial one, how the patients will be traced and followed for up to 5 years, how data will be collected on adverse events, etc. Furthermore, the protocol does not mention that a key objective of the registry will be the determination of the incidence rate of PML. We suggest the Sponsors provide a full protocol for this proposed registry and consider what their objectives are and what can be achieved by obtaining the data and by a study that does not include a control group. Furthermore, we suggest that all patients regardless of the length of therapy be followed for a minimum of 5 years from the date of last dose of Tysabri.

- The company should provide details about tracking patients and other methods to minimize the loss of patients to follow-up. A long-term epidemiological cohort study of exposed Tysabri patients compared with MS patients not exposed to Tysabri might be more advisable.
- Current Plan for Epidemiological Study of PML in Insurance Claims Databases: The Sponsor plans to study the incidence and risk factors of PML in a claims database and in a large Midwestern health plan. However, because PML is so rare, it is unlikely that there will be any PML cases in the database. If any are identified, the numbers will be too small to derive any risk factors. The death rate associated with PML as an underlying cause of death in the United States in 2002 was 0.6/10,000,000 population (16 cases per 288,000,000 U.S. population). The death rate associated with PML in which this code was mentioned as a cause of death (immediate, contributing, or underlying) on death certificates in 2002 was 2.8/10,000,000 (81 cases per 288,000,000 U.S. population)[2]. Since it is believed that a large proportion of PML cases are fatal, one can see from mortality data that insurance claims databases are likely to be too small to identify even one case. We suggest the Sponsors set aside plans to conduct this study in insurance claims databases or provide data on the number of cases of PML in such databases. We believe a mandatory patient-based registry would also aid in the detection and determination of the rate of PML.

[2] Public Use Data Tape Documentation. Multiple Cause of Death for ICD-10 1999-2002 data. U.S. Dept of Heath and Human Services, Public Health Service, National Center for Health Statistics, Hyattsville, MD. Census data is available at http://www.census.gov/sopest/sex.html.

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