TYSABRI®
(natalizumab)

ADVISORY COMMITTEE
BRIEFING DOCUMENT

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Peripheral and Central Nervous System Drugs
Advisory Committee
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CONTENTS

LIST OF DISPLAYS

EXECUTIVE SUMMARY

Natalizumab (TYSABRI®) was approved for treatment of patients with relapsing forms of multiple sclerosis (MS) on 23 November 2004 after priority review of 1-year data from two ongoing 2-year studies. Priority review and accelerated approval was determined to be appropriate because of the strength of the efficacy and safety data available at 1 year. Following the recognition of two cases of progressive multifocal leukoencephalopathy (PML) in patients who had been receiving natalizumab in combination with interferon β-1a (Avonex®) for over 2 years, the Sponsor (Biogen Idec and Elan Pharmaceuticals), in discussions with FDA, suspended commercialization and dosing in clinical studies to minimize the risk to treated patients while investigating the relationship between PML and natalizumab therapy.

The Sponsor has completed a comprehensive clinical, radiological, and laboratory investigation of patients exposed to natalizumab in clinical trials. In addition, the two pivotal MS clinical studies are complete and the 2-year results have been evaluated. These findings were submitted to the FDA in September 2005 as a Supplemental Biologics License Application (sBLA). The Sponsor believes that the results of the analysis of natalizumab safety and the 2-year efficacy data in patients with relapsing MS strongly support the reintroduction of natalizumab for prescription use. The FDA has granted Priority Review to this application, a designation reserved for products that, "if approved, would be a significant improvement compared to marketed products," again acknowledging the unique profile of natalizumab in MS, a disease with high unmet medical need.

In this Briefing Document we review all currently available clinical and safety data describing natalizumab and its use in relapsing MS. In addition, we describe a Risk Management Action Plan (RiskMAP) that is intended to 1) educate physicians and patients about the risks of natalizumab treatment, in particular the risk of PML, 2) facilitate prescribing natalizumab in accordance with the usage statement, 3) provide guidance on how to actively assess and manage patients receiving treatment, and 4) proactively collect new safety data so that our assessment of PML risk remains accurate. The Plan is based upon current medical and scientific knowledge of PML and information gained from the safety evaluation of natalizumab-treated patients.

Data presented in this document support our belief that:

- TYSABRI (natalizumab) provides substantial clinical benefit to patients with relapsing forms of MS and that the risk-benefit profile of the drug warrants its reintroduction to patients, and that
- the Sponsor has developed a RiskMAP that is designed to manage the risk of PML and to further assess PML risk and the overall safety of TYSABRI.

Summary of the Clinical Development of Natalizumab

Unmet Need in Multiple Sclerosis

MS is a serious and disabling disease of young adults, striking in the prime of their lives, with a peak age of onset in the fourth decade of life. Most individuals present with the relapsing-remitting form of the disease (RRMS) and experience recurrent attacks, which, over time, result in accumulating permanent physical disability and cognitive decline. About 70% of these individuals will eventually enter a phase of progressive neurological decline (secondary progressive MS [SPMS]), with or without superimposed relapses. Current treatments are minimally effective for SPMS. The inevitable outcome in the majority of patients is one of permanent neurological dysfunction and, on average, a shortened life expectancy by 6 to 7 years. This outcome is due either to the increased risk of completed suicide (Sadovnik *et al*, 1991) or complications related to MS and advanced disability in approximately 50% of deaths (Sadovnik *et al*, 1991; Bronnum-Hansen *et al*, 2004).

Currently, in the US, four therapies are approved for the treatment of relapsing forms of MS. The interferons, Betaseron® (interferon β-1b SC [subcutaneous]), Avonex® (interferon β-1a IM [intramuscular]), and Rebif® (interferon β-1a SC), are cytokines with antiviral, antiproliferative, and immunomodulatory activities. Copaxone® (glatiramer acetate) is a mixture of synthetic polypeptides; the mechanism of action of this agent is not well understood. These therapies each provide a modest, but important, clinical benefit; they all have demonstrated a reduction in relapse rate of approximately 29% to 33% over 2 years (IFNB MS Study Group, 1993; Jacobs *et al*, 1996; PRISMS Study Group, 1998; Johnson *et al*, 1995).

In controlled clinical trials, only Avonex and Rebif have been shown to reduce the progression of sustained disability as measured by the Expanded Disability Status Scale (EDSS). These agents reduce the proportion of subjects progressing at 2 years by 37% and 30%, respectively (Jacobs *et al*, 1996; PRISMS Study Group, 1998).

Another treatment, Novantrone® (mitoxantrone), is a chemotherapeutic agent used to treat patients with severe, RRMS or SPMS. Use of mitoxantrone is limited by cardiac toxicity, as well as the risk of myelodysplastic syndromes, including acute myelogenous leukemia.

Although the safety profiles of the interferons and glatiramer acetate are acceptable, they are not without multiple side effects that affect patient compliance. Currently, it is estimated that 15% to 20% of patients treated with available therapies discontinue treatment annually. In the US alone, the pool of patients who have been previously treated, but have fallen out of therapy, is estimated to exceed 50,000. Thus, there is a large group of patients with active MS who are currently not receiving any approved therapy. In addition, as many as 75,000 individuals currently receiving available therapies in the US report ongoing symptoms of active disease.

Scientific Rationale for Natalizumab

Natalizumab is a humanized IgG_4 monoclonal antibody directed against the α4-integrin (α4β1 and α4β7) molecules expressed on the surface of all leukocytes, excluding neutrophils. α4-integrin-expressing inflammatory cells cross the blood-brain barrier via an adhesive

interaction mediated by the leukocyte integrin and its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), present on endothelial cells lining brain capillaries. VCAM-1 is up-regulated on endothelial cells and on microglial cells near the sites of inflammation (Elices *et al*, 1990; Lobb and Hemler, 1994; Peterson *et al*, 2002).

Studies by Yednock and others have shown the clinical efficacy of α4-integrin blockade in experimental allergic encephalomyelitis (EAE), an animal model of MS (Yednock *et al*, 1992; Baron *et al*, 1993; Kent *et al*, 1995; Brocke *et al*, 1999). These data demonstrated that α4-integrin blockade by a bound antibody can prevent leukocyte migration into the brain and thus support the hypothesis that α4-integrins are a fundamental target for MS treatments. In addition, these observations support the hypothesis that blockade of leukocyte accumulation in the brain will prevent the local destruction of myelin and neurons that characterizes MS lesions. Natalizumab is the first antibody directed at this target and clinical data clearly indicate the relevance of this treatment strategy.

Regulatory History

Recognizing the unmet medical need in MS and the potential that natalizumab provides a meaningful therapeutic advancement over existing therapies, the FDA agreed to review 1-year safety and efficacy data from the ongoing 2-year MS trial program. Review of these data led to the approval of natalizumab for the treatment of relapsing forms of MS on 23 November 2004. The approval was contingent upon providing 2-year data from the ongoing MS trials once they were completed.

In February 2005, following identification of one confirmed and one suspected case of PML in MS patients from clinical studies, the Sponsor voluntarily suspended commercial distribution and dosing in all clinical trials (at that time, studies were ongoing in MS, Crohn's disease, and rheumatoid arthritis). In response to these events, the Sponsor, in collaboration with the FDA and European Medicines Agency (EMEA), and with the support of the National Institutes of Health (NIH), immediately embarked on a comprehensive evaluation of patients who received natalizumab in clinical trials. The purpose of this evaluation was to assess the status of treated individuals and to search for any undiagnosed cases of PML or other opportunistic infections. In the course of this investigation, one additional case of PML was identified in a patient with Crohn's disease. In this patient, PML had been misdiagnosed as malignant astrocytoma. No additional confirmed cases of PML were identified in over 3,000 patients examined as part of the comprehensive safety assessment.

Also, during this evaluation, an analysis of the final safety and efficacy data from the 2-year pivotal studies in MS patients was conducted. Findings at 2 years confirmed the efficacy and safety profile seen after 1 year of treatment and showed significant effects on disability progression.

After considering all these findings, the Sponsor submitted the current sBLA, which, like the original BLA, received a Priority Review designation.

Summary of Major Efficacy and Safety Findings

Natalizumab has been studied in patients with relapsing forms of MS. The efficacy and safety findings from the two pivotal studies indicate that the benefit of natalizumab therapy is greater than that of currently approved MS drugs.

The major efficacy findings include results from Study 1801, which compared natalizumab to placebo as monotherapy. The study demonstrated that natalizumab therapy resulted in:

- a 42% reduction in the risk of disability progression compared to placebo, as measured by changes on EDSS, the primary endpoint at 2 years ($p<0.001$). The percentage of patients estimated to progress was 17% and 29% with natalizumab and placebo, respectively
- significant effects on all relapse endpoints over 2 years, including a 68% reduction in the annualized relapse rate *versus* placebo, with 67% of natalizumab-treated patients relapse-free compared to 41% of patients on placebo
- substantial and significant positive MRI effects over 2 years supporting the observed clinical effects
- improved quality of life as measured by the physical and mental components of the SF-36, and
- consistent and significant effects across subgroups, based upon baseline demographics and disease activity.

Further efficacy findings were seen in Study 1802, in which natalizumab was administered to patients who were concurrently receiving treatment with Avonex, which served as an active control. These patients were experiencing disease activity despite active treatment. The study demonstrated that natalizumab, when added to Avonex, resulted in:

- a 24% reduction in the risk of disability progression, as measured by changes on the EDSS ($p=0.024$). The percentage of patients estimated to progress was 23% with natalizumab plus Avonex as compared with 29% on Avonex alone
- significant effects on all relapse endpoints, when compared to Avonex, over 2 years, including a 55% reduction in the annualized relapse rate, with 54% of natalizumab-treated patients relapse-free compared to 32% of patients on Avonex
- substantial and significant MRI effects when compared to Avonex therapy alone over 2 years, supporting the observed clinical effects
- improved quality of life when compared to Avonex therapy alone, as measured by the physical component of the SF-36 with a trend on the mental component, and
- consistent and significant effects across subgroups, based upon baseline demographics and disease activity.

Major safety findings are based on the 3,919 subjects who have received natalizumab treatment during clinical trials in MS and in other indications, resulting in 5,505 patient-years of natalizumab exposure. In placebo-controlled trials in MS, 1,617 patients have received 2,910 patient-years of natalizumab exposure. The integrated analyses of safety from trials of natalizumab in MS demonstrate the following:

- Overall, treatment with natalizumab was well tolerated.
- Common and serious adverse events were similar in natalizumab-treated patients and controls.
- Approximately 4% of MS patients experienced a hypersensitivity reaction; of these patients, approximately 1% experienced a serious reaction.
- The overall incidence and rate of common and serious infections were similar in natalizumab-treated patients and control patients.
- Three cases of PML were identified in natalizumab-treated patients (two patients with MS and one patient with Crohn's disease), 2 of which were fatal. This represents an approximate incidence of PML of 1 per 1000 (95% confidence interval: 0.2 to 2.8 per 1000).
- Serious opportunistic infections did occur on natalizumab treatment. These infections were mostly in patients with Crohn's disease who had significant co-morbidities or who were immunocompromised due to immunosuppressant use.
- Approximately 6% of patients who received natalizumab in clinical studies developed persistent anti-natalizumab antibodies, which were associated with loss of efficacy and a higher incidence of infusion-related adverse events.

Summary of Risk Management Action Plan (RiskMAP)

The Sponsor proposes to resume marketing of natalizumab based upon revised product labeling that would limit its use to patients with relapsing MS and warn against use in combination with other immunomodulatory agents. In addition, the label would describe the newly identified risks of natalizumab treatment. Furthermore, the Sponsor proposes to initiate a RiskMAP to educate physicians and patients of the risks of natalizumab treatment and to actively assess and manage these risks on an ongoing basis. The RiskMAP is based upon current medical and scientific knowledge of PML and information gained from the safety evaluation of natalizumab-treated patients. The RiskMAP will include:

- an enrollment form for physicians and patients that serves as a prescription for natalizumab, collects information regarding risk factors for PML, and requires an acknowledgement by physicians and patients that they understand the risks associated with natalizumab treatment

- a mandatory authorization process for infusion sites that must be completed prior to shipment of natalizumab to that site
- a controlled, centralized, distribution system that ships natalizumab only to authorized infusion sites, allowing for directed delivery of education tools and timely receipt of new safety information
- tracking of the destination and number of all vials shipped through the new distribution system
- educational tools for patients and physicians, to promote informed benefit-risk decisions, to ensure appropriate use of natalizumab, and to reinforce the importance of early detection of PML through clinical vigilance
- large registry studies to continually assess the safety of natalizumab in the commercial setting
- a PML Surveillance Program designed to enroll all physicians and patients who use natalizumab at initiation of treatment in order to better understand the risk of PML.

The Sponsor believes that appropriate product labeling and the proposed RiskMAP will create appropriate use conditions such that:

- natalizumab is used as a single disease modifying agent (i.e., monotherapy) and not in combination with other immunomodulatory or immunosuppressive treatments (except for short courses of corticosteroids for the treatment of acute relapses)
- patients and physicians receive significant education regarding the risks associated with natalizumab so that informed benefit-risk decisions can be made regarding initiation of natalizumab treatment
- patients are routinely assessed for PML, using the opportunity afforded through the monthly interactions between the health care providers and patients at the time of infusion
- patients with possible PML are rapidly identified so that natalizumab can be immediately discontinued and the proper assessments completed
- the Sponsor receives timely information regarding safety issues related to natalizumab in these patients.

A detailed evaluation plan has been developed to communicate the results of this plan to the FDA on an ongoing basis.

Conclusions

MS is a serious and disabling disease for which there exists a substantial unmet need for new and more effective treatments. The Sponsor believes that natalizumab will help fill this therapeutic void because it is a significant therapeutic advance over existing therapies and has demonstrated

important efficacy across a range of patient populations and degrees of disease severity. These effects are confirmed by comparison to both placebo and active control. We have identified PML as a rare, but significant, risk. However, we believe that this risk can be managed through the proposed RiskMAP. We believe that reintroduction of natalizumab as monotherapy in the setting of a comprehensive RiskMAP will provide relapsing MS patients and their physicians with the information they need to make informed benefit-risk decisions about the use of this highly effective therapy, while actively managing recognized risks.

1 INTRODUCTION AND BACKGROUND

This Briefing Document has been prepared for members of the Peripheral and Central Nervous System Drugs Advisory Committee to provide clinical and MRI data describing the benefits and risks of TYSABRI® (natalizumab) as treatment for patients with relapsing forms of multiple sclerosis (MS).

Natalizumab was approved for treatment of patients with relapsing forms of MS on 23 November 2004 after priority review of 1-year data from two ongoing 2-year studies. Natalizumab is administered as an intravenous (IV) infusion, at a dose of 300 mg, every 4 weeks. Accelerated approval was conditional on providing confirmatory 2-year data. Following the recognition of two cases of progressive multifocal leukoencephalopathy (PML) in patients who had been receiving natalizumab in combination with β-interferon (Avonex®) for over 2 years, the Sponsor (Biogen Idec and Elan Pharmaceuticals), in discussions with FDA, suspended commercialization and dosing in clinical studies to minimize the risk to treated patients while investigating the relationship between PML and natalizumab therapy. The Sponsor reviewed the entire natalizumab safety database to identify potential events that warranted further investigation. In addition, the Sponsor conducted a formal re-evaluation of patients who received natalizumab in clinical studies for MS, Crohn's disease (CD), and rheumatoid arthritis (RA) in order to identify any undetected cases of PML or other serious infections. These findings were submitted to the FDA in September 2005 as a Supplemental Biologics License Application (sBLA) along with the 2-year safety and efficacy results from the now-completed pivotal studies in MS. The Sponsor believes that the results strongly support the reintroduction of natalizumab as monotherapy. The purpose of this Advisory Committee meeting is to discuss the risk-benefit profile of natalizumab in patients with relapsing forms of MS.

The following summarizes key regulatory and clinical activities that led to FDA's approval of natalizumab, the Sponsor's voluntary suspension of its use, the subsequent submission of additional safety and efficacy data, and the present Advisory Committee meeting.

- The Sponsor submitted the original Biologics License Application (BLA) on 23 May 2004. Although 2 years of data are typically required for the registration of a product for the treatment of MS, the FDA agreed to review 1-year safety and efficacy data from the ongoing 2-year MS trial program. Because of the strength of the efficacy and safety profile after 1 year of treatment, the Sponsor submitted the BLA supporting the use of natalizumab in relapsing MS patients. FDA granted the application Priority Review status due to the recognized unmet medical need in MS and natalizumab's potential as a significant therapeutic advancement over existing therapies. The BLA included efficacy and safety data of natalizumab as a monotherapy in treatment-naïve patients and as add-on therapy in patients with disease activity while on Avonex. Overall, the safety profile of natalizumab showed that the incidence of adverse events, including serious adverse events, was balanced between active and control groups.

- Based upon these data, FDA approved TYSABRI for treatment of patients with relapsing forms of MS on 23 November 2004.

- Marketing and clinical trial dosing of natalizumab was voluntarily suspended on 28 February 2005 following identification of one confirmed and one suspected case of PML in MS patients from clinical studies. During the 3-month period between approval and voluntary suspension, approximately 7,000 patients received natalizumab prescribed by their physicians.

- Immediately following voluntary suspension of dosing of natalizumab, the Sponsor reviewed the entire clinical study safety database in order to identify any additional cases suggestive of PML or other opportunistic infections. This re-evaluation identified a third case of PML in a patient with CD who was originally reported to have died of a malignant astrocytoma. In addition to this retrospective review, the Sponsor, in collaboration with the FDA and European Medicines Agency (EMEA), and with the support of the National Institutes of Health (NIH), immediately embarked on a comprehensive evaluation of patients who received natalizumab as part of clinical studies. The purpose was to assess the status of treated individuals and to look for any undiagnosed cases of PML or other opportunistic infections. No additional confirmed cases of PML have been identified in 3,116 patients examined as part of the comprehensive safety assessment.

- In September 2005, the Sponsor submitted an sBLA that included efficacy and safety data from the two completed Phase 3 studies, the final results of the comprehensive safety evaluation for PML in clinical trial patients, a revised product label, and a risk management plan. The application was once again designated for Priority Review.

- FDA convened the Peripheral and Central Nervous System Drugs Advisory Committee to discuss the risks and benefits of re-introducing natalizumab into the market as treatment for patients with MS, based upon the currently available safety and efficacy data.

This Briefing Document presents a clinical overview of MS, including a description of currently available therapies (the remainder of Section 1); the clinical data demonstrating the efficacy of natalizumab as treatment for patients with MS (Section 2); the clinical trial safety data following 2 years of exposure to natalizumab, results of the safety evaluation of clinical-trial patients for the incidence of PML, as well as the limited post-marketing safety data (Section 3); the Sponsor's Risk Management Action Plan (RiskMAP) to both minimize and continually assess the risk of PML, as well as other serious infections, following re-introduction of natalizumab to the market (Section 4); and finally, the benefits and risks of natalizumab as treatment for patients with MS (Section 5).

Based upon data provided, the Sponsor believes that natalizumab has a benefit-risk profile that supports approval for the following indication:

TYSABRI® is indicated only for the treatment of patients with relapsing forms of multiple sclerosis to delay the progression of physical disability and to reduce the frequency of clinical exacerbations. The safety and efficacy of TYSABRI® beyond two years are unknown.

Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

The Sponsor also proposes to prominently warn against concurrent use with other MS treatments (e.g., immunosuppressants, immunomodulators), and use in patients who are immunocompromised.

1.1 MULTIPLE SCLEROSIS

1.1.1 Clinical Course of Multiple Sclerosis

MS is a chronic disease of the brain and spinal cord. In temperate zones such as the US, the incidence of MS is approximately 1 to 5/100,000 per year (US National MS Society; NMSS), with a US prevalence estimated at 350,000 to 400,000. It is a disease of young adults, primarily women, with disease onset typically occurring between the ages of 20 and 40. The first clinical manifestations of MS usually take the form of a clinically isolated syndrome (CIS) affecting the optic nerve (optic neuritis), spinal cord (transverse myelitis), or brainstem/cerebellum (Runmarker and Anderson, 1993). Estimates of the number of patients who eventually go on to develop MS vary widely, but, in the case of optic neuritis, the presence of MS-like lesions on MRI at the time of the attack indicates a greater than 80% chance of developing clinically definite MS within 10 years (O'Riordan *et al*, 1998; Sailer *et al*, 1999).

Approximately 90% of individuals develop the relapsing-remitting form of the disease (RRMS), which is characterized by episodic bouts of neurological worsening separated by periods of relative stability. About 70% of these individuals will eventually enter a phase of progressive neurological decline (secondary progressive MS; SPMS) with or without superimposed relapses; 50% will do so within a decade of diagnosis (Weinshenker *et al*, 1989). Natural history studies indicate that the median time to when a walking aid is required to walk half a city block (an EDSS of 6) is approximately 15 years after diagnosis (Weinshenker *et al*, 1989; Runmarker and Anderson, 1993).

The inevitable outcome in the majority of RRMS patients is one of evolution to SPMS with increasing permanent neurological dysfunction and, on average, a shortened life expectancy due to complications of advanced disability with MS in approximately 40% to 50% of deaths (Sadovnik *et al*, 1991; Bronnum-Hansen *et al*, 2004), or the 2- to 7-fold increase in suicide in patients with MS compared to the general population. Thus, MS is a progressively disabling, life-shortening disease.

1.1.2 Pathophysiology of Multiple Sclerosis

Demyelination and nerve fiber transection is thought to occur when activated T lymphocytes cross the blood-brain barrier (BBB) and initiate a series of events leading to activation of endothelial cells, recruitment of additional lymphocytes and monocytes, and release of pro-inflammatory cytokines. MS lesions typically consist of immune cells, as well as demyelinated axons, oligodendrocytes attempting remyelination, proliferating astrocytes, and varying degrees of axonal transection. Cytokines such as tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ) interact with immune cells, amplifying this process. The initiating event of the inflammatory cascade is unknown; however, adhesion and trans-endothelial migration of inflammatory cells from the bloodstream across the BBB and into the central nervous system (CNS) is thought to be an early and critical step in this process.

Emerging data demonstrate that irreversible axonal loss occurs early in the course of MS. Because transected axons fail to regenerate in the CNS, early effective treatment aimed at suppressing MS lesion formation is of paramount importance. As early as disease onset, axons are transected in lesions with active inflammation (Trapp *et al*, 1998; Bjartmar and Trapp, 2001; Ferguson *et al*, 1997). The degree of demyelination is related to the degree of inflammation and the exposure of demyelinated axons to the inflammatory environment, as well as non-inflammatory mediators (Trapp *et al*, 1998; Kornek *et al*, 2000; Bitsch *et al*, 2000). There is also destruction of oligodendrocytes with impaired remyelination in demyelinating lesions (Peterson *et al*, 2002; Chang *et al*, 2002). The loss of oligodendrocytes leads to a reduction in the capacity to remyelinate and may result in the loss of trophic factors that support neurons and axons (Bjartmar *et al*, 1999).

The typical inflammatory lesions of MS can occur throughout the CNS, but certain sites seem particularly vulnerable, such as the optic nerve, brainstem, spinal cord, and periventricular regions of the cerebrum. It is the resulting loss of myelin and nerve fibers in these areas that leads to impaired neuronal conduction and symptoms such as weakness, sensory loss, visual loss, double vision, and imbalance. In RRMS, these episodes of demyelination typically result in several weeks of neurological dysfunction followed by partial or full recovery. However, more severe attacks may result in permanent deficits. The recurrent attacks over time lead to accumulating physical disability and cognitive decline.

1.1.3 Outcome Measures for Multiple Sclerosis

A number of measures, including clinical measures, those based on magnetic resonance imaging (MRI) scans, and those based on quality of life, are often used to assess a product's efficacy in MS.

1.1.3.1 Disability

For over 40 years, the Expanded Disability Status Scale (EDSS) and its predecessor, the Disability Status Scale, have been the most extensively used tools to track the course of disability in MS. The EDSS classifies the most common MS-associated neurological impairments into disability levels ranging from 0 to 10, with each successive step describing a worsening of disease (Display 1-1). In the lower half of the EDSS scale, disease progression is primarily defined by increasing levels of disability in specific functional systems measured during neurological examination. Scores of 1.0 through 3.5 describe mild to moderate disability in the functional systems, while scores of 4.0 and above indicate increasingly severe disability that affects ambulation, including the need for assistive devices such as a cane (an EDSS of 6.0), a walker (an EDSS of 6.5), or a wheelchair (an EDSS of 7.0). Higher scores designate patients confined to bed.

Display 1-1 Kurtzke Expanded Disability Status Scale

0.0	Normal neurological exam (all grade 0 in Functional Systems (FS); Cerebral grade 1 acceptable).
1.0	No disability, minimal signs in one FS (i.e., grade 1 excluding Cerebral grade 1).
1.5	No disability, minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 to 1), though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2, or two FS grade 3; or five FS grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk some 500 meters without aid or rest.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0.)
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations generally 4+ in several systems.)
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)
10.0	Death due to MS.

Kurtzke JR. Rating neurological impairment in multiple sclerosis: An expanded disability scale (EDSS). *Neurology* 1983; 33: 1444-1452.

In clinical trials, a two-step increase in EDSS is the minimum change that can be measured reliably while still representing a clinically significant degree of worsening. Sustained disability for 12 weeks excludes the temporary fluctuations in clinical status that may occur with an exacerbation. These changes and the length of time to confirm a sustained progression are commonly used in clinical trials designed to study the long-term effects of new therapies on MS; therefore, this was used as the 2-year primary endpoint in the natalizumab pivotal studies. In addition, the ability of a treatment to delay the time to significant EDSS milestones, i.e., an EDSS of 4 or 6, are important, since these scores often signify a transition to secondary progressive disease.

To address the limitations of the available MS clinical rating scales, including the EDSS, a task force initiated by the NMSS recommended the use of the MS Functional Composite (MSFC) (Whitaker *et al*, 1995). Unlike traditional MS clinical outcome measures that are derived from the standard neurological examination, the MSFC is based on quantitative tests of leg function/ambulation (the Timed 25-Foot Walk), arm function (the 9-Hole Peg Test), and cognitive function (the Paced Auditory Serial Addition Test [PASAT 3]) which expand upon the measurements of the EDSS and assess effects in clinical dimensions not well captured by this scale. The MSFC was thus included as a secondary endpoint in the natalizumab pivotal studies.

1.1.3.2 Relapses

Relapses define MS. These acute events are the means by which the disease first manifests and are an integral part of the disease until well into the SPMS phase of the illness. Acute clinical exacerbations may resolve completely, but in the RRMS patient, unresolved disability from acute relapses is a principal source of disability progression. In addition, relapses are important events to patients, affecting quality of life and impacting their ability to work and perform activities of daily living. The FDA has an established regulatory history acknowledging an effect on exacerbations as clinically meaningful.

Data from the Lyon EDMUS database demonstrates that progression to the EDSS milestones of 4 (the first level at which "relatively severe" disability is seen, Display 1-1) and 6 (the level at which there is a need for assistance to walk, such as with a cane or a crutch) is hastened by relapses early in the disease course; the time to disability progression was reduced by 2 to 4 years by each relapse (Confavreux *et al*, 2003). More recently, Lublin *et al* demonstrated that 42% of the 224 patients in the NMSS task force database who experienced a single relapse on study were left with residual neurological deficits as measured by an increase in EDSS score (Lublin *et al*, 2003). The proportion of patients with residual deficits increased following a second relapse, as did the degree of worsening as measured by the EDSS (Lublin *et al*, 2003).

Recognizing the importance of relapses in MS, all previous Phase 3 studies of disease-modifying therapies in MS have included relapse rates as an efficacy endpoint. Two therapies were approved solely on the basis of effects on relapses (Betaseron® and Copaxone®). Annualized relapse rate was the primary endpoint at 1 year in the natalizumab Phase 3 studies and the principal secondary endpoint at 2 years.

1.1.3.3 Magnetic Resonance Imaging

The advent of magnetic resonance imaging (MRI) has shed new light on the natural history of MS. MRI is a sensitive tool for monitoring disease activity, detecting 5 to 10 times more disease activity in both RRMS and SPMS patients than is clinically apparent (Isaac *et al*, 1988; Willoughby *et al*, 1989; Khoury *et al*, 1994; Thompson *et al*, 1991; Thompson *et al*, 1992). T2-weighted sequences in MS patients detect new areas of acute demyelination, as well as more chronic areas of demyelination and gliosis. For this reason, T2-weighted MRI is a good technique for monitoring the accumulation of lesions over time, either as a count of active lesions or a change in the total volume of such lesions.

Infusion of gadolinium-diethylenetriamine pentaacetic acid (Gd-DPTA) during acquisition of T1-weighted sequences allows for visualization of BBB breakdown secondary to the inflammation characteristic of acute MS lesions. The evidence to date suggests that gadolinium (Gd)-enhancement is a useful marker of disease activity that correlates with clinical relapse (Molyneux *et al*, 1998; Kappos *et al*, 1999; McFarland *et al*, 2002).

New hypointense lesions on T1-weighted sequences in MS patients correspond either with inflammatory Gd-enhancing lesions (comprising edema, demyelination, axonal loss, or combinations of these pathologies) (Bruck *et al*, 1997) or as chronic lesions with considerable axonal loss. Approximately half of the acute T1 hypointensities on MRI will evolve into chronic "T1 black holes," which correlate with disability progression (Simon *et al*, 2000).

Demonstrable effects of a therapy on MRI lesion development is important as supportive data for effects on relapse and disability endpoints.

1.1.3.4 Quality of Life

Health-related quality-of-life instruments can assess dimensions of disease not well captured by other clinical or radiographical measures. These other measures do not adequately account for patient perception of well-being and the ability to perform the routine activities of daily life. A number of studies have shown that MS negatively impacts health-related quality-of-life (Miller *et al*, 2000; Rudick *et al*, 1992; Solari *et al*, 1999; Freeman *et al*, 1999; Nortvedt *et al*, 2000). Quality of life was assessed in the Phase 3 studies using a validated, widely-used, general-purpose instrument, the Health Status Questionnaire (SF-36), which has both mental and physical components.

1.2 CURRENT THERAPY FOR MULTIPLE SCLEROSIS

Patients with MS have limited therapeutic options. A number of symptomatic therapies exist, including corticosteroids for acute relapses, as well as medications for spasticity, depression, urinary dysfunction, pain, and other MS-related symptoms. However, only four therapies are currently approved in the US as disease-modifying agents for the treatment of relapsing forms of MS (Display 1-2): These medications include the β-interferons (Betaseron® (interferon β-1b SC [subcutaneous]), Avonex® (interferon β-1a IM [intramuscular]), and Rebif® (interferon β-1a SC) and glatiramer acetate (Copaxone®). These therapies each provide a modest, but important

clinical benefit, all demonstrating a reduction in relapse rate of approximately 29% to 33% over 2 years (IFNB MS Study Group, 1993; Jacobs *et al*, 1996; PRISMS Study Group, 1998; Johnson *et al*, 1995).

In controlled clinical trials, only Avonex and Rebif have been demonstrated to delay sustained disability progression as measured by the EDSS. These agents reduce the proportion of subjects progressing at 2 years by 37% and 30%, respectively (Jacobs *et al*, 1996; PRISMS Study Group, 1998). However, a recent Cochrane review affirmed the efficacy of β-interferons in RRMS, but efficacy beyond 1 year was called into question (Filippini *et al,* 2003). The most frequent side effects from β-interferons are flu-like symptoms and, in addition, for SC formulations, injection site reactions. Although not serious or life-threatening, such side effects negatively impact patient quality of life and consequently, reduce compliance with therapy.

Serious adverse events of β-interferons include rare reports of hypersensitivity reactions, depression and suicide, decreased peripheral blood counts, hepatic injury, cardiomyopathy, and various autoimmune disorders (Betaseron Package Insert [PI], 2003; Rebif PI, 2004; Avonex PI, 2005). Importantly, development of neutralizing antibodies to interferons is associated with loss of efficacy. Antibodies that develop to any β-interferon cross-react with other interferons leading to loss of efficacy for the entire class in such patients (IFNB MS Study Group, 1996; PRISMS Study Group, 2001; Kappos *et al*, 2005).

Copaxone (glatiramer acetate [GA]) is the acetate salt of a mixture of synthetic polypeptides composed of 4 amino acids, L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. Copaxone is administered daily with SC injections (Copaxone PI, 2004). Similar to β-interferons, GA decreases relapse rate by approximately 30%, but has no proven effect on sustained progression (Johnson *et al,* 1995) and produces only a 30% reduction in the development of new T2-hyperintense lesions on MRI (Comi *et al,* 2001). There are no clear effects of GA on the rate of brain atrophy (Ge *et al*, 2000; Rovaris *et al*, 2001; Wolinsky *et al,* 2001; Sormani *et al,* 2004), cognition (Weinstein *et al,* 1999), or quality of life. A recent Cochrane review has cast doubt on the efficacy of GA, even going so far as to state that the routine use of Copaxone may not be warranted (Munari *et al,* 2004). The most notable side effects with GA are injection site reactions and acute systemic reactions of uncertain etiology.

Although the safety profiles of the β-interferons and GA are acceptable, they are not without multiple side effects that impact patient compliance. Currently, it is estimated that 20% to 25% of treated patients discontinue therapy annually. In fact, in the US alone, the pool of patients who have been previously treated, but have fallen out of therapy exceeds 50,000. In addition, as many as 75,000 individuals currently receiving available therapies in the US report ongoing symptoms of active disease. Thus, there is a large group of patients with active MS who are currently not able to receive any approved therapy.

Display 1-2 Currently approved treatments for relapsing forms of MS

	Interferon-β				
	Avonex® (IFNβ-1a)	Rebif® (IFNβ-1a)	Betaseron® (IFNβ-1b)	Copaxone® (glatiramer acetate)	TYSABRI® (natalizumab)
Type	Recombinant human protein, glycosylated	Recombinant human protein, glycosylated	Recombinant bacterial protein, non-glycosylated	Synthetic polypeptide mixture	Recombinant humanized monoclonal antibody
Dose	30 μg	22 μg, 44 μg	0.25 mg (8 MU)	20 mg	300 mg
Route	Intramuscular	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous
Frequency	Once weekly	3 times/week	Every other day	Daily	Once every 4 weeks
Proportion with neutralizing antibodies	5%	24%	45%	100% but unknown how many are neutralizing	6%
Efficacy: reduction in proportion of patients with disability progression (a)	37%	22 to 30%	Not demonstrated	Not demonstrated	42%
Efficacy: reduction in relapse rate (a)	32% (b)	29 to 32%	31%	29%	68%
Major toxicities	Depression, hepatic injury, anaphylaxis, decreased peripheral blood counts	Depression, hepatic injury, anaphylaxis, decreased peripheral blood counts	Depression, injection site necrosis, anaphylaxis, hepatic injury, decreased peripheral blood counts		Progressive multifocal leukoencephalopathy, hypersensitivity reactions

(a) Relative to placebo.
(b) Based on 2-year completers.

Another treatment, mitoxantrone (Novantrone®), a chemotherapeutic agent, is used for patients with severe RRMS or SPMS. Although the drug had significant effects on relapse and disability endpoints (Hartung *et al*, 2002), the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recently recommended that, given the small size of the only pivotal study with this product (188 patients, 3 treatment groups, approximately 60 patients per arm), the clinical efficacy of mitoxantrone be demonstrated in an additional larger clinical study before it is widely used for the treatment of patients with MS (Goodin *et al,* 2003).

Side effects with mitoxantrone include nausea, urinary tract infections, menstrual disorders, amenorrhea, mild alopecia, increased γ–glutamyltranspeptidase, and leucopenia, and there is a significant risk of the development of myelodysplastic syndromes, including acute myelogenous leukemia (Vicari *et al,* 1998; Brassat *et al,* 2002; Ghalie *et al* 2002; Cattaneo *et al,* 2003; Heesen *et al,* 2003; Tanasescu *et al,* 2004; Voltz *et al,* 2004). In one study of 1,774 patients with breast cancer, the cumulative probability of developing secondary leukemia was estimated to be 1.1% and 1.6% at 5 and 10 years, respectively. There is also the potential for cardiotoxic effects at any time with mitoxantrone, which requires that left ventricular ejection fraction be evaluated by echocardiogram or MUGA before initiating treatment and before each subsequent dose of drug. Because of its cardiotoxic effects, patients cannot receive a cumulative dose of mitoxantrone that exceeds 140 mg/m^2, limiting the maximum duration of therapy to 2 to 3 years. This limits use of mitoxantrone to only the most severe MS patients.

1.3 THE UNMET MEDICAL NEED IN MULTIPLE SCLEROSIS

MS is a serious and disabling disease of young adults, striking in the prime of their lives. The inevitable outcome in the majority of patients is one of permanent neurological dysfunction and, on average, a shortened life expectancy, either by increased risk of completed suicide in approximately 30% of deaths (Sadovnik *et al*, 1991) or complications related to MS and advanced disability in approximately 50% of deaths (Bronnum-Hansen *et al*, 2004).

It is estimated that approximately 200,000 subjects in the US are currently receiving treatment with one of the approved MS therapies (Biogen Idec internal data). However, despite the demonstrated efficacy of these treatments and their widespread use, there is a substantial population of patients with RRMS who remain untreated for their disease. A proportion of these patients have disease with relatively little evidence of active inflammation clinically (relapses) or by MRI and hence choose not to initiate treatment. Others have active RRMS, but choose not to be treated out of fear of self-injection or potential adverse effects from the available treatments. Still others have tried one or more of the existing therapies in the past, yet discontinued treatment due to side effects. Finally, many subjects choose to stop therapy due to a perceived lack of efficacy of the available treatments.

Among those patients who do receive treatment, a significant number continue to experience disease activity clinically and on MRI. This is an expected outcome of the partially effective approved medications, each of which leads to an approximately 30% reduction in relapse rate and limited impact on disability progression (IFNB MS Study Group, 1993; Jacobs *et al*, 1996; PRISMS Study Group, 1998; Johnson *et al*, 1995). Data from the Phase 3 trials of β-interferon in MS show that 62% to 75% of subjects experienced at least one relapse during these 2-year trials

despite interferon treatment (IFNB MS Study Group, 1993; Jacobs *et al*, 1996; PRISMS Study Group, 1998). Similarly, 66% of subjects in the Phase 3 MS trial of GA experienced at least one relapse during the 2-year period, a proportion that was not significantly different from placebo (Johnson *et al*, 1995).

Therefore, a substantial unmet medical need exists for MS treatments that offer greater efficacy, that are well tolerated, and that offer dosing convenience. Monthly IV administration may be viewed as desirable by those who are deterred by daily, every-other-day, or weekly self-injection. Further, there exists an unmet medical need for therapies that can be used to control disease activity when one therapy fails. Although a variety of therapeutic strategies are currently used in clinical practice to manage breakthrough disease while on treatment (e.g., switching therapy, changing dose and frequency of interferon, combination therapy), the similar efficacy between available medications and lack of clinical data demonstrating the effectiveness of any of these strategies in breakthrough patients makes the decision of what to do for these patients largely empirical. Natalizumab Study 1802, described in this document, is the first large, well-controlled study to specifically address the unmet need in this population.

Further, as noted above, emerging data demonstrates that irreversible axonal loss occurs early in the course of MS. Thus, the expeditious introduction of a novel therapeutic such as natalizumab would be expected to substantially reduce the irreversible damage in the CNS that MS subjects endure during the course of their disease.

1.4 ALPHA-4 INTEGRINS

α4-integrins are heterodimeric transmembrane proteins that are expressed at high levels on the surface of all circulating leukocytes with the exception of neutrophils. These integrins are believed to play a critical role in immune cell adhesion to the endothelial cell layer on blood vessels, facilitating their subsequent migration into inflamed tissues. The interaction between α4β1 and its targets is an important component of the inflammation that occurs in the CNS of MS patients. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and on microglial cells near the sites of inflammation (Elices *et al*, 1990; Lobb and Hemler, 1994; Peterson *et al*, 2002). Further, osteopontin, which exhibits many properties of a proinflammatory cytokine, is also upregulated in MS lesions (Chabas *et al*, 2001).

Natalizumab is a recombinant humanized IgG4κ monoclonal antibody that is a member of an emerging class of agents known as the Selective Adhesion Molecule (SAM) Inhibitors. Natalizumab binds to both known types of α4-integrins, α4β1-integrin (also called VLA-4), and α4β7, thereby inhibiting the molecular interactions of these integrins with cognate receptors on endothelial cells, VCAM-1 and MAdCAM-1, respectively. By inhibiting these molecular interactions, natalizumab prevents the recruitment and egress of leukocytes into sites of inflammation. A further mechanism of natalizumab action may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with other ligands in the extracellular matrix (osteopontin and fibronectin) and on parenchymal cells, such as microglial cells (VCAM-1). As such, natalizumab may act to suppress ongoing inflammatory activity already present at the disease site, and inhibit further

recruitment of immune cells into inflamed tissues. Thus, treatment of patients with MS with natalizumab may block entry of mononuclear leukocytes into the CNS and attenuate the inflammatory process that results in demyelination and axonal damage and ultimately provide clinical benefit by reducing the number of clinical relapses and the progression of disability, including motor, visual, and cognitive function.

1.5 INTENDED PATIENT POPULATION

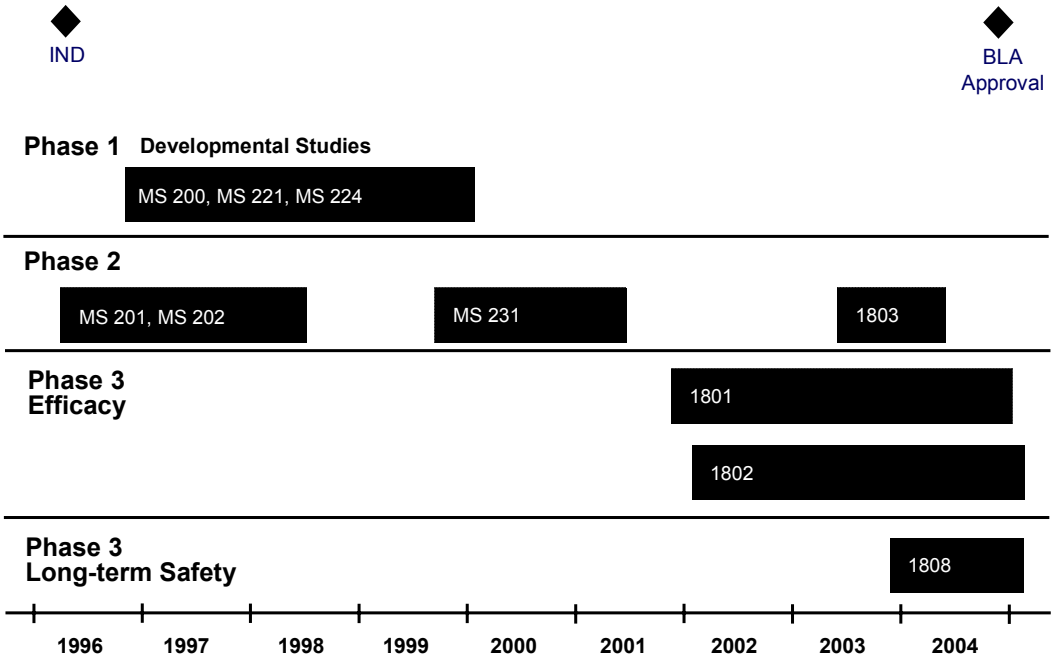
Natalizumab demonstrated anti-inflammatory activity in preclinical studies and was thus developed as a treatment for relapsing MS patients. This included patients with relapsing forms of the disease, regardless of EDSS or disease duration, since it was predicted that the mechanism of action of natalizumab would interrupt the ongoing inflammatory process and provide clinical benefit. The Phase 3 program was designed to assess efficacy and safety in two significant patient populations 1) treatment-naïve patients with mild to moderate disability (EDSS 0 to 5.0) with recent clinical disease activity (1 relapse in the year prior to study entry), and 2) patients with mild to moderate disability with continuing disease activity despite treatment with β-interferon (1 relapse in the year prior to study entry while receiving Avonex). Natalizumab was shown to be highly effective in both patient populations across a broad range of endpoints. These results will be discussed in Section 2. However, there are segments of the MS population where the use of natalizumab may not be justified, either because data are lacking or because the benefit/risk ratio is altered. This will be discussed in Section 3.

1.6 CLINICAL DEVELOPMENT PROGRAM OF TYSABRI

Natalizumab has been studied as a treatment for MS, CD, and RA for approximately 10 years (Display 1-3). The MS program is the most advanced and, indeed, natalizumab has been approved in this indication.

Clinical development in MS began with single-dose studies followed by a large multi-dose Phase 2 study, MS231. These initial studies and those in CD used weight-based dosing and discovered that doses in the 3 to 6 mg/kg range were effective without significant differences in efficacy or safety between doses. Based upon pharmacokinetic and pharmacodynamic data from these studies, a fixed dose of 300 mg was chosen to provide dosing needed to achieve an adequate level of α4-integrin receptor saturation (70%) throughout the dosing interval across a broad patient spectrum. The dose of 300 mg natalizumab administered every 4 weeks as an IV infusion over 1 hour was evaluated in the two Phase 3 trials, Studies 1801 and 1802, and is the dose that was approved. After completing their participation in Studies 1801 and 1802, patients could enroll into an open-label, single-arm study, 1808, in which they continued to receive 300 mg natalizumab every 4 weeks.

Display 1-3 Clinical development program of natalizumab in MS



Many patients, especially in the US, are currently being treated with GA (Copaxone), and it was anticipated that natalizumab, if commercially available, might be added to GA therapy. One of the proposed mechanisms of action of GA depends on the passage of GA-activated T cells into the CNS, whereas natalizumab blocks trafficking of T cells from the circulation into the CNS. Thus, it was theoretically possible that the efficacy or safety of GA or natalizumab could be altered by concomitant GA use. Study 1803 explored this possibility through the addition of natalizumab to 20 mg of GA in 110 patients with RRMS. No significant adverse effects were seen in this 6-month study.

2 OVERVIEW OF EFFICACY

Efficacy of natalizumab over 2 years has been demonstrated in two Phase 3 trials (Polman *et al*, 2006; Rudick *et al*, 2006). In Study 1801, natalizumab was given as monotherapy to treatment-naïve MS patients and its efficacy was compared to placebo. In Study 1802, natalizumab was given to patients who were experiencing relapses despite concurrent Avonex therapy and its efficacy was compared to that of Avonex (interferon β-1a) plus placebo. Data through 2 years have confirmed the benefit that led to accelerated approval at 1 year. These data show that natalizumab is highly efficacious in delaying the time to onset of sustained progression of disability, in reducing annualized relapse rate, in attenuating MRI lesions, and in improving the quality of life of patients compared both to placebo and the active Avonex control group.

Both Phase 3 studies had similar designs. In Study 1801, 942 untreated RRMS patients were randomized to receive natalizumab or placebo for 120 weeks (30 infusions) using a 2:1 allocation. In Study 1802, 1,171 patients who had been receiving weekly IM injections of 30 µg Avonex, but who had relapsed despite this treatment, were randomized using a 1:1 allocation to add natalizumab or placebo to their regimen, also for 120 weeks.

Efficacy parameters assessed included EDSS scores, MS relapses, brain MRI scans, MSFC scores, visual function tests, and quality of life. EDSS and MSFC were measured every 12 weeks, brain MRI scans and quality of life questionnaires at baseline and every year, and MS relapses on an ongoing basis.

Treatment with natalizumab as monotherapy in treatment-naïve patients had profound effects on the time to onset of sustained progression in disability and on annualized relapse rate, the two primary endpoints (Display 2-1). These significant effects were confirmed *versus* Avonex alone in Study 1802. The studies are discussed individually in Sections 2.2.1 (monotherapy) and 2.2.2 (add-on therapy).

Display 2-1 Summary of major efficacy endpoints at 2 years

	Monotherapy Study 1801		**Add-on therapy** Study 1802	
	Placebo	300 mg natalizumab	Avonex + placebo	Avonex + 300 mg natalizumab
Number of patients	315	627	582	589
Percentage of patients with sustained progression of disability	29%	17%	29%	23%
Hazard ratio (95% confidence interval)	0.58 (0.43, 0.77)		0.76 (0.61, 0.96)	
Risk reduction	42%		24%	
p-value	p<0.001		p=0.024	
Annualized relapse rate	0.733	0.235	0.749	0.336
Relative reduction	68%		55%	
p-value	p<0.001		p<0.001	

2.1 PATIENT POPULATIONS STUDIED

The patient population in the two Phase 3 studies were relapsing MS patients according to the criteria of the International Panel on the Diagnosis of Multiple Sclerosis (McDonald *et al*, 2001). Patients with primary- or secondary-progressive MS were excluded. However, the patient populations targeted for each study were quite different.

Patients in Study 1801 needed to be essentially naïve to treatment with an immunomodulatory drug for MS. Specifically, patients could not have had treatment with any immunomodulator (β-interferon or GA) for a period greater than 6 months and not within 6 months of study start. The result was a young, mostly female MS population with a moderate degree of baseline disease activity (typical of the general MS population), very few of whom had tried another immunomodulator prior to study entry (Display 2-2).

In Study 1802, patients were required to be receiving Avonex for the previous year and to have had a relapse during that time while on Avonex treatment. This resulted in a population somewhat older than that in Study 1801, with longer disease duration. However, patients in Study 1802 had a similar degree of disease activity as those in Study 1801, despite Avonex treatment.

In summary, the patient population studied in the clinical program was sufficiently large, encompassing a broad range of ages and disease severity, and is representative of the current relapsing MS population with active disease, consistent with the approved indication.

Display 2-2 Demographic and baseline disease characteristics

	Monotherapy Study 1801		**Add-on therapy** Study 1802	
	Placebo	300 mg natalizumab	Avonex + placebo	Avonex + 300 mg natalizumab
Number of patients randomized	315	627	582	589
Demography				
Age (years): median (min, max)	37 (19, 50)	36 (18, 50)	39 (19, 55)	39 (18, 55)
Gender (% female)	67	72	72	75
Race (% white)	94	96	93	93
Weight (kg): median (min, max)	71 (40, 145)	69 (42, 126)	70 (40, 149)	70 (40, 138)
Baseline disease characteristics				
Time since onset of symptoms (years): median (min, max)	6 (0, 33)	5 (0, 34)	8 (1, 34)	7 (1, 34)
Time since diagnosis of MS (years): median (min, max)	2 (0, 23)	2 (0, 24)	5 (0, 30)	4 (0, 27)
EDSS score: median (min, max)	2.0 (0.0, 6.0)	2.0 (0.0, 6.0)	2.5 (0.0, 5.5)	2.0 (0.0, 6.0)
Number (%) of relapses within the 12 months prior to study entry				
0	6 (2)	6 (<1)	1 (<1)	0
1	180 (57)	368 (59)	357 (61)	390 (66)
2	102 (32)	197 (31)	174 (30)	153 (26)
3	20 (6)	43 (7)	39 (7)	32 (5)
4 or more	7 (2)	13 (2)	11 (2)	12 (2)
Missing	0	0	0	2 (<1)
Median (min, max)	1 (0, 5)	1 (0, 12)	1 (0, 5)	1 (1, 7)
Percentage of patients with active MRI scan at baseline	45%	51%	35%	33%
Percentage of patients who had received prior β-interferon or glatiramer acetate	8%	8%	100%	100%

2.2 EFFICACY RESULTS FROM THE PHASE 3 STUDIES

Each of the Phase 3 studies was designed with two sets of primary and secondary endpoints. The primary and secondary endpoints were selected to measure the effects of natalizumab on the inflammatory aspects of the disease after a mean of 1 year of follow-up in each study (900 patient-years of observation in Study 1801; 1,200 patient-years in Study 1802). Thus, the primary endpoint for this analysis was the annualized rate of clinical relapses, with supporting MRI measures of inflammatory disease activity as secondary endpoints. Ranked in order of importance, these endpoints were the mean number of new or newly enlarging T2-hyperintense lesions (measuring lesion accumulation over time) and the mean number of Gd-enhancing lesions (measuring acute disease activity). The proportion of patients remaining relapse-free was the third secondary endpoint. Analyses and timing of these endpoints were pre-specified with FDA such that, were the results deemed compelling, an application for early regulatory approval could be submitted.

The second series of endpoints were assessed at the conclusion of each study following 2 years of natalizumab treatment. The endpoints for this final analysis were selected to determine natalizumab's effects on measures associated with MS disease progression. Therefore, the primary endpoint at 2 years was time to onset of sustained progression in disability as measured by changes in EDSS scores. Similar to the 1-year analysis, secondary endpoints were additional MRI and clinical measures that would support the primary analysis. Secondary endpoints at 2 years, ranked in order of importance, were the rate of MS relapses (to confirm 1-year relapse observations), the mean volume of T2-hyperintense lesions (a measure of overall MS disease burden), the mean number of T1-hypointense lesions (a measure of axonal loss), and progression of disability as determined by changes in the MSFC (to confirm and expand upon disability effects as measured by the EDSS). Additional exploratory endpoints, quality of life (SF-36) and visual function, were assessed to support the primary and secondary efficacy endpoints.

Given two primary endpoints at two different time points (annualized relapse rate at 1 year, time to disability progression at 2 years), the Hochberg procedure for multiple comparisons (Hochberg, 1988) was used for the evaluation of the primary endpoint. Further, each set of secondary endpoints was prioritized in order of importance as listed above. A closed testing procedure was used for each set such that if statistical significance was not achieved for an endpoint within a set, all endpoints(s) of a lower rank in that set were not considered statistically significant. Analyses of tertiary endpoints did not include adjustments for multiple comparisons.

2.2.1 Results from the Monotherapy Study, 1801

2.2.1.1 Clinical Relapses

As noted in Section 1.1.3.2, acute clinical exacerbations or relapses are the primary source of disability in the early stages of MS. As such, annualized relapse rate as an outcome measure of efficacy in clinical studies of MS therapies has become standard practice. Each of the currently licensed disease-modifying therapies in MS reduces the frequency of relapses by about 30%.

A relapse was prospectively defined in the study protocols as new or recurrent neurologic symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied

by new objective neurological findings upon examination by an examining neurologist. New or recurrent neurological symptoms that occurred less than 30 days following the onset of a confirmed relapse were considered part of the same relapse. Objective neurological changes on examination by the examining neurologist were required to confirm the occurrence of a relapse. Examining neurologists conducting relapse and disability assessments were prohibited from discussing history or symptoms with the patient, thus avoiding potential bias. Only events meeting this strict definition were considered for determination of the effects of natalizumab on relapse endpoints.

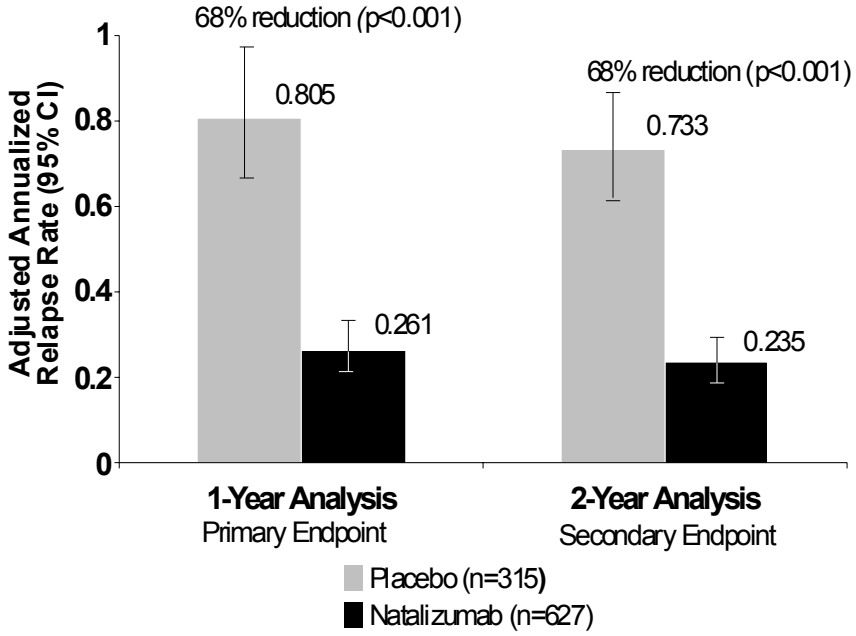
Relapse rate was calculated as the total number of relapses experienced, divided by the total number of days of exposure to study drug, multiplied by 365. All data from randomized patients were included in this analysis up until the time that their last visit occurred, until the time they took alternative medication for MS, or until they withdrew from the study. Relapse rates were compared between treatment groups using a likelihood ratio test assuming relapses to be Poisson distributed.

The proportion of patients who were relapse-free was a secondary endpoint for the 1-year analysis and was analyzed by logistic regression.

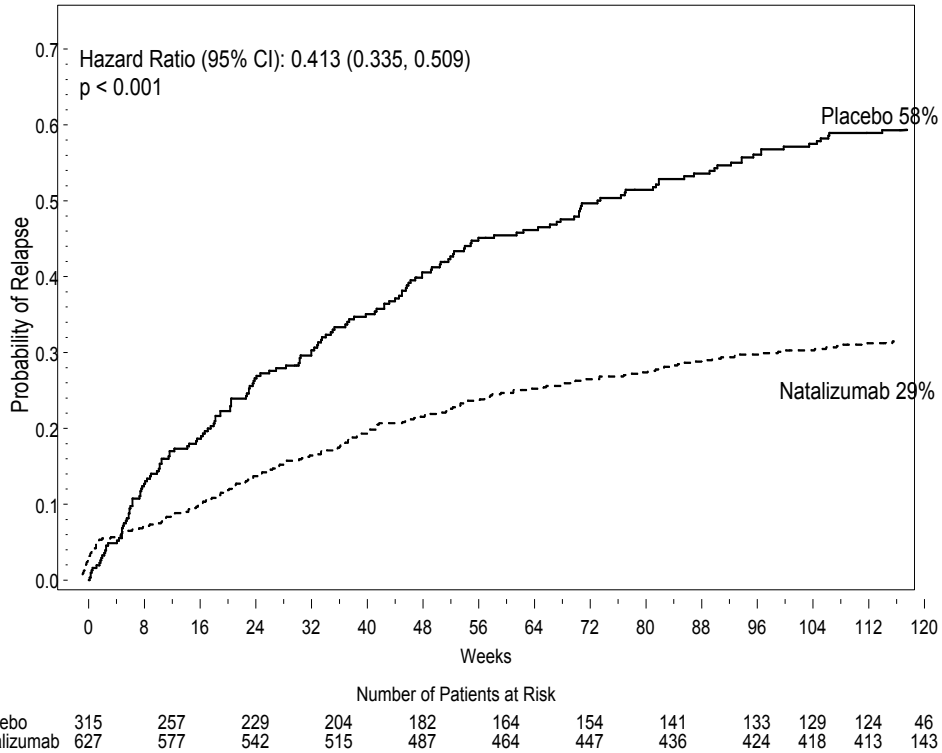
Treatment with natalizumab resulted in a substantial decrease of 68% in the annualized relapse rate *vs* placebo over both 1 and 2 years ($p<0.001$ for both time points). Annualized relapse rate at 2 years was 0.733 (95% confidence interval [CI]: 0.619, 0.869) in the placebo group compared to 0.235 (95% CI: 0.193, 0.285) for the natalizumab group (Display 2-3). A total of 418 natalizumab-treated patients (67%) remained relapse-free during the 2-year study period compared to 129 (41%) patients who received placebo, representing a 63% relative increase over placebo, a statistically significant difference ($p<0.001$). Natalizumab treatment also significantly reduced the risk of relapse as shown in Display 2-4. The Kaplan-Meier curves demonstrating the probabilities of relapse over time begin to diverge shortly after the second natalizumab dose and continue to diverge to the last observed timepoint of 120 weeks. A statistically significant difference between the groups is already apparent by 6 weeks.

Of the relapses that did occur in the natalizumab group, fewer required treatment with methylprednisolone when compared to those in the placebo group, suggesting that relapses that did occur on natalizumab treatment were less severe. The rate of relapses requiring steroid treatment was 0.133 in the natalizumab group *vs* 0.432 in the placebo group, a reduction of 69% ($p<0.001$). In addition, there was a significant reduction of 65% in the rate of MS-related hospitalizations (48 in 37 patients [6%] in the natalizumab group *vs* 66 hospitalizations involving 41 patients [13%] in the placebo group), again indicating relapses of lesser severity.

Display 2-3 Natalizumab as monotherapy: annualized relapse rate at 1 and 2 years



Display 2-4 Natalizumab as monotherapy: time to first relapse



2.2.1.2 Disability Endpoints

Disability as Measured by Changes in EDSS

Given the importance of the accumulation of disability to MS patients, the primary 2-year objective of the natalizumab studies was to determine whether natalizumab could effectively slow this process. Historically, the demonstration of an effect of MS therapeutics on disability progression has been difficult. Indeed, of the four available therapies for RRMS, only two, Avonex and Rebif, have been shown to delay progression of sustained disability by approximately 30% in relapsing MS patients. Therefore, the primary endpoint at 2 years was time to onset of a sustained progression in disability as measured by a two-step change in EDSS score defined as

- an increase of 1.0 point or more on EDSS for patients with a baseline EDSS of at least 1.0, or
- an increase of 1.5 points or more on EDSS for patients with a baseline EDSS of 0.

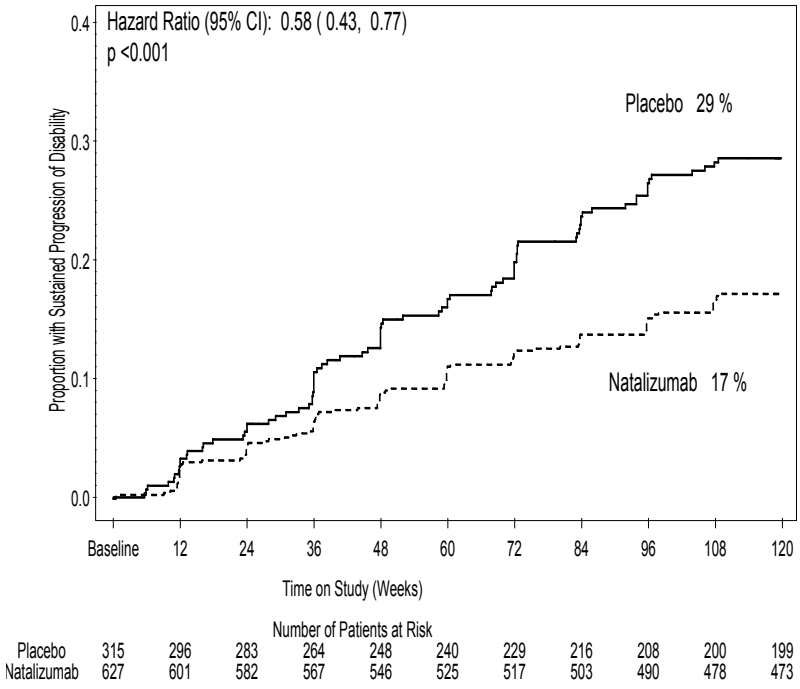
Changes in EDSS score had to be sustained for at least 12 weeks to exclude temporary fluctuations in clinical status that often occur with an exacerbation and had to be confirmed on examination by the examining neurologist. A change in EDSS score sustained for 24 weeks (6 months) is a more conservative definition that can also be used to further decrease the influence of transient disease fluctuations and increase the specificity of the disability measurement. Further, a two-step increase in EDSS is the standard method to determine progression in MS clinical trials since, given the inherent variability of the measure, this is the minimum change that can be measured reliably while still representing a clinically significant degree of worsening. In addition, disability progression could not be measured during an acute relapse to avoid misinterpreting relapse-related changes with true disability progression. This is a more stringent definition than that which has been used previously in MS clinical studies.

The time to onset of a sustained progression in disability was analyzed using a Cox proportional-hazards model. The Kaplan-Meier product-limit method was used to calculate the proportion of patients who had progressed. Patients who did not progress during the study were censored at the time they added rescue treatment with an available MS therapy (which was allowed per protocol once sustained progression was achieved).

When compared to placebo, natalizumab treatment resulted in a 42% decrease in the risk of disability progression, as measured by sustained changes on EDSS (hazard ratio of 0.58, 95% CI: 0.43, 0.77, $p<0.001$, Display 2-5). The percentage of patients progressing by 2 years was estimated to be 29% and 17% for the placebo and natalizumab groups, respectively.

Using the more conservative definition of progression, i.e., a two-step change in EDSS sustained for 24 weeks (6 months), the magnitude of natalizumab treatment effect increased to 54% relative to placebo (hazard ratio of 0.46, 95% CI: 0.33, 0.64, $p<0.001$). The percentage of patients progressing by 2 years was estimated to be 23% and 11% for the placebo and natalizumab groups, respectively.

Display 2-5 Natalizumab as monotherapy: time to onset of sustained progression in disability at 2 years



In addition, natalizumab significantly delayed progression to key EDSS milestones. Time to progression to an EDSS of 4.0 or more was significantly prolonged with natalizumab treatment ($p<0.001$). The estimated percentage of patients who progressed to a sustained EDSS of 4.0 or greater at 2 years was 13% in the placebo group and 5% in the natalizumab group. The hazard ratio was 0.33 (95% CI: 0.19, 0.57) representing a 67% reduction in the risk of progressing to an EDSS of 4.0 or more following natalizumab treatment. Time to progression to an EDSS of 6.0 or more was also significantly prolonged with natalizumab treatment ($p=0.002$). The estimated percentage of patients who progressed to a sustained EDSS of 6.0 or greater at 2 years was 6% in the placebo group and 2% in the natalizumab group. The hazard ratio was 0.30 (95% CI: 0.14, 0.64) indicating a 70% reduction in the risk of progression to an EDSS of 6.0 or more with natalizumab treatment. EDSS of 4.0 is the first level at which disability is termed "relatively severe," while a 6.0 or greater defines the level at which there is a need for assistance to walk, such as with a cane or a crutch (Display 1-1). Thus, natalizumab's impact on these key milestones is a clinically relevant result.

Disability as Measured by Changes in the MSFC

There are three components to the MSFC:

(i) the average scores from 4 trials on the 9-Hole Peg Test (9HPT)

(ii) the average scores of two Timed 25-Foot Walk trials (T25FW), and

(iii) the number correct on the PASAT 3.

Scores for the three dimensions of the scale – arm (9HPT), leg (the T25FW), and cognitive function (PASAT 3) – are combined to create a single score that can be used to detect changes over time in MS patients. This is done by creating a standardized score for each component and averaging them to create an overall composite score. A higher composite score indicates improvement from baseline. The change from baseline MSFC at 2 years (Week 108) was a secondary endpoint and was analyzed by Friedman's analysis of covariance on ranked scores, adjusted for the baseline score.

Natalizumab treatment led to significant improvements in each of the components of the MSFC as well as the overall score (Display 2-6). These results were consistent with the significant effects on disability progression as measured by EDSS, while expanding upon them, showing effects in clinical dimensions not well measured by the EDSS, such as upper limb function and cognitive function.

Display 2-6 Natalizumab as monotherapy: MSFC and components - change from baseline to 2 years

	Placebo	300 mg natalizumab
Number of patients randomized	315	627
MSFC		
Mean	-0.16	0.04
Median	-0.04	0.09
		p<0.001
Timed 25-foot Walk		
Mean	-0.50	-0.20
Median	-0.15	-0.05
		p<0.001
9-Hole Peg Test		
Mean	-0.13	0.09
Median	-0.03	0.13
		p<0.001
PASAT 3		
Mean	0.13	0.22
Median	0.10	0.10
		p=0.005

2.2.1.3 Visual Function

Visual function is commonly impaired as a result of disease activity in MS patients, having a significant impact on daily life. We measured the impact of natalizumab on visual function as an exploratory endpoint using Low-Contrast Sloan Letter Charts. Low-contrast letter acuity testing (perception of light gray letters of progressively smaller size on a white background) is a standardized method that allows for rapid binocular assessments of visual acuity at a sensitivity greater than that of standard Snellen testing or other methods that test high-contrast (black letters on white) visual acuity (Balcer *et al*, 2000). Low-contrast vision, as captured by low-contrast letter acuity and contrast sensitivity (minimum contrast level [shade of gray] at which patients can perceive letters of a single large size), relates to real-world visual function (such as recognition of faces) and is often abnormal in subjects with 20/20 vision by Snellen chart. Further, as the primary outcome measure in the Optic Neuritis Treatment Trial (Beck *et al*, 1992), it is a well-established tool to assess clinical outcomes in MS subjects. In addition, decreases in visual function as measured by low-contrast sensitivity testing have been shown to correlate with worsening quality of life and axonal loss in the retinal nerve fiber layer (Fisher *et al*, 2006). Visual acuity was tested using contrast-level charts of 100%, 2.5%, and 1.25% using a standard protocol.

As expected given its low sensitivity for change, there were no differences between the groups when using the 100% contrast-level chart. However, significant treatment effects were seen on the more sensitive low-contrast charts. On the 2.5% chart, there was an increase of 0.4 for the natalizumab group compared with a decrease of 1.2 for the placebo group ($p=0.005$). On the 1.25% chart, the mean increase in the natalizumab group was 0.9 compared to a decrease of 0.4 in the placebo group ($p=0.019$).

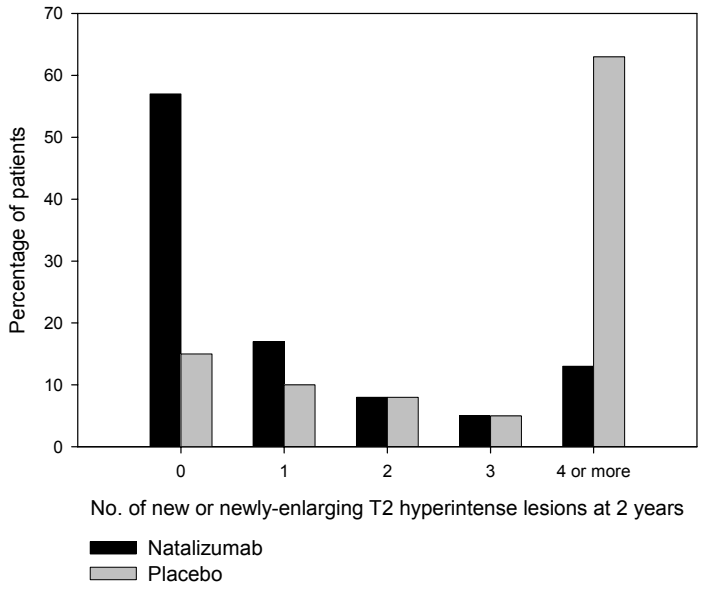
2.2.1.4 Lesions on Brain MRI Scans

T2-hyperintense lesions

Changes in T2-hyperintense lesions reflect inflammatory changes and changes in the overall burden of disease over time. While Gd-enhancing lesions are an indicator of the degree of active inflammation at the time of imaging, the number of T2-hyperintense lesions is an indicator of the degree of inflammatory disease activity over a time interval, since the changes left by acute inflammation (e.g., gliosis, demyelination) are readily visible on T2-weighted imaging. In addition, T2-volume is a marker of accumulating burden of disease. As such, demonstration of a treatment effect on these measures provides objective evidence in support of the primary and secondary clinical endpoints.

Both the number and volume of accumulating T2-hyperintense lesions were evaluated. Through Year 2, there was an 83% reduction in the number of new or newly-enlarging T2-hyperintense lesions in natalizumab-treated patients compared to placebo patients ($p<0.001$). In the natalizumab group, 57% of patients developed no lesions over the 2 years of observation. This is in stark contrast to the placebo group where 63% developed four or more lesions during the same time interval (Display 2-7).

Display 2-7 **Natalizumab as monotherapy: number of new or newly-enlarging T2-hyperintense lesions at 2 years**



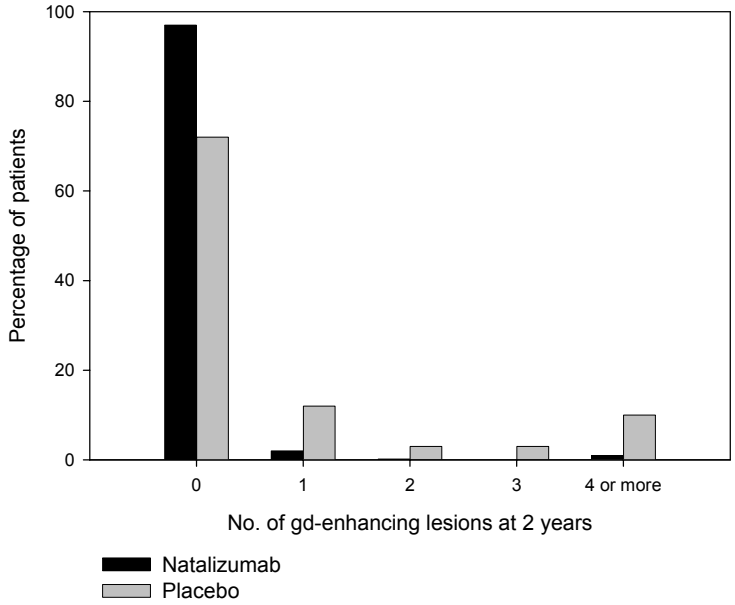
The dramatic effect of natalizumab treatment on T2-hyperintense lesion number was reflected in the reduction in accumulation of disease burden as measured by T2-hyperintense lesion volume. During the 2 years of treatment with natalizumab, there was a decrease in T2-lesion volume as compared with an increase with placebo treatment. Patients receiving placebo saw a mean *increase* in T2-lesion volume of 2891 mm^3 compared with a mean *decrease* of 905 mm^3 in patients receiving natalizumab ($p<0.001$). Given the skewed nature of these data, median changes were also assessed. Median volume *increased* by 583 mm^3 in placebo-treated patients and *decreased* by 548 mm^3 in natalizumab-treated patients ($p<0.001$). This reflects an 8.8% median *increase* in the burden of disease relative to baseline in the placebo group compared to a 9.4% median *decrease* in the natalizumab group, again, a highly significant result ($p<0.001$).

Gd-enhancing lesions

Gd-enhancing lesions are a marker of BBB breakdown and acute inflammation at the time of imaging. This MRI outcome was selected to evaluate natalizumab's potential to reduce the formation of active inflammatory lesions, which, when of sufficient size and located in clinically eloquent areas of the CNS, lead to a clinical exacerbation.

Natalizumab led to a 92% reduction *vs* placebo in the mean number of Gd-enhancing lesions on the MRI scan obtained after 2 years of treatment ($p<0.001$). The mean number of Gd-enhancing lesions seen in the placebo group was 1.2 compared to only 0.1 in the natalizumab group. Gd-enhancing lesions were completely absent in 97% of patients in the natalizumab group compared to 72% of patients in the placebo group (Display 2-8).

Display 2-8 Natalizumab as monotherapy: number of Gd-enhancing lesions at 2 years



T1-hypointense lesions

New T1 hypointensities on brain MRI scans often correspond with inflammatory Gd-enhancing lesions. Acutely, this signal is thought to primarily reflect a reduction in axons and extracellular edema (Bruck *et al*, 1997) and has been supported by MR (magnetic resonance) spectroscopy studies (Brex *et al*, 2000) demonstrating decreases in N-acetyl aspartate, a metabolite found exclusively in neurons and axons. Approximately half of these acute T1 hypointensities (more so with "ring-enhancing" patterns) will evolve into chronic "T1 black holes" that exhibit robust correlations with disability progression (Simon *et al*, 2000). An increase in volume of T1-hypointense lesions volume is reflective of increasing tissue destruction.

Natalizumab reduced the mean number of T1-hypointense lesions by 76% relative to placebo ($p<0.001$). Over 2 years, a mean of 4.6 lesions developed in the placebo group *vs* 1.1 in the natalizumab group. This was also reflected in the T1-hypointense lesion volume over 2 years. Patients receiving placebo saw a mean *increase* in lesion volume of 548 mm^3 over baseline values compared with a mean *decrease* of 1508 mm^3 for those patients on natalizumab treatment ($p<0.001$). Given the skewed nature of these data, median changes were also assessed. Median lesion volume decreased by 6 mm^3 in placebo-treated patients and by 449 mm^3 in natalizumab-treated patients ($p<0.001$). This reflects a median decrease of 1.5% in lesion volume relative to baseline in the placebo group compared to a 23.5% median decrease in the natalizumab group, again, a highly significant result ($p<0.001$).

Summary

Overall, the significant impact of natalizumab on clinical outcomes was mirrored by potent effects on MRI measures of MS disease activity. Gd-enhancing lesions on T1-weighted MRI, which most often represent acute BBB breakdown associated with areas of active inflammation were profoundly reduced in the natalizumab group, with nearly all subjects (97%) exhibiting no Gd-enhancing lesions on their 2-year MRI scan. This finding is significant because of the established association between Gd-enhancing lesions and the evolution of more chronic pathology represented by T1-hypointense lesions (black holes), which are thought to represent permanent demyelination and axonal damage (Simon *et al*, 2000). Similarly striking reductions were found for all MRI endpoints.

2.2.1.5 Quality of Life

A number of studies have shown that MS negatively impacts health-related quality of life (Miller *et al*, 2000; Rudick *et al*, 1992; Solari *et al*, 1999; Freeman *et al*, 1999; Nortvedt *et al*, 2000). However, clinical measures such as EDSS and MSFC do not adequately account for patient perception of well-being and the ability to perform the routine activities of daily life. No approved MS therapy has shown improvement in these measures in well-controlled trials. The SF-36 is one of the most widely accepted generic health status measures and is a validated quality-of-life measure with both mental and physical component summary scores. Higher scores on the instrument indicate better quality of life and increases in the score over time indicate improvement. Subjects in the natalizumab group had a mean increase of 2.00 (improvement) on the mental component scale at 2 years as compared to a mean decrease of 0.53 (worsening) in the placebo group (p=0.011). A similar difference was seen on the physical component scale where subjects in the natalizumab group had a mean increase of 0.67 (improvement) compared to a mean decrease of 1.34 (worsening) in the placebo group, again a significant result (p=0.003).

2.2.1.6 Comparison of Results in Sub-Populations

To explore the robustness of the efficacy results and factors that may impact clinical efficacy, we conducted several pre-specified sub-group analyses. These analyses specifically evaluated the influence of baseline demographic and MS disease characteristics on response to natalizumab treatment. The factors chosen were those shown to influence progression and relapse activity in prior clinical trials of MS, as well as natural history studies of untreated MS populations. Thus, we explored the impact of age, sex, baseline EDSS, the number of T2-hyperintense lesions at baseline, presence or absence of Gd-enhancing lesions at baseline, and pre-study relapse rate on disability progression and clinical relapses.

Consistent with previous studies, untreated patients with active MS at baseline (i.e., those in the placebo group, with a high degree of baseline disease activity as measured by clinical relapses or MRI activity) experienced more relapses during the trial period and had a higher risk of disease progression than those with lesser degrees of activity. Similarly, women less than 40-years-old with higher baseline EDSS scores in the placebo group tended to exhibit more disease activity during the trial.

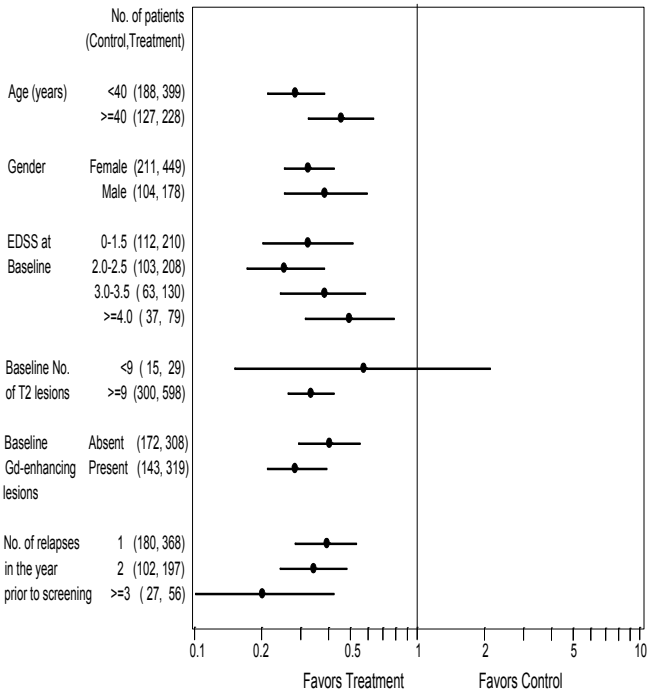
In contrast, regardless of baseline demographics or disease activity, natalizumab treatment resulted in substantial benefit, consistently reducing relapse rates (Display 2-9) and delaying disability progression (Display 2-10) in each of these sub-populations, even in those with the highest degree of disease activity. The only sub-group that was inconsistent was patients with fewer than 9 baseline T2-hyperintense lesions, despite a significant effect on those with greater than 9 baseline T2-hyperintense lesions. This is likely due to very few patients in the sub-group with fewer than 9 baseline T2-hyperintense lesions and very little disease activity in either treatment group.

In summary, the sub-group analyses confirm the robustness of the efficacy results and fail to identify patient groups unlikely to respond to natalizumab treatment. The strength of these results is in their consistency – substantial reductions in relapse rate and risk of progression strikingly similar across the target population, regardless of baseline characteristics or disease state.

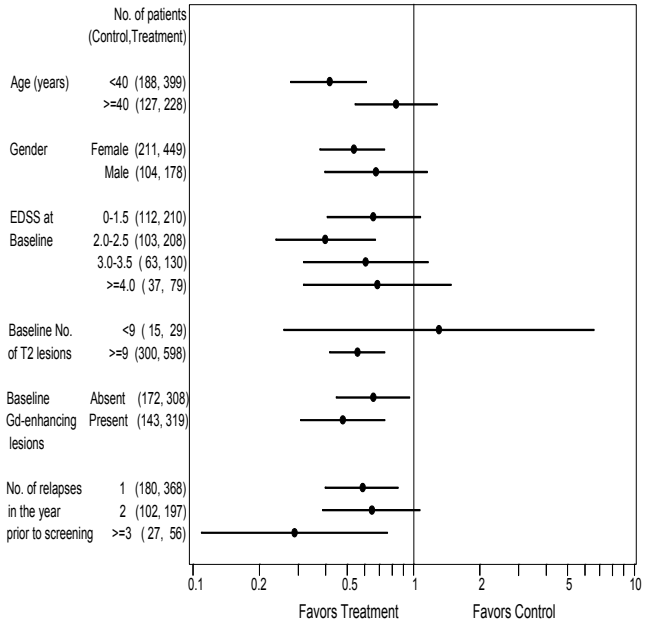
2.2.1.7 Conclusions from the Monotherapy Study, 1801

The results from Study 1801 indicate that natalizumab is an effective treatment as monotherapy for RRMS. Natalizumab treatment resulted in significant effects on relapse rates, disability progression, and all MRI measures, the primary and secondary endpoints of the study. Analysis of Kaplan-Meier curves indicate that the impact on relapse rates and disability progression was apparent early after treatment initiation, and was sustained throughout the treatment period with patient groups continuing to diverge at the final timepoint. Further, these findings were consistent across sub-groups. Additional positive effects were seen on measures of relapse severity and quality of life.

Display 2-9 **Ratios (natalizumab:placebo) of relapse rates (with 95% CIs) in sub-populations**



Display 2-10 **Hazard ratios (with 95% CIs) for time to onset of sustained progression in disability in sub-populations**



2.2.2 Results from the Add-on Study, 1802

2.2.2.1 Rationale for Study Design

As noted in Section 1.2, there are four currently available treatments for MS. However, a significant number of patients who received these treatments continue to experience disease activity clinically and on MRI. This is an expected outcome of the partially effective approved medications, each of which leads to an approximately 30% reduction in relapse rate (IFNB MS Study Group 1993, Jacobs *et al*, 1996; PRISMS Study Group, 1998; Johnson *et al*, 1995). Data from the Phase 3 trials of β-interferon in MS show that 62% to 75% of patients experienced at least one relapse during these 2-year trials despite interferon treatment (IFNB MS Study Group, 1993, Jacobs *et al*, 1996; PRISMS Study Group, 1998). Similarly, 66% of subjects in the Phase 3 MS trial of GA experienced at least one relapse during the 2-year period, a number that was not significantly different from placebo (Johnson *et al*, 1995). Although a variety of therapeutic strategies are currently in use in clinical practice to manage breakthrough disease while on treatment (e.g., switching therapy, changing dose and frequency of interferon, combination therapy), these practices are largely empirical as there are no randomized, controlled trials to assess the efficacy of these approaches.

Study 1802 was designed as an add-on trial to evaluate the efficacy of natalizumab against active control for patients breaking through Avonex monotherapy. The choice of β-interferon was supported by available data on the proposed mechanisms of action of the available drugs. As discussed above, natalizumab has a well-defined mechanism of action, specifically targeting cellular adhesion and trans-endothelial migration via α4-integrins. Although the exact mechanism by which interferon-β exerts efficacy in MS is not known, interferon-β induces a large number of cellular processes involved in cytokine secretion and cellular phenotype changes. Interferon-β downregulates interferon-γ induced MHC class II molecule production, decreases secretion of TH1 pro-inflammatory cytokines (TNF-α, IL-2 and interferon-γ) and increases secretion of TH2 anti-inflammatory cytokines (IL-4 and IL-10)(Rep *et al*, 1996; Kozovska *et al*, 1999; Rudick *et al*, 1998). In addition, interferon-β may affect leukocyte trafficking through suppression of the chemokines RANTES and MIP-1α, as well as their receptor CCR5 (Zang *et al*, 2001). There is, therefore, scientific rationale to expect that the blockade of α4-integrins by natalizumab, when added to interferon-β, may have an additive or synergistic effect when added to interferon-β alone.

2.2.2.2 Summary of Results

The methods for determination and analysis of the study endpoints were the same as those used in the monotherapy study, 1801. As the Sponsor is warning against use of natalizumab in combination with other immunomodulatory treatments, results from the add-on study, 1802, are only briefly described.

Consistent with Study 1801, in Study 1802, natalizumab, as an add-on therapy, had substantial and significant effects as compared with active control on all primary and secondary endpoints, as well as supportive endpoints:

- Natalizumab when added to Avonex resulted in a 24% relative reduction in the risk of disability progression over 2 years as measured by changes on the EDSS sustained for 12 weeks (p=0.024). The percentage of patients progressing was 23% with natalizumab plus Avonex compared to 29% on Avonex alone.

- Natalizumab when added to Avonex resulted in a 18% relative reduction in the risk of disability progression over 2 years as measured by changes on the EDSS sustained for 24 weeks, but this did not reach statistical significance (p=0.166).

- In the Avonex plus natalizumab group at 2 years, there were trends towards reduced risk of progression to an EDSS of 4 or greater by 29% (p=0.187), and to an EDSS of 6 or greater by 35% (p=0.162).

- Treatment resulted in stabilization or improvement of physical functioning as measured by the MSFC. There was a trend towards improvement in cognitive function.

- Treatment resulted in significant effects in visual acuity as measured by Low-Contrast Sloan Letter Charts. On the 2.5% chart, there was an increase of 0.8 for the Avonex plus natalizumab group compared with a decrease of 0.5 for the Avonex group (p=0.006). On the 1.25% chart, the mean increase in the Avonex plus natalizumab group was 1.9 compared to an increase of 0.2 in the Avonex group (p=0.003).

- Natalizumab when added to Avonex resulted in significant effects on all relapse endpoints, when compared to Avonex alone, over 2 years:

    - a 55% relative reduction in the annualized relapse rate (p<0.001)

    - 54% of natalizumab-treated patients remained relapse-free compared to 32% of patients on Avonex (p<0.001)

    - a significant delay in the time to first relapse in natalizumab-treated patients with a difference between the treatment groups apparent by 6 weeks and persisting to the last observed time point

    - fewer relapses in the natalizumab group required treatment with methylprednisolone when compared to those in the Avonex group, and there were fewer MS-related hospitalizations, indicating less severe relapses on natalizumab treatment.

- The effects of natalizumab were consistent across sub-groups, including age, sex, race, weight, baseline disease activity, and MS disease history.

- Natalizumab when added to Avonex resulted in improved quality of life when compared to Avonex alone as measured by the physical component of the SF-36 with a trend on the mental component.

- Clinical benefit with natalizumab was supported by substantial and significant MRI effects when compared with Avonex over 2 years:

- an 83% relative reduction in the accumulation of new or enlarging T2-hyperintense lesions
- an 89% relative reduction in the number of Gd-enhancing lesions
- a 44% relative reduction in the number of new T1-hypointense lesions
- a 2.9% median decrease in T2-hyperintense lesion burden compared to a 4.2% median increase on Avonex.

2.3 EFFICACY CONCLUSIONS

The primary objectives of Studies 1801 and 1802 were to determine whether natalizumab, when compared to placebo as a monotherapy, or active control as an add-on therapy, reduced the frequency of exacerbations and delayed the time to sustained disability progression. The objectives were achieved and the results were clear: natalizumab is a highly effective treatment for relapsing MS, with levels of efficacy beyond those demonstrated with currently available therapies. The magnitude of the effect, along with the breadth and consistency of these findings, set natalizumab apart from other MS therapies. Natalizumab was efficacious across a broad range of clinical and radiographic measures commonly used to gauge disease activity, including clinical exacerbations, disability progression, cognitive and visual function, quality of life, brain inflammation, and burden of disease. In addition, pre-planned sensitivity and sub-group analyses confirmed the robust nature of the primary results, regardless of baseline demographics and disease activity.

3 OVERVIEW OF CLINICAL SAFETY

This section presents an overview of the integrated safety experience with natalizumab in the clinical setting. Overall, the data following 2 years of exposure to natalizumab are consistent with data seen at 1 year with the current product labeling.

The discussion will concentrate on the safety experience in placebo-controlled MS studies. To do this, data from eight placebo-controlled studies were pooled (Studies MS200, MS202, MS221, MS201, MS231, 1801, 1802, and 1803; Display 1-3) resulting in an MS population of 1,617 natalizumab-treated patients of whom 1,271 received the approved dose of 300 mg. The 1,617 natalizumab-treated patients contribute a total of 2,910 person-years of placebo-controlled exposure to natalizumab (Display 3-1). Approximately two-thirds of them were treated for 2 years or longer. The 1,135 patients who received placebo in the eight studies form the comparison group.

1,615 patients who received either natalizumab or placebo in a placebo-controlled MS study were then enrolled into the open-label MS study, 1808 (Display 1-3), and again received the approved dose of 300 mg. In total, 2,321 patients received natalizumab in MS studies contributing to a total of 3,804 person-years of exposure (Display 3-1). One patient, a 5-year-old girl, received 10 doses of natalizumab on a compassionate-use basis, but is not included in the pooling.

The experience in active Crohn's disease (CD) will also be noted for events of interest with natalizumab treatment, e.g., infections and malignancy. Four placebo-controlled treatment studies in CD were pooled. Each study was of short-term duration with a maximum of three infusions. This pooling results in 1,182 patients who received natalizumab, of whom 983 received the approved dose of 300 mg. The 506 patients who received placebo serve as control. As in MS, many of these patients enrolled into maintenance or extension studies. In total, 1,598 CD patients received natalizumab at any time, of whom 1,378 received the approved dose of 300 mg. The 1,598 CD patients who ever received natalizumab contribute 1,701 person-years of exposure (Display 3-1).

A Phase 2, placebo-controlled study in 299 rheumatoid arthritis (RA) patients, of whom 150 received natalizumab, has completed. Thereafter, 155 patients went on to participate in an open-label extension. The approved dose of 300 mg was used in these trials.

Most of the discussion presented in this section will focus on hypothesized mechanism-based toxicity of integrin blockade. α4-integrins are known to mediate several homing and adhesive functions, including those of hematopoietic progenitor cells in the bone marrow. Theoretically, this mechanism of action could be associated with potential risk for infections or altered tumor surveillance. Further, therapeutic proteins have the potential for formation of antibodies against the product, which could result in hypersensitivity-like reactions following administration.

Display 3-1 Natalizumab treatment: duration and exposure

	Multiple sclerosis	Crohn's disease	Total
Exposed at any time			
Number exposed to natalizumab	2321 (100)	1598 (100)	3919 (100)
Number exposed for 1 year or more	1254 (54)	689 (43)	1943 (50)
Number exposed for 2 years or more	1121 (48)	319 (20)	1440 (37)
Number exposed for 3 years or more	111 (5)	35 (2)	146 (4)
Mean exposure (years)	1.64	1.06	1.40
Median exposure (years)	1.65	0.69	0.98
Overall exposure (person-years)	3804	1701	5505
Placebo-controlled studies			
Number exposed to natalizumab	1617 (100)	1182 (100)	2799 (100)
Number exposed for 1 year or more	1189 (74)	0	1189 (42)
Number exposed for 2 years or more	1121 (69)	0	1121 (40)
Mean exposure (years)	1.80	0.36	1.19
Median exposure (years)	2.30	0.39	0.46
Overall exposure (person-years)	2910	425	3336

NOTE: Numbers in parentheses are percentages.

3.1 NON-SERIOUS ADVERSE EVENTS IN MULTIPLE SCLEROSIS CLINICAL STUDIES

In placebo-controlled MS studies, the incidence of common adverse events was balanced between natalizumab-treated patients and patients who received placebo: 96.0% of natalizumab-treated patients and 97.3% of placebo-treated patients reported at least one adverse event (Display 3-2). The most common events were headache, MS relapse, nasopharyngitis, fatigue, back pain, arthralgia, pain in extremity, depression, upper respiratory tract infection (not otherwise specified [NOS]), and urinary tract infection (NOS).

Only 2 events occurred at an incidence of 2.0% or higher in natalizumab-treated patients: pharyngitis (7.7% natalizumab, 5.2% placebo) and rigors (3.4%, 1.1%). Therefore, events that occurred at an incidence of 1.0% or more on natalizumab treatment were evaluated. Only nine events met this cut-off: influenza (13.9% natalizumab, 12.9% placebo), pharyngitis (7.7%, 5.2%), muscle cramp (5.1%, 3.7%), peripheral edema (3.8%, 2.2%), gastroenteritis NOS (3.5%, 1.9%), rigors (3.4%, 1.1%), sinus congestion (3.2%, 1.9%), tonsillitis (3.2%, 2.0%), and irregular menstruation (2.3%, 1.1%).

Adverse events that led to discontinuation of study drug occurred in 5.8% of natalizumab-treated patients and in 4.8% of placebo-treated patients, with urticaria/generalized urticaria being the most common cause of discontinuation in natalizumab-treated patients (1.2%).

Display 3-2 Placebo-controlled MS studies: incidence of adverse events experienced by at least 10% of patients in either treatment group

	Placebo	Natalizumab
Number of patients dosed	1135 (100.0)	1617 (100.0)
Number of patients with an event	1104 (97.3)	1552 (96.0)
Headache	436 (38.4)	634 (39.2)
Multiple sclerosis relapse	622 (54.8)	519 (32.1)
Nasopharyngitis	340 (30.0)	477 (29.5)
Fatigue	305 (26.9)	445 (27.5)
Back pain	250 (22.0)	294 (18.2)
Arthralgia	197 (17.4)	282 (17.4)
Pain in extremity	190 (16.7)	269 (16.6)
Depression	168 (14.8)	247 (15.3)
Upper respiratory tract infection NOS	169 (14.9)	247 (15.3)
Urinary tract infection NOS	179 (15.8)	245 (15.2)
Nausea	167 (14.7)	231 (14.3)
Influenza	146 (12.9)	225 (13.9)
Insomnia	158 (13.9)	222 (13.7)
Asthenia	191 (16.8)	218 (13.5)
Paraesthesia	177 (15.6)	218 (13.5)
Hypoaesthesia	193 (17.0)	208 (12.9)
Dizziness	152 (13.4)	205 (12.7)
Diarrhoea NOS	141 (12.4)	202 (12.5)
Sinusitis NOS	122 (10.7)	184 (11.4)
Influenza like illness	141 (12.4)	175 (10.8)
Fall	136 (12.0)	124 (7.7)

NOTE 1: Numbers in parentheses are percentages.
2: A patient was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the natalizumab column.
NOS: Not otherwise specified.

3.2 DEATHS

There were 18 treatment-emergent deaths in the entire natalizumab program (Display 3-3). In the placebo-controlled MS experience, there were 5 deaths (2 patients had received natalizumab and 3 had received placebo) and an additional 4 deaths within the open-label experience (all patients on natalizumab). There were 6 deaths in the CD program in natalizumab-treated patients, and 3 deaths in the RA studies (2 natalizumab patients and 1 placebo patient). When considering the numbers of deaths, it is important to note that for CD, the exposure to natalizumab was approximately 3-fold greater than exposure to placebo.

In the MS studies, apart from PML, no other safety signal was apparent from the study deaths. In the CD studies, one patient died from PML. Two additional deaths in CD were associated with opportunistic infections - bronchopulmonary aspergillosis and pneumocystis carinii pneumonia.

These patients had significant co-morbidities, which may have contributed to the development of these infections (for further discussion, see Section 3.6.3.1).

Display 3-3 Deaths in the clinical program

MS studies

Patient number (age/sex)	Number of infusions	Study	Cause of death
Natalizumab			
401005 (49/F)	25	1801	Alcohol intoxication
620011 (38/M)	5	1801	Metastatic malignant melanoma
176101 (5/F)	10	1804	Respiratory distress
142101 (46/F)	37 (with Avonex)	1808	PML
131002 (27/M)	31	1808	Suicide
158104 (51/F)	31	1808	Seizure due to MS, arrhythmia
Placebo			
154114 (47/F)	6 (with Avonex)	1802	Cardiac arrest
169102 (23/F)	18 (with Avonex)	1802	Respiratory arrest
11499 (66/F)	4	MS231	Pleural carcinomatosis/seizure

CD studies

Patient number (age/sex)	Number of infusions	Study	Cause of death
Natalizumab			
CD009005 (73/M)	10	CD351	Pulmonary aspergillosis
CD015004 (60/M)	8	CD351	PML
CD024202 (67/M)	22	CD351	Acute myocardial infarction, left ventricular rupture, hemopericardium, cardiac tamponade, cardiogenic shock
CD072001 (42/M)	1	CD301	CO_2 asphyxiation
CD090004 (49/F)	3	CD301	Acute renal failure
CD563003 (69/M)	34	CD351	Pneumocystis carinii pneumonia

RA studies

Patient number (age/sex)	Number of infusions	Study	Cause of death
Natalizumab			
323001 (53/F)	3	RA201	Hemoptysis, respiratory failure
312001 (59/F)	1	RA251	End-stage rheumatoid pulmonary disease
Placebo			
360023 (67/M)	5	RA201	Circulatory and respiratory insufficiency

3.3 SERIOUS ADVERSE EVENTS IN MULTIPLE SCLEROSIS CLINICAL STUDIES

Of the 1,617 natalizumab-treated MS patients in the placebo-controlled experience, 251 (15.5%) experienced at least one serious adverse event (SAE). Of the 1,135 patients who received placebo, 214 (18.9%) experienced a SAE. The most common SAEs (by System Organ Class, SOC) were nervous system disorders (5.9% natalizumab, 10.2% placebo), with MS relapse contributing significantly to this incidence (4.7%, 9.0%). This was followed by infections and infestations (2.4%, 2.2%) with appendicitis and urinary tract infection NOS (<1% in both groups) as the most common events. The incidence of SAEs in the remaining organ systems occurred in less than 1% of natalizumab-treated patients, with the exception of gastrointestinal disorders (1.2% natalizumab, 0.8% placebo) and injury, poisoning, and procedural complications (1.7%, 0.9%). Although less than 1%, there was a small difference in the immune system disorders SOC (0.8% natalizumab, 0.2% placebo) given the occurrence of hypersensitivity reactions (see Section 3.4). Display 3-4 shows the incidence of SAEs by SOC.

Display 3-4 Placebo-controlled MS studies: incidence of serious adverse events by System Organ Class

	Placebo	Natalizumab
Number of patients dosed	1135 (100.0)	1617 (100.0)
Number of patients with a serious adverse event	214 (18.9)	251 (15.5)
Nervous system disorders	116 (10.2)	95 (5.9)
Infections and infestations	25 (2.2)	39 (2.4)
Injury, poisoning, and procedural complications	10 (0.9)	28 (1.7)
Gastrointestinal disorders	9 (0.8)	19 (1.2)
Neoplasms – benign, malignant, and unspecified	19 (1.7)	15 (0.9)
Musculoskeletal and connective tissue disorders	11 (1.0)	15 (0.9)
General disorders and administration site conditions	8 (0.7)	13 (0.8)
Immune system disorders	2 (0.2)	13 (0.8)
Psychiatric disorders	16 (1.4)	13 (0.8)
Reproductive system and breast disorders	6 (0.5)	12 (0.7)
Hepatobiliary disorders	9 (0.8)	11 (0.7)
Renal and urinary disorders	3 (0.3)	7 (0.4)
Surgical and medical procedures	4 (0.4)	6 (0.4)
Investigations	6 (0.5)	6 (0.4)
Blood and lymphatic system disorders	2 (0.2)	5 (0.3)
Vascular disorders	4 (0.4)	4 (0.2)
Skin and subcutaneous tissue disorders	4 (0.4)	4 (0.2)
Metabolism and nutrition disorders	3 (0.3)	3 (0.2)
Cardiac disorders	5 (0.4)	2 (0.1)
Pregnancy, puerperium and perinatal conditions	3 (0.3)	2 (0.1)
Social circumstances	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	7 (0.6)	0

NOTE 1: Numbers in parentheses are percentages.
2: A patient was counted only once within each SOC.
3: SOCs are presented by decreasing incidence in the natalizumab column.

3.4 HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions are a known risk factor with administration of biologic agents. These reactions can be acute or delayed, local or systemic, and can range from mild to life-threatening anaphylactic-type reactions. The approved label warns prescribers about the risk for hypersensitivity reactions with administration of natalizumab. The incidence of such reactions in trials is unchanged from the 1-year submission.

For the purpose of the natalizumab studies in MS, the term "hypersensitivity reaction" includes all events reported by the treating investigator as "hypersensitivity," "allergic reaction," "anaphylactic/anaphylactoid," "urticaria," or "hives." These events were categorized based on both clinical judgment as to the type of event and severity. Patients who experienced an event reported as hypersensitivity were required by the protocol to discontinue study drug. The highest incidence of acute hypersensitivity reactions in the natalizumab placebo-controlled experience occurred in the monotherapy study, 1801, in patients without concomitant treatment with an immunomodulator or immunosuppressant.

In Study 1801, twenty-five (4%) natalizumab patients experienced 27 hypersensitivity reactions: 12 patients with urticaria or generalized urticaria, one with allergic dermatitis, eight with a reaction called "hypersensitivity," and five with "anaphylactic/anaphylactoid" reactions (urticaria plus other signs) (one patient with a reaction called "hypersensitivity" during their 7th infusion was re-dosed and had an "anaphylactic/anaphylactoid" reaction during their 13th infusion). Fifteen reactions occurred on the second infusion. Eight (1.3%) hypersensitivity reactions were reported as SAEs, of which 5 (0.8%) were considered serious systemic reactions (i.e., anaphylactic/anaphylactoid). Five of the eight patients with SAEs experienced respiratory or chest complaints, but only one patient required supplemental oxygen. No cardiovascular compromise was associated with any of these events, although one patient did receive epinephrine. All patients recovered without sequelae.

In the MS experience in Study 1802 and in the CD experience, the incidence of hypersensitivity reactions was slightly lower (2.1% and 1.6%, respectively). There were no cases of anaphylactic or anaphylactoid reactions in Study 1802 and there were only two in the CD studies. This may reflect the more frequent use of immunomodulators or immunosuppressant medications as part of these studies.

In summary, the incidence of hypersensitivity reactions in patients treated with natalizumab monotherapy is approximately 4% with serious systemic reactions occurring at an incidence of less than 1%. This is an expected event with the use of therapeutic proteins. The reactions tended to occur early in the treatment course, but could happen with any infusion. Although the specific mechanisms of the reactions have not been determined, clinically, the reactions appeared to be typical IgE- or IgG-mediated immediate-type hypersensitivity reactions. All patients recovered without sequelae.

3.5 MALIGNANCY

Tumor immunosurveillance is mediated in part by T lymphocytes. Immunosuppressive drugs, such as azathioprine and cyclosporin, which impair lymphocyte function, have been associated with an increased risk of malignancy. Thus, it has been hypothesized that alterations in immune function may increase the occurrence of certain malignancies.

In the placebo-controlled MS experience, malignancies were uncommon. The rate of malignancy in the natalizumab-treated group was 0.38 per 100 person-years compared to 0.73 per 100 person-years in the placebo group (Display 3-5). The rate of malignancy in natalizumab-treated patients with CD was somewhat higher than that seen in MS patients: 1.60 malignancies per 100 person-years in the natalizumab group compared to 0.60 in the placebo group. This difference may not reflect a true difference between the two patient populations since the placebo-controlled CD study period covers up to 16 weeks, compared to 2 years for the MS population. Regardless, when combined, the overall rate of malignancy in all placebo-controlled studies of MS and active CD is similar with 0.54 per 100 person-years in the natalizumab group compared to 0.72 per 100 person-years in the placebo group.

Review of the types of malignancies reported does not indicate a potential increased risk for a specific tumor type. Of note, there were 14 reports of breast cancer. However, the reports were similar in both treatment groups, i.e., 7 occurred in the placebo group and 7 occurred in the natalizumab group. One patient each in the placebo and natalizumab treatment group had a history of breast cancer.

One case of B-cell lymphoma has been reported in an open-label CD study. The patient had received three doses of natalizumab when dosing in clinical studies was suspended. He was diagnosed with lymphoma 3 months later. The patient had received 14 months of 6-mercaptopurine at the time of diagnosis of lymphoma and had received infliximab in the past, both of which have been associated with the occurrence of lymphoma. In addition, the literature suggests that patients with CD may have an increased risk of lymphoma. Thus, an association between this report of lymphoma and natalizumab treatment cannot be determined.

In summary, the occurrence of malignancy on natalizumab treatment was uncommon. The incidence of malignancy was balanced between the natalizumab and control groups. The rates of malignancies with natalizumab treatment are within the expected rates per comparison with the existing cancer registries, such as the National Cancer Institute's Surveillance Epidemiology and End Results. Even though these data cover over 2 years of treatment experience in MS, any effects of natalizumab treatment on malignancy may take much longer to manifest and continued monitoring of this potential risk is planned through post-marketing surveillance and the patient registry (Section 4.2).

Display 3-5 Placebo-controlled studies of MS and of treatment of active CD: rate of malignancies

	Multiple sclerosis		Crohn's disease		MS and CD combined	
	Placebo	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab
Number of patients dosed	1135	1617	506	1182	1641	2799
Total person-years	2060.36	2910.37	165.66	438.63	2226.02	3348.99
Total number of malignancies (event rate)	15 (0.73)	11 (0.38)	1 (0.60)	7 (1.60)	16 (0.72)	18 (0.54)
Basal cell carcinoma	4 (0.19)	4 (0.14)	0	0	4 (0.18)	4 (0.12)
Breast cancer NOS	3 (0.15)	3 (0.10)	0	1 (0.23)	3 (0.13)	4 (0.12)
Colon cancer NOS	0	1 (0.03)	0	1 (0.23)	0	2 (0.06)
Lung adenocarcinoma NOS	0	0	0	2 (0.46)	0	2 (0.06)
Bladder cancer NOS	0	0	0	1 (0.23)	0	1 (0.03)
Breast cancer in situ	1 (0.05)	1 (0.03)	0	0	1 (0.04)	1 (0.03)
Breast cancer invasive NOS	0	0	0	1 (0.23)	0	1 (0.03)
Cervical carcinoma stage 0	0	1 (0.03)	0	0	0	1 (0.03)
Malignant melanoma	2 (0.10)	0	0	1 (0.23)	2 (0.09)	1 (0.03)
Metastatic malignant melanoma	0	1 (0.03)	0	0	0	1 (0.03)
Breast cancer metastatic	1 (0.05)	0	0	0	1 (0.04)	0
Breast cancer stage III	1 (0.05)	0	0	0	1 (0.04)	0
Malignant pleural effusion	1 (0.05)	0	0	0	1 (0.04)	0
Secretory adenoma of pituitary	1 (0.05)	0	0	0	1 (0.04)	0
Squamous cell carcinoma of skin	1 (0.05)	0	0	0	1 (0.04)	0
Uterine cancer NOS	0	0	1 (0.60)	0	1 (0.04)	0

NOTE 1: Entries are number of events (event rate). Event rate = (total number of events/total person-years) x 100.

2: Preferred terms are presented by decreasing rate in the combined natalizumab column.

NOS: Not otherwise specified.

3.6 INFECTION

Natalizumab blocks the adhesion of α4-integrin-expressing leukocytes to their cognate receptors on the endothelium and plays a key role in the homing of mucosal lymphocytes. It has been hypothesized that this mechanism of action could prevent the entry and adherence of lymphocytes to sites of infection and alter the risk of infection, prolong recovery from infection or reduce response to antimicrobial treatment. Therefore, patients were closely monitored for infections in all natalizumab studies.

This section describes the overall rates of infection and common infections (Section 3.6.1), and infections that were classified as serious (Section 3.6.2). Opportunistic infections were also fully evaluated (Section 3.6.3.1). Special emphasis is placed on the herpes family of viruses given the occurrence of a serious viral infection (PML) in natalizumab-treated patients (Section 3.6.3.2). A comprehensive discussion on PML is provided in Section 3.6.3.3.

3.6.1 Overall Occurrence of Infection

The incidence of infections in placebo-controlled studies of MS was balanced between natalizumab-treated and placebo-treated patients (73.7% *vs* 73.9%, respectively, Display 3-6) and occurred at rates of 1.54 and 1.50 infections per person-year, respectively. The overall incidence of both upper and lower respiratory tract infections was very similar in both groups (natalizumab *vs* placebo: 59.6% *vs* 59.8% upper respiratory tract; 13.3% *vs* 12.2% lower respiratory tract). Only four types of infection were more common (by 1.0% or more) in natalizumab-treated patients: influenza (13.9% natalizumab, 12.9% placebo), pharyngitis (7.7%, 5.2%), gastroenteritis NOS (3.5%, 1.9%), and tonsillitis (3.2%, 2.0%). Since the longest duration of exposure to natalizumab was in patients who participated in Studies 1801 and 1802, the incidence of infections was analyzed by 6-month intervals to determine if there was an increasing risk of infection with increasing natalizumab exposure. The risk of infection remained constant throughout the treatment period with no evidence for increasing infection risk with increasing exposure to natalizumab (Display 3-7). Very few infections resulted in the permanent discontinuation of study drug: 11 natalizumab-treated patients (0.7%) and 5 (0.4%) placebo-treated patients (Display 3-8) discontinued treatment due to an infection.

The incidence of infection was somewhat higher in natalizumab-treated CD patients where 40.4% of 1,182 natalizumab-treated patients and 35.8% of 506 placebo-treated patients experienced at least one infection. Again, very few infections resulted in permanent discontinuation of study drug: 7 natalizumab-treated patients (0.6%) and 5 (1.0%) placebo-treated patients discontinued treatment due to an infection. Further, in the CD population who received natalizumab at any time, there was no evidence for increasing risk of infection with increasing exposure to natalizumab.

Display 3-6 Placebo-controlled MS studies: infections with an incidence of 1% or more

	Placebo	Natalizumab
Number of patients dosed	1135 (100.0)	1617 (100.0)
Number of patients with an infection	839 (73.9)	1192 (73.7)
Nasopharyngitis	340 (30.0)	477 (29.5)
Upper respiratory tract infection NOS	169 (14.9)	247 (15.3)
Urinary tract infection NOS	179 (15.8)	245 (15.2)
Influenza	146 (12.9)	225 (13.9)
Sinusitis NOS	122 (10.7)	184 (11.4)
Upper respiratory tract infection viral NOS	88 (7.8)	134 (8.3)
Pharyngitis	59 (5.2)	125 (7.7)
Bronchial infection	71 (6.3)	95 (5.9)
Gastroenteritis viral NOS	80 (7.0)	88 (5.4)
Herpes simplex	53 (4.7)	80 (4.9)
Vaginosis fungal NOS	40 (3.5)	64 (4.0)
Gastroenteritis NOS	21 (1.9)	56 (3.5)
Rhinitis infective	39 (3.4)	51 (3.2)
Tonsillitis	23 (2.0)	51 (3.2)
Bladder infection NOS	16 (1.4)	38 (2.4)
Ear infection NOS	28 (2.5)	38 (2.4)
Tooth infection	22 (1.9)	37 (2.3)
Tooth abscess	25 (2.2)	36 (2.2)
Conjunctivitis infective	25 (2.2)	35 (2.2)
Herpes zoster	16 (1.4)	33 (2.0)
Lower respiratory tract infection NOS	18 (1.6)	33 (2.0)
Upper respiratory tract infection bacterial	29 (2.6)	33 (2.0)
Cystitis NOS	19 (1.7)	32 (2.0)
Respiratory tract infection NOS	15 (1.3)	30 (1.9)
Tooth caries NOS	20 (1.8)	27 (1.7)
Vaginitis	12 (1.1)	25 (1.5)
Bronchitis NOS	24 (2.1)	22 (1.4)
Viral infection NOS	15 (1.3)	21 (1.3)
Pharyngitis viral NOS	9 (0.8)	19 (1.2)
Gingival infection	6 (0.5)	18 (1.1)
Pharyngitis streptococcal	20 (1.8)	18 (1.1)
Pneumonia NOS	10 (0.9)	18 (1.1)
Urinary tract infection bacterial	18 (1.6)	18 (1.1)
Laryngopharyngitis NOS	12 (1.1)	16 (1.0)
Pharyngitis bacterial	14 (1.2)	12 (0.7)

NOTE 1: Numbers in parentheses are percentages.

2: A patient was counted only once within each preferred term.

3: Preferred terms are presented by decreasing incidence in the natalizumab column.

NOS: Not otherwise specified.

Display 3-7 Placebo-controlled MS studies: incidence of infections by exposure to natalizumab

	0-6 months	6-12 months	12-18 months	18-24 months	24-31 months
Number of patients dosed	1617	1157	1123	1088	1064
Total person-years	834.09	554.31	522.26	501.63	497.66
Total number of infections (event rate)	1321 (1.58)	913 (1.65)	812 (1.55)	811 (1.62)	624 (1.25)
95% CI for rate	1.50, 1.67	1.54, 1.76	1.45, 1.67	1.51, 1.73	1.16, 1.36

NOTE: Event rate = total number of events/total person-years.

Display 3-8 Placebo-controlled MS studies: incidence of infections that led to discontinuation of study drug

	Placebo	Natalizumab
Number of patients dosed	1135 (100.0)	1617 (100.0)
Number of patients with an infection that led to discontinuation of study drug	5 (0.4)	11 (0.7)
Pneumonia NOS	1 (<0.1)	2 (0.1)
Urinary tract infection NOS	0	2 (0.1)
Abscess NOS	0	1 (<0.1)
Breast abscess	0	1 (<0.1)
Diarrhoea infectious	0	1 (<0.1)
Gastroenteritis cryptosporidial	0	1 (<0.1)
Hepatitis B	0	1 (<0.1)
Herpes zoster	0	1 (<0.1)
Infectious mononucleosis	0	1 (<0.1)
Lower respiratory tract infection NOS	0	1 (<0.1)
Nasopharyngitis	0	1 (<0.1)
Progressive multifocal leukoencephalopathy	0	1 (<0.1)
Abscess intestinal	1 (<0.1)	0
Erysipelas	1 (<0.1)	0
Molluscum contagiosum	1 (<0.1)	0
Skin and subcutaneous tissue abscess NOS	1 (<0.1)	0

NOTE 1: Numbers in parentheses are percentages.

2: A patient was counted only once within each preferred term.

3: Preferred terms are presented by decreasing incidence in the natalizumab column.

NOS: Not otherwise specified.

3.6.2 Serious Infections

In the placebo-controlled MS studies, 39 natalizumab-treated patients (2.4%) experienced an infection reported as serious *vs* 26 placebo-treated patients (2.3%). Appendicitis and urinary tract infection NOS were the most common serious infections (0.4% natalizumab *vs* 0.3% placebo for appendicitis; 0.4% *vs* 0.2% for urinary tract infection NOS, Display 3-9). Pneumonias, including bronchopneumonia, lobar pneumonia, and atypical pneumonia, represent 6 (0.4%) serious infections in natalizumab-treated patients and 2 (0.2%) infections in placebo-treated patients. These patients responded appropriately to antibiotic therapy.

Similar to the MS experience, the incidence of serious infections in the placebo-controlled CD studies was comparable in the two treatment groups: 2.5% and 2.6% in the natalizumab and placebo groups, respectively. The most frequently reported type of serious infection was an abscess within the gastrointestinal tract, e.g., perianal (0.6% *vs* 0.6%) and abdominal (0.3% *vs* 0.2%). Abscess NOS, abscess intestinal, appendiceal, psoas, peritoneal, and rectal occurred in <0.1% to 0.4% of patients in either treatment group.

Display 3-9 Placebo-controlled MS studies: incidence of serious infections

	Placebo	Natalizumab
Number of patients dosed	1135 (100.0)	1617 (100.0)
Number of patients with a serious infection	26 (2.3)	39 (2.4)
Appendicitis	3 (0.3)	6 (0.4)
Urinary tract infection NOS	2 (0.2)	6 (0.4)
Pneumonia NOS	2 (0.2)	3 (0.2)
Viral infection NOS	0	3 (0.2)
Infection NOS	1 (<0.1)	2 (0.1)
Pyelonephritis NOS	1 (<0.1)	2 (0.1)
Sinusitis NOS	1 (<0.1)	2 (0.1)
Urosepsis	1 (<0.1)	2 (0.1)
Abdominal abscess NOS	0	1 (<0.1)
Bronchopneumonia NOS	0	1 (<0.1)
Cellulitis streptococcal	0	1 (<0.1)
Condyloma acuminatum	0	1 (<0.1)
Febrile infection	0	1 (<0.1)
Gastroenteritis cryptosporidial	0	1 (<0.1)
Hepatitis B	0	1 (<0.1)
Infectious mononucleosis	0	1 (<0.1)
Lobar pneumonia NOS	0	1 (<0.1)
Osteomyelitis NOS	1 (<0.1)	1 (<0.1)
Pilonidal sinus infected	0	1 (<0.1)
Pneumonia primary atypical	0	1 (<0.1)
Progressive multifocal leukoencephalopathy	0	1 (<0.1)
Sinusitis chronic NOS	0	1 (<0.1)
Tonsillitis acute NOS	0	1 (<0.1)
Abscess intestinal	1 (<0.1)	0
Bladder infection NOS	1 (<0.1)	0
Bronchial infection	1 (<0.1)	0
Cystitis NOS	2 (0.2)	0
Erysipelas	2 (0.2)	0
Gastroenteritis NOS	1 (<0.1)	0
Gastroenteritis viral NOS	2 (0.2)	0
Influenza	1 (<0.1)	0
Nasopharyngitis	1 (<0.1)	0
Pyelonephritis acute NOS	1 (<0.1)	0
Skin and subcutaneous tissue abscess NOS	2 (0.2)	0

NOTE: 1: Numbers in parentheses are percentages.
2: A patient was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the natalizumab column.
NOS: Not otherwise specified.

3.6.3 Additional Infections of Note

3.6.3.1 Opportunistic and Other Uncommon Infections

Serious Opportunistic Infections

As with other biologic therapies used to treat inflammatory disorders, serious opportunistic infections have been observed in patients receiving natalizumab. These have occurred more commonly in patients with CD in association with significant co-morbidities or immunocompromise due to immunosuppressant use. No opportunistic infections were observed in patients who received placebo or in the limited RA experience.

In the placebo-controlled MS experience, two natalizumab-treated patients experienced a serious opportunistic infection. Of these, one patient experienced PML and is described in Section 3.6.3.3. One patient experienced cryptosporidium diarrhea, which the investigator felt was prolonged due to natalizumab treatment. The event of cryptosporidium diarrhea occurred in a 31-year-old male who had received 17 natalizumab infusions. He was admitted to the hospital after a 10-day history of diarrhea and abdominal pain. Stool cultures were positive for cryptosporidium. The subject responded well to conservative measures, including rehydration. The event was considered resolved 70 days after his symptoms first started. Crytosporidial infections do occur in immunocompetent hosts and, in general, the infection is a self-limited illness with an average time to recovery ranging from several days up to 5 weeks (Leav *et al*, 2003).

Based upon these cases, the incidence and rate of serious opportunistic infections in the placebo-controlled MS studies were calculated and are presented in Displays 3-10 and 3-11, respectively. The incidence of opportunistic infections in the natalizumab group was 0.12% (95% CI: 0.01%, 0.45%). The rate of opportunistic infection, including PML, in MS patients receiving natalizumab was 0.0007 (95% CI: 0.0001, 0.0025) infections per person-year. The rate in MS patients who received placebo was 0 (95% CI: 0.0000, 0.0018) per person-year. When the open-label natalizumab experience in MS is added (the second patient with PML is included in the calculation), the overall incidence of opportunistic infection is 0.13% (95% CI: 0.03%, 0.38%) and the rate is 0.0008 (95% CI: 0.0002, 0.0023) per person-year, similar to the incidence and rate from the placebo-controlled experience.

Display 3-10 MS studies: incidence of serious opportunistic infections

	Placebo-controlled studies		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	1135 (100.0)	1617 (100.0)	2321 (100.0)
Number of patients with an opportunistic infection	0	2 (0.12)	3 (0.13)
Exact 95% CI for proportion	0.00, 0.32	0.01, 0.45	0.03, 0.38
Gastroenteritis cryptosporidial	0	1 (0.06)	1 (0.04)
Progressive multifocal leukoencephalopathy	0	1 (0.06)	2 (0.09)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.

Display 3-11 MS studies: rate of serious opportunistic infection

	Placebo-controlled studies		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	1135	1617	2321
Total person-years	2060.36	2910.37	3803.82
Total number of opportunistic infections	0	2 (0.0007)	3 (0.0008)
Exact 95% CI for rate	0.0000, 0.0018	0.0001, 0.0025	0.0002, 0.0023
Gastroenteritis cryptosporidial	0	1 (0.0003)	1 (0.0003)
Progressive multifocal leukoencephalopathy	0	1 (0.0003)	2 (0.0005)

NOTE: Entries are number of events (event rate). Event rate = total events/total person-years.

In the placebo-controlled CD experience, there was one possible serious opportunistic infection in natalizumab-treated patients. This was a case of cytomegalovirus (CMV) infection of the colon that occurred in a 33-year-old woman 80 days after her second dose of natalizumab, which she was taking concomitantly with azathioprine. The patient reported a 10-day history of fever and night sweats and was admitted for evaluation. Endoscopic biopsy revealed an increase in chronic inflammatory cells, consistent with CD. However, PCR for CMV DNA was positive. Approximately 2 weeks later, the CMV infection resolved spontaneously and the subject was discharged from the hospital.

Based upon this case, the incidence and rate of serious opportunistic infections in the placebo-controlled studies in CD are presented in Displays 3-12 and 3-13, respectively. The incidence of serious opportunistic infections was 0.08% (95% CI: 0.00%, 0.47%). The rate of opportunistic infection in CD patients receiving natalizumab was 0.0024 (95% CI: 0.0001, 0.0131) infections per person-year. The rate in CD subjects who received placebo was 0 (95% CI: 0.0000, 0.0205) per person-year.

Displays 3-12 and 3-13 also show the incidence and rate of serious opportunistic infections in the cumulative CD experience, i.e., any patient who received one or more natalizumab infusions in a clinical trial. A total of five serious opportunistic infections were identified in the CD experience leading to an incidence of 0.31% (95% CI: 0.10%, 0.73%) and a rate of 0.0029 (95% CI: 0.0010, 0.0069) per person-year in the CD population, which, given the number of patients exposed, is similar to that seen in the shorter placebo-controlled studies. The opportunistic infections that did occur included one case of CMV colitis described above, as well as one case each of pulmonary aspergillosis, pneumocystis carinii pneumonia (PCP), mycobacterium avium complex (MAC) pneumonia, and PML. The case of PML is described in Section 3.6.3.3. The case of pulmonary aspergillosis occurred in a 73-year-old man with CD who developed peritonitis following a perforated duodenal ulcer 1 month after his last infusion of natalizumab. He had received a total of 10 natalizumab infusions and was taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and high dose prednisolone (50 mg daily). After several weeks in the hospital requiring ICU support, a CT scan showed bilateral infiltrates, and sputum cultures grew aspergillus. He subsequently died from his illness.

The case of PCP occurred in a 69-year-old man with CD who was hospitalized for hepatic encephalopathy, acute renal failure (ARF), and anemia. The subject had a history of cirrhosis with esophageal varices and ascites prior to study entry. He received his 34th infusion of natalizumab 1 month prior to developing hepatic encephalopathy. Two months after the last dose of natalizumab, he developed acute renal failure, pulmonary edema, and sepsis requiring intubation. Sputum was positive for pneumocystis carinii and he eventually died of sepsis.

The case of MAC pneumonia occurred in a 65-year-old woman with CD with a history of use of high-dose oral corticosteroids (prednisone 60 mg per day), although this had been tapered to 5 mg per day prior to the event. She initially presented after her fifth infusion of natalizumab with a non-productive cough and sinus infection, which was treated empirically with azithromycin. Her symptoms did not improve over the next month, and bronchoalveolar lavage revealed MAC by acid fast bacilli (AFB) stain. Sputum cultures grew *Staphylococcus aureus*. She discontinued

natalizumab and was treated with rifabutin, ethambutol, ciprofloxacin, and azithromycin. She made a full recovery.

In addition to opportunistic infections, there was one case of suspected peritoneal tuberculosis discovered during abdominal surgery in a patient with worsening CD 7 months after his last natalizumab infusion. Although pathology was suspicious for this diagnosis, all AFB stains and cultures were negative. Concomitant medications at the time of the event included azathioprine, which he had been receiving since 2003.

Summary

Serious opportunistic infections were observed in the natalizumab clinical program. The most frequent type of serious opportunistic infection was PML, of which there were three confirmed cases that are discussed in Section 3.6.3.3. More patients with CD experienced opportunistic infections than in MS, where the only non-PML opportunistic infection seen was a case of cryptosporidial diarrhea. This is likely due to differences in co-morbidities and concomitant medications between patients with CD and those with MS, as can be seen by the case descriptions. Indeed, the 0.31% incidence of opportunistic infections observed in the CD patients in these studies was comparable to that observed in CD patients in studies of anti-TNF therapies. In a population-based cohort study from Stockholm County, Sweden, of 217 patients with inflammatory bowel disease, 2 (0.9%) developed severe opportunistic infections, one fatal case of PCP pneumonia and one case of listeria meningitis (Ljung *et al*, 2004). In another study of 500 patients also treated with anti-TNF therapies, there was one case of histoplasmosis and one case of *Candida* esophagitis complicated by a fatal pneumonia. Another case of histoplasmosis was observed after study completion (Colombel *et al*, 2004). Finally, in the Belgian expanded access program for infliximab, among a cohort of 478 RA patients followed for one year, there was one death from PML (Durez, 2002). While it is likely that natalizumab was a factor in the non-PML opportunistic infections in these studies, it is reasonable to conclude that co-morbidities and concomitant medications also played an important role.

Display 3-12 CD studies: incidence of serious opportunistic infections

	Placebo-controlled studies of active CD		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	506 (100.0)	1182 (100.0)	1598 (100.0)
Number of patients with an opportunistic infection	0	1 (0.08)	5 (0.31)
Exact 95% CI for proportion	0.00, 0.73	0.00, 0.47	0.10, 0.73
Cytomegalovirus infection	0	1 (0.08)	1 (0.06)
Bronchopulmonary aspergillosis	0	0	1 (0.06)
Mycobacterium avium complex infection	0	0	1 (0.06)
Pneumocystis carinii pneumonia	0	0	1 (0.06)
Progressive multifocal leukoencephalopathy	0	0	1 (0.06)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Total includes all patients who received 1 or more natalizumab infusions and all events occurring within 12 weeks of last infusion.

Display 3-13 CD studies: rate of serious opportunistic infection

	Placebo-controlled studies of active CD		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	506	1182	1598
Total person-years	180.09	425.19	1700.7
Total number of opportunistic infections	0	1 (0.0024)	5 (0.0029)
Exact 95% CI for rate	0.0000, 0.0205	0.0001, 0.0131	0.0010, 0.0069
Cytomegalovirus infection	0	1 (0.0024)	1 (0.0006)
Bronchopulmonary aspergillosis	0	0	1 (0.0006)
Mycobacterium avium complex infection	0	0	1 (0.0006)
Pneumocystis carinii pneumonia	0	0	1 (0.0006)
Progressive multifocal leukoencephalopathy	0	0	1 (0.0006)

NOTE: 1. Entries are number of events (event rate). Event rate = total events/total person-years.
2: Total includes all patients who received 1 or more natalizumab infusions and all events occurring within 12 weeks of last infusion.

3.6.3.2 Herpes Viral Infections

Because of natalizumab's effect on lymphocytes and the occurrence of PML in natalizumab-treated patients, viral infections were of particular interest. The herpes family of viruses was of interest given 1) viral reactivation leads to infection, and 2) the tropism that these virus have for the CNS.

The incidence of infections in the herpes family from the placebo-controlled studies of MS and CD are shown in Display 3-14. The incidence of herpetic infections was approximately 1% higher in natalizumab-treated MS patients than in placebo-treated MS patients (natalizumab *vs* placebo: 7.2% *vs* 6.1% for MS; 1.7% *vs* 1.2% for CD). There were no differences in the number of patients with Epstein-Barr virus infections, i.e., mononucleosis. Cytomegalovirus (CMV) is discussed separately below.

There were no reports of serious herpes infections in MS patients during clinical trials. However, there were four reports of serious herpes infections in the CD trials, all in natalizumab-treated patients. Two patients were treated with intravenous acyclovir for herpes zoster and one patient received acyclovir for herpes vaginitis. The fourth patient, who received natalizumab in a maintenance CD study, developed a primary varicella pneumonia following varicella exposure from her son who had contracted chicken pox. She recovered fully following intravenous acyclovir treatment. There were no reports of disseminated herpetic infection, herpes meningitis, or herpes encephalitis in natalizumab clinical trials.

During the 3 months that natalizumab was on the US market, there were two reports of serious herpes infections in the CNS in natalizumab-treated patients. The first was a fatal case of herpes simplex encephalitis that occurred 3 months after a single dose of natalizumab in a patient who had received the maximum lifetime dose of mitoxantrone. The second was a case of herpes simplex meningitis that developed several hours after a single dose of natalizumab. This patient recovered fully with acyclovir treatment. It should be noted that HSV encephalitis is the most common cause of sporadic viral encephalitis in the US and most often occurs in immune-competent individuals. There were no other atypical or opportunistic infections that occurred during the post-marketing experience (see Section 3.12).

Display 3-14 Placebo-controlled studies of MS and of treatment of active CD: incidence of herpes family viral infections

	Multiple sclerosis		Crohn's disease	
	Placebo	Natalizumab	Placebo	Natalizumab
Number of patients dosed	1135 (100.0)	1617 (100.0)	506 (100.0)	1182 (100.0)
Number of patients with a herpes family viral infection	69 (6.1)	116 (7.2)	6 (1.2)	20 (1.7)
Exact 95% CI for proportion	4.8, 7.6	6.0, 8.5	0.4, 2.6	1.0, 2.6
Herpes simplex	53 (4.7)	80 (4.9)	4 (0.8)	14 (1.2)
Herpes zoster	16 (1.4)	33 (2.0)	1 (0.2)	4 (0.3)
Herpes viral infection NOS	4 (0.4)	5 (0.3)	0	1 (<0.1)
Cytomegalovirus hepatitis	0	1 (<0.1)	0	0
Infectious mononucleosis	0	1 (<0.1)	0	0
Cytomegalovirus infection	1 (<0.1)	0	0	1 (<0.1)
Herpes simplex ophthalmic	1 (<0.1)	0	0	0
Mononucleosis heterophile test positive	0	0	1 (0.2)	0

NOTE: Numbers in parentheses are percentages. A patient was counted only once within each term.
NOS: Not otherwise specified.

CMV reactivation can occur in the setting of immunosuppression, so CMV infections were analyzed separately in both the placebo-controlled and open-label experience in MS and CD (Displays 3-15 to 3-18). The only case of possible opportunistic infection due to CMV was a serious case of CMV infection of the colon in a patient with CD described above in Section 3.6.3.1. The remaining cases of CMV that occurred were non-serious and involved elevations in liver function tests, suggestive of primary CMV infections. In the MS placebo-controlled experience, there was one non-serious CMV infection in the placebo group and one non-serious primary CMV hepatitis in a natalizumab-treated subject; thus the incidence of CMV infections in both natalizumab and control groups were similar. There was an additional patient who developed elevated liver function tests reported as a serious adverse event (AST 620 U/L, ALT 992 U/L, GGT 48 U/L) following her second infusion of natalizumab in the setting of concomitant Avonex use during the MS open-label experience. Subsequent ELISA testing was positive for IgM to CMV.

In the open-label trials of CD, there were also two cases of non-serious CMV hepatitis in natalizumab-treated patients. The incidence of CMV infections in CD was 0.08% (95% CI: 0.00%, 0.47%) for the placebo-controlled experience and 0.19% (95% CI: 0.04%, 0.55%) when the open-label experience is included. There were no CMV infections in the placebo group in the CD experience (95% CI: 0.00%, 0.73%). The rates of CMV infection followed a similar pattern (Display 3-18).

Display 3-15 MS studies: incidence of CMV infections

	Placebo-controlled studies		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	1135 (100.0)	1617 (100.0)	2321 (100.0)
Number of patients with a CMV infection	1 (0.09)	1 (0.06)	2 (0.09)
Exact 95% CI for proportion	0.00, 0.49	0.00, 0.34	0.01, 0.31
Cytomegalovirus hepatitis	0	1 (0.06)	1 (0.04)
Cytomegalovirus infection	1 (0.09)	0	0
Liver function test abnormal	0	0	1 (0.04)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.

Display 3-16 MS studies: rate of CMV infection

	Placebo-controlled studies		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	1135	1617	2321
Total person-years	2060.36	2910.37	3803.82
Total number of CMV infections	1 (0.0005)	1 (0.0003)	2 (0.0005)
Exact 95% CI for rate	0.0000, 0.0027	0.0000, 0.0019	0.0001, 0.0019
Cytomegalovirus hepatitis	0	1 (0.0003)	1 (0.0003)
Cytomegalovirus infection	1 (0.0005)	0	0
Liver function test abnormal	0	0	1 (0.0003)

NOTE: Entries are number of events (event rate). Event rate = total events/total person-years.

Display 3-17 CD studies: incidence of CMV infections

	Placebo-controlled studies of active CD		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	506 (100.0)	1182 (100.0)	1598 (100.0)
Number of patients with a CMV infection	0	1 (0.08)	3 (0.19)
Exact 95% CI for proportion	0.00, 0.73	0.00, 0.47	0.04, 0.55
Cytomegalovirus infection	0	1 (0.08)	1 (0.06)
Cytomegalovirus hepatitis	0	0	2 (0.13)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Total includes all patients who received 1 or more natalizumab infusions and all events occurring within 12 weeks of last infusion.

Display 3-18 CD studies: rate of CMV infection

	Placebo-controlled studies of active CD		Total natalizumab experience
	Placebo	Natalizumab	
Number of patients dosed	506	1182	1598
Total person-years	180.09	425.19	1700.7
Total number of CMV infections	0	1 (0.0024)	3 (0.0018)
Exact 95% CI for rate	0.0000, 0.0205	0.0001, 0.0131	0.0004, 0.0052
Cytomegalovirus infection	0	1 (0.0024)	1 (0.0006)
Cytomegalovirus hepatitis	0	0	2 (0.0012)

NOTE: 1. Entries are number of events (event rate). Event rate = total events/total person-years.
2: Total includes all patients who received 1 or more natalizumab infusions and all events occurring within 12 weeks of last infusion.

Summary

Herpetic infections were seen on natalizumab treatment. It is not unexpected that these infections would occur in a cohort of this size as these infections are common and most often occur in normal individuals. There was a small difference of approximately 1% in the incidence of these infections between natalizumab-treated patients and controls in MS, a difference that was less in the CD experience (0.6%).

3.6.3.3 Progressive Multifocal Leukoencephalopathy

Background on PML

PML is an infectious disease of the central nervous system caused by infection of oligodendrocytes by the JC virus (JCV). JCV is a human polyoma virus that is believed to infect the majority of healthy individuals at an early age. The seroprevalence of anti-JCV antibodies in healthy individuals has been estimated to range from 20% to 80% depending upon the testing methodology being used (Knowles *et al*, 2003; Knowles and Sasnauskas, 2003).

PML occurs predominantly in immunocompromised individuals with an age-adjusted death rate due to PML of 3.3 per million persons (in 1994), 89% of whom were AIDS patients (Holman *et al*, 1998). However, rare PML cases have also been reported in patients with autoimmune disorders who received immunosuppressive therapy; among these, three patients with RA (Sponzilli *et al*, 1975; Rankin *et al*, 1995; Durez *et al*, 2002), one of whom was treated with tumor necrosis factor (TNF) antagonist (Durez *et al*, 2002). There was also a report of PML in a CD patient, but the concomitant treatments were not specified (Garrels *et al*, 1996).

The exact mechanism by which PML develops is not known. It is hypothesized to be a stochastic process dependent upon multiple steps in the life-cycle of the JCV and its interactions with the immune system. The site of primary JCV infection is not known, but detection of JCV in tonsillar stromal cells and B lymphocytes may indicate a respiratory means of infection (Sabath and Major, 2002). The virus is also known to infect CD34+ hematopoietic precursor cells and kidney cell lines and is found in association with these tissues. One possible hypothesis is that following primary infection in the tonsil, JCV may traffic via B-cells from the primary source of infection to sites of latency in the kidney and bone marrow. This is supported by the identification of JCV in these tissues (Sabath and Major, 2002). The site of viral rearrangement and the mechanism by which the JCV enters into the brain from its sites of latency is also not known. It is hypothesized that systemic distribution of JCV may occur via direct hematogenous spread of virus or may be facilitated by B-lymphocytes and CD34+ precursor cells through low-affinity interactions of JCV with sialic acid residues on the surfaces of these cell types (Wei *et al*, 2000; Eash *et al*, 2004). JCV may eventually gain access to the brain via migration of these cells across the BBB or direct infection of the brain via interactions between JCV and 5HT2a receptors on the BBB (Elphick *et al*, 2004). Once in the brain, steps leading to lysis of oligodendrocytes and transformation of astrocytes are not understood.

The presence of JCV in the blood and urine of patients with PML and healthy, immunocompetent individuals has been described (Kitamura *et al*, 1990; Tornatore *et al*, 1992; Dorries *et al*, 1994; Sundsfjord *et al*, 1994; Agostini *et al*, 1996; Dubois *et al*, 1996; Knowles *et al*, 1999; Dorries *et*

al, 2003). These findings are neither predictive nor diagnostic of PML in these patients; thus the relationship of blood or urine viral load to PML is unclear.

The clinical presentation of PML is largely dependent upon the size and distribution of the white matter lesions that develop as a result of viral infection, demyelination, and glial cell lysis. However, clinical features of the presentation help differentiate it from the demyelination associated with MS. In contrast to MS, PML involvement of the spinal cord or optic nerves is extremely rare. Instead, about one-third of patients will present with visual field loss or cortical blindness with another third presenting with altered mentation or behavior changes (Dworkin *et al*, 2002). Also unlike MS, hemiparesis is a common presenting symptom. These symptoms are typically subacute in onset and follow a slowly progressive course. Often, patients and their families are the first to notice the onset of PML through changes in the ability to perform routine activities of daily living, even prior to presentation with changes on neurological examination.

MRI is a very sensitive tool for the detection of PML lesions in the setting of clinical signs or symptoms, although it lacks specificity. Typical MS lesions, demyelination from other causes (e.g., encephalomyelitis, HIV encephalopathy), gliosis, and edema can often have a similar appearance to early PML lesions. However, there are features of PML lesions that help differentiate them from other etiologies (Post *et al*, 1999; Display 3-19). PML lesions are typically asymmetric, subcortical, and diffuse with ill-defined borders, involving subcortical U-fibers and white matter tracts, but usually sparing the overlying cerebral cortex and gray matter. The lesions are typically hyperintense on T2-weighted and fluid-attenuation inversion recovery (FLAIR) sequences, without edema or mass effect. The existence of atrophy in association with the lesion is also atypical. The lesions typically affect the cerebrum, brainstem, or cerebellum, but are rarely found in spinal cord. In addition, Gd-enhancement on T1-weighted imaging is unusual, although Gd-enhancement has been described during recovery from PML and may be an indicator of better outcome (Berger *et al*, 1998; Hoffmann *et al*, 2003; Langer-Gould *et al*, 2005).

PCR analysis of the CSF for JC viral DNA is a highly sensitive and specific test for the diagnosis of PML. The specificity of this test approaches 100%, with a sensitivity ranging from 60% to 90% (Henson *et al*, 1991; Gibson *et al*, 1993; Weber *et al*, 1994a; Weber *et al* 1994b; Vago *et al*, 1996). In cases with a high clinical suspicion of PML and negative CSF results, repeat testing often leads to detection of JC viral DNA. As such, PCR analysis of the CSF for JC viral DNA has grown to be the preferred method to confirm the diagnosis of PML.

Untreated, PML patients have a mortality rate of 30% to 50% during the first 3 months (Koralnik, 2004). Prior to the introduction of highly active antiretroviral treatment (HAART) for HIV, about 10% of patients with PML survived for longer than 1 year. However, since the advent of HAART, about 50% of patients with PML survive for longer than 1 year due to restoration of immune function as CD4 counts increased, the so-called immune reconstitution inflammatory syndrome (Geschwind *et al*, 2001; Berger *et al*, 1998; Clifford *et al*, 1999; Tantisiriwat *et al*, 1999).

Currently, there is no established drug treatment for PML. Various medications have been tested, including acyclovir, idoxuridine, vidarabine, amantadine, adenine arabinoside, cytosine arabinoside (cytarabine), cidofovir, interferon α, interleukin-2 (IL-2), zidovudine, camptothecin,

and topotecan (Koralnik, 2004; Dworkin *et al*, 2002; Seth *et al*, 2003; Collazos, 2003; Mamidi *et al*, 2002; Przepiorka *et al*, 1997; Redington *et al*, 2002; Padgett *et al*, 1983). However, the survival of patients with PML appears to be best correlated with immune reconstitution. In transplant patients with PML, early dosage reduction or/and discontinuation of immunosuppressive therapy was associated with favorable clinical outcome after PML diagnosis (Crowder *et al*, 2005; Shitrit *et al*, 2005).

Display 3-19 Brain MRI features to be considered in the differential diagnosis of MS and PML

	MS	PML
Location of new lesions	Mostly focal, may affect entire brain and spinal cord, in white and possibly gray matter; Posterior fossa lesions rarely seen	Diffuse, mainly sub-cortical, rarely periventricular, almost exclusively in white matter, although occasional extension to gray matter seen; Posterior fossa frequently involved (cerebellum)
Borders	Sharp edges, shapes mostly round or finger-like (especially periventricular), confluent with other single lesions, U-fibers may be involved	Ill-defined edges, infiltrating, irregular in shape, confined to white matter, sparing gray matter, pushing against cortex, U-fibers destroyed
Mode of extension	Focal, enlarging of lesions within days/weeks, later decreasing in size within months	Diffuse, asymmetrical, extending homogeneously, no confluence with other lesions, defined to white matter tracks, sparing cortex, continuous progression
Mass effect	Acute lesions may show some mass effect	No mass effect even in large lesions (but process is slightly pushing against cortex)
T2-weighted sequence	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside ring structure; Sub-acute/chronic lesions: hyperintense, no ring structure	Diffuse hyperintense, slightly increased intensity of newly involved areas compared to old areas, little irregular signal intensity of lesions
T1-weighted sequence	Acute lesions: densely hypointense (large lesion) or isointense (small lesion), increasing signal intensity over time in 80%, decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense from the onset, signal intensity decreasing over time and along the affected area, no reversion of signal intensity
Flair sequence	Hyperintense, sharply delineated	Hyperintensity more obvious, true extension of abnormality more clearly visible than in T2-weighted images
Enhancement	Acute lesions: dense homogeneous enhancement, sharp edges Sub-acute lesions: ring-enhancement Chronic lesions: no enhancement	Usually no enhancement even in large lesions, in HIV+ patients some peripheral enhancement possible, especially under therapy
Atrophy	Focal atrophy possible due to focal white matter degeneration, no progression	No focal atrophy since extending pathological process is slightly pushing against cortex (extension of tissue)

Based on Yousry *et al*, 2006.

Summary of the Three Confirmed Cases of PML

Natalizumab dosing was suspended on 28 February 2005, when it was discovered that an MS patient who had received over 2 years of natalizumab therapy in combination with Avonex had been diagnosed with PML, and that there was another similarly treated MS patient with suspected PML. In the subsequent weeks, the second MS patient was confirmed to have PML, and it was discovered that a patient in a CD trial of natalizumab who was thought to have died in December 2003 of an astrocytoma had, in fact, succumbed to PML. The three cases are now summarized.

The first patient was a 46-year-old female with MS who presented to her neurologist in September 1999 with right-sided paresthesia and dysesthesia and right upper extremity clumsiness. MRI of the brain demonstrated 4 non-enhancing T2-hyperintense lesions in the corona radiata bilaterally. Six weeks later, she presented with new blurring of the vision in her right eye. Visual acuity was 20/15 in the left eye, 20/100 in the right. Spinal fluid analysis in November 1999 yielded 1 white blood cell, normal protein and glucose, and no oligoclonal bands. In January 2000, follow-up MRI scan of the brain revealed 2 new subcortical lesions in the right parietal region, hyperintense on FLAIR imaging, hypointense on T1. Avonex was initiated in March 2000.

Over the period from March 2000 until study entry in April 2002, she experienced 3 relapses, the most recent of which was in March 2002 and involved band-like pain around the abdomen, lower extremity weakness, and spasticity requiring treatment with methylprednisolone. Her EDSS score in March 2002 prior to study entry was 2.5.

The patient enrolled in Study 1802 in April 2002. She received 30 infusions of natalizumab before entering the open-label extension study in July 2004 in which she received an additional seven. She had no exacerbations or suspected relapses during her time in Study 1802. She developed 5 new or enlarging T2-hyperintense lesions during the first year of Study 1802 and one during the second year. She was negative for anti-natalizumab antibodies and the concentration of natalizumab was similar to the mean of the 1801 and 1802 populations throughout her participation in Study 1802. In November 2004, she began to experience motor dysfunction, cognitive and language difficulties, which progressed to right hemiparesis in December 2004. Brain MRI from December 2004 revealed left frontal T2-hyperintensity and T1-hypointensity with extension into the centrum semiovale and corona radiata without Gd-enhancement. She received two courses of high dose steroids over the next few months, but continued to decline. She received her last dose of natalizumab on 18 January 2005. She was readmitted to the hospital on 12 February 2005 with worsening clinical status. Repeat MRI in February 2005 showed extension of the lesion seen previously. Extensive work-up over the next week revealed JC viral DNA in the CSF, resulting in the diagnosis of PML. She died on 24 February 2005. Post-mortem examination revealed normal organs without evidence of opportunistic infection. The brain examination revealed extensive, severe cavitation mainly in the left hemisphere as well as multiple non-cavitated, ovoid areas throughout the white matter of both hemispheres typical of PML (reactive astrocytes with enlarged, hyperchromatic nuclei). (Kleinschmidt-DeMasters and Tyler, 2005).

The second patient is a 46-year-old male who experienced his first symptoms of relapsing/remitting MS beginning in 1983. Past medical history is significant for auricular zoster

and Ramsay-Hunt syndrome and melanoma. Family history is notable for a sister with MS. He had been on interferon β-1a (Avonex) since 1998, and experienced three relapses the year before enrolling in Study 1802 in September 2002. During Study 1802, he experienced no relapses or evidence of progression. He was negative for anti-natalizumab antibodies and the concentration of natalizumab was similar to the mean of the 1801 and 1802 populations throughout his participation in Study 1802. In October 2004, his MRI scan showed a small periventricular Gd-enhancing lesion on the right and a small right frontal, subcortical, non-enhancing, T2-hyperintense lesion. In November 2004, he exhibited behavioral changes followed by hemiparesis and cognitive impairment. His last dose of natalizumab was in December 2004. In February 2005, despite treatment with high dose intravenous methylprednisolone, he continued to deteriorate. Brain MRI in February 2005 demonstrated extension of the previously identified lesion. He underwent an extensive work-up, including CSF analysis and brain biopsy, which resulted in the diagnosis of PML. Cidofovir treatment was initiated without clinical effect. JC viral load decreased in the plasma and CSF over the next few months. This corresponded to further deterioration in his clinical course and development of Gd-enhancing lesions on MRI consistent with IRIS (Immune Reconstitution Inflammatory Syndrome). He continued to receive treatment with cidofovir, and cytarabine was added. Approximately 3 months following discontinuation of natalizumab, he began to improve. Currently, he is able to hold high-level conversations about his medical course and treatment. He is able to converse, but has significant residual cognitive impairment with left hemiparesis and ataxia. (Langer-Gould *et al*, 2005).

The final patient was a 60-year-old male with a history of CD for 28 years. Over the course of his illness, he had been treated with azathioprine, oral budesonide, corticosteroids, and four doses of infliximab. The patient had had pre-existing signs of impaired hematopoiesis, predominantly lymphopenia and anemia, since 1996. He received azathioprine beginning in 1999. He initiated natalizumab as part of ENACT-1 (a Phase 3 study in patients with active CD) in March 2002 and received three doses concomitantly with azathioprine prior to being randomized to placebo in ENACT-2 (a Phase 3 maintenance study). He remained on azathioprine and placebo until November 2002 when azathioprine was discontinued due to refractory pancytopenia. In February 2003, he began open-label treatment with natalizumab. He was negative for anti-natalizumab antibodies in ENACT-1, ENACT-2, and the open-label extension study. The concentration of natalizumab while on drug was similar to the mean of the overall population. In July 2003, he presented 1 month after his fifth dose of natalizumab with a 1-week history of cognitive decline. Brain MRI scan demonstrated a large T2-hyperintense lesion in the right frontal lobe, and additional hyperintense lesions in the left frontal and temporal lobes that did not enhance with gadolinium. He underwent a partial resection of the lesion, the pathology of which was read as an anaplastic astrocytoma, WHO Grade III. He was treated with corticosteroids and anticonvulsants, but was too ill for radiation therapy. Follow-up MRI six weeks after surgery showed tumor extension. He deteriorated clinically and died in December 2003. The case was reported by the treating physician to Biogen Idec and Elan as a malignant astrocytoma, based upon the final pathology report. This was reported to regulatory authorities and investigators as per usual procedure. In February, as a result of the one confirmed and one suspected case of PML, Biogen Idec and Elan initiated a reassessment of the case, which was determined to be PML following consultation with two independent neuropathologists with expertise in PML (Van Assche *et al*, 2005).

In summary, three confirmed cases of PML have been identified: two MS patients and one CD patient. Both MS subjects received natalizumab for over 2 years in addition to Avonex. The CD subject received eight doses of natalizumab over an 18-month period and was immunocompromised due to chronic azathioprine use as manifested by persistent lymphopenia. Two of the cases were fatal, one MS and one CD patient. All three patients presented with subtle clinical changes early in their disease course that were noted by the patients or their families.

Review of the Safety Evaluation Procedure

Following the voluntary suspension of natalizumab, Biogen Idec and Elan performed a review of the entire natalizumab safety database and found only the CD case reported above. In addition, Biogen Idec reviewed the safety database for Avonex and found no cases of PML in patients receiving Avonex monotherapy in over 600,000 patient years of exposure. Furthermore, review of the FDA spontaneous adverse event reporting system identified no PML case report in patients receiving β-interferon monotherapy.

Additionally, in collaboration with regulatory authorities in the US and Europe and the NIH in the US, the Sponsors embarked on a comprehensive prospective evaluation of all MS subjects who had received natalizumab as part of the Phase 3 program. Prior to the safety evaluation, an Independent Adjudication Committee (IAC) was established. The IAC consisted of three voting members, with expertise in neurovirology, neuroradiology, and clinical neurology.[1] The purpose of this evaluation was to systematically assess whether any clinical trial patients exposed to natalizumab had evidence of incipient PML or any other opportunistic infection.

Patients involved in CD and RA trials were also included if the last infusion of natalizumab was within twenty months of dosing suspension in February 2005. MS patients prescribed natalizumab by their physicians had only received 1 to 3 infusions of natalizumab following initial approval in November 2004 and were not systematically reviewed, but prescribing physicians were notified by a "Dear Healthcare Provider" letter recommending evaluation and reporting of adverse events. Referred cases were eligible for IAC evaluation.

The primary responsibility of the IAC was to assess patients who had been referred to them based on any of the following: (1) any active neurological deterioration for which PML could not be excluded as a diagnosis, (2) MRI abnormalities for which PML could not be ruled out, and (3) CSF with detectable JC viral DNA titers. The IAC made an independent and final decision as to whether or not a patient had PML and made related recommendations to the Sponsor and investigators. The IAC prospectively established criteria for the neuroradiologic evidence and laboratory assays for the diagnosis of PML. A diagnosis of "confirmed PML" was defined by

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1 IAC members:
Dr. Eugene O. Major, PhD, Chief, Laboratory of Molecular Medicine and Neuroscience, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA, an expert in the virology of the JC virus; the Chair of the IAC.
Dr. David Clifford, Professor of Neurology, Washington University School of Medicine, St. Louis, MO, USA, an expert in the management and treatment of the neurological aspects of HIV and PML, served as committee's clinical expert.
Dr. Tarek Yousry, Professor and Chief of Neuroradiology, Institute of Neurology, Queen Square, London, UK, an expert on the imaging of neuroinflammation, served as the committee's neuroradiology expert.

presence of progressive clinical disease, MRI signs typical of PML, detection of JC viral DNA in CSF, or pathologic confirmation. Sufficient evidence to exclude PML consisted of 1) lack of progressive neurological disease, 2) MR lesions not typical of PML or stable over time, 3) no detectable JC viral DNA in the CSF if the MRI was suspicious. A case was deemed "indeterminate" if there was clinical or MRI suspicion of PML and follow-up clinical, MRI, or CSF data could not be obtained.

A total of 3,826 eligible study participants (2,248 MS patients, and 1,578 CD/RA patients) were notified to report to their treating physician/investigators for an assessment. Investigators were requested to perform the assessment procedure, including medical history, neurological examination, brain MRI, and CSF collection. Blood samples were also collected for PCR analysis of JC viral DNA as an exploratory adjunct. MRI scans were assessed by Central Reader Centers with expertise in neurological disorders, including the two Central Reader Centers for the original Phase 3 MS studies. A consensus guideline was developed prospectively to standardize criteria to help distinguish MS white matter abnormalities from those of PML (Display 3-19).

In all, 3,389 (89%) study patients with MS, CD, or RA were assessed by their treating physician, 3,116 of whom had received natalizumab. The remaining 273 patients had received placebo as part of a clinical trial and were included as a control group. Of the 437 that were not assessed, 377 were accounted for, whilst the remaining 60 (22 MS patients, 38 CD/RA patients) were lost to follow-up.

Amongst the 3,389 patients who participated, 2,046 were MS study patients, over 97% of whom were seen within 3 months of their last natalizumab dose. Six MS patients were referred to the IAC for further evaluation. Of these clinical trial patients, five were referred due to neurological worsening and one due to possible PML based on MRI findings. MRI scan review effectively ruled out the diagnosis of PML in the five patients referred based on clinical concern. Repeat MRI and CSF analysis excluded PML in the case referred based on MRI findings.

An additional three MS cases were referred to the IAC; one by the Sponsor (pediatric case) and two from the post-marketing setting. Based on review of all information on the pediatric case, the IAC determined that the case was not PML. One case from post-marketing was deemed not PML based on improvement clinically and on MRI, as well as the absence of JCV detection in CSF at 2 different time points. The second case from post-marketing was classified as "indeterminate" since CSF and follow-up MRI could not be obtained. The IAC felt that this patient's neurological symptoms were most likely to be MS progression.

Of the 1,349 CD/RA patients who participated in the safety evaluation, 21% were seen within 3 months of their last dose, 91% within 6 months. Thirty-five patients were referred to IAC: one due to clinical or neurological symptoms, 32 based on suspicious changes on MRI, one due to high plasma JCV copy number, and one due to an inability to perform MRI in a patient with a normal neurological examination. The higher rate of referral to the IAC for CD compared to MS was predominantly driven by the lack of baseline MRI scans for comparison in the CD population. Most IAC-referred cases were deemed not PML based on review of neurological examination, MRI and, if available, CSF testing. For the 10 cases in which concern still remained, repeat MRI assessments were performed and all were diagnosed as "not PML" based

on lack of clinical progression, lack of MRI progression over two months following the initial MRI leading to referral to the IAC, and in some cases, results of CSF testing.

Although not essential, MRI scans of the brain with and without Gd-enhancement and a FLAIR sequence was a useful tool for excluding a diagnosis of PML in the MS cases. The existence of pre-treatment and on-treatment MRI scans increased specificity and assisted in interpretation of the follow-up MRI scans obtained at varying timepoints, especially in the setting when the patient's neurological condition was worsening. During the safety evaluation process, comparison to previous scan was required in approximately 35% percent of MS cases because of the presence of lesions for which PML could not be definitely excluded. After comparison to a prior scan, the neuroradiologist was able to exclude PML in greater than 99% of MS cases.

CSF was available for testing in 396 patients. JCV was not detected in any of these cases, including 19 patients referred to IAC for evaluation based on clinical or MRI criteria. In addition to samples from patients treated with natalizumab, the Sponsor collaborated with the Karolinska Institute and NIH to evaluate plasma and CSF samples from 411 patients with MS and other neurological disorders to serve as CSF and plasma controls. No detectable JCV was found in these CSF samples, confirming the specificity of the CSF assay for only active cases of PML. Each of the three patients with confirmed PML had JC viral DNA detected by this system.

Plasma was tested for the presence of JC viral DNA as an exploratory measure. The entire consenting study population (2,370 patients) was evaluated using a high-throughput automated system of DNA extraction and PCR analysis. In addition, a random subset of samples was assessed using a manual low-throughput method. Although the manual method was demonstrated to be an order of magnitude more sensitive than the high-throughput system, given the techniques involved, testing using this method was only possible in approximately 10% of the overall population (209 patients). Of the 2,370 patients from the safety evaluation tested for JCV viremia, only 5 patients (0.2%) had detectable JC viral DNA, 3 of whom had never received natalizumab. In addition, JC viral DNA was not detected in the 411 samples from the Karolinska Institute. These results were confirmed using the manual extraction method. In addition, of the random subset of 209 patients tested by the manual method, an additional 5 (2.4%) samples had detectable JC viral DNA. None of the patients with detectable JC viral DNA in their plasma by either method had clinical features or MRI findings suggestive of PML.

Serum samples were also available from the three patients with confirmed PML from both before and after diagnosis. Only one patient, the patient with CD, had detectable JC viral DNA in the serum prior to onset of symptoms. The other two patients had no detectable JC viral DNA despite being symptomatic clinically for the disease and having changes on brain MRI.

The observations in these groups of patients is consistent with the data from the literature demonstrating that the presence of JC viral DNA in plasma is neither predictive nor diagnostic of PML.

Summary of PML Safety Evaluations

The comprehensive safety assessment launched by the Sponsor following the identification of PML in natalizumab-treated patients uncovered no additional confirmed cases of PML in the over 3,000 patients examined. Nearly all patients who had received natalizumab in recent MS, CD, and RA studies were accounted for during the assessments, making it unlikely that any cases of PML were missed. The occurrence of PML was limited to two MS cases and one CD case, as originally described. The incidence of PML amongst subjects treated with natalizumab in clinical trials in MS and CD is therefore approximately 1/1,000 with a 95% CI ranging from 0.2 to 2.8/1,000. Plasma testing proved to be neither predictive, nor diagnostic of PML, consistent with the published literature (Kitamura *et al*, 1990; Tornatore *et al*, 1992; Dorries *et al*, 1994; Sundsfjord *et al*, 1994; Agostini *et al*, 1996; Dubois *et al*, 1996; Knowles *et al*, 1999; Dorries *et al*, 2003). Indeed. clinical and MRI abnormalities were present in two of the three patients with PML before JC viral DNA was detected in the plasma. In addition, JC viral DNA was detected in plasma in several subjects in the study who had no clinical or radiographic signs of PML, including three who had never received natalizumab. These results suggest that, plasma JCV testing is not useful in predicting the likelihood of PML in asymptomatic patients. Physicians and patients should remain vigilant for signs and symptoms of PML and have a low threshold to suspend treatment and initiate appropriate diagnostic work-up (MRI, CSF analysis) in natalizumab-treated patients presenting with new neurological decline.

3.7 LABORATORY ABNORMALITIES

In addition to the expected pharmacologic effect of natalizumab on the elevation of lymphocyte counts, a mild, transient reduction in hemoglobin concentrations was noted during natalizumab therapy. The mild decrease in hemoglobin levels was not of clinical significance during the trials, and was readily reversible on natalizumab withdrawal.

There were no notable abnormalities in any other laboratory values associated with natalizumab treatment, including tests of hepatic or renal function.

3.8 IMMUNOGENICITY

In the Phase 3 studies, anti-natalizumab antibody responses were categorized as “transiently” antibody-positive or “persistently” antibody-positive. Transiently antibody-positive patients had detectable anti-natalizumab antibodies at a single time point and were antibody-negative at subsequent time points. The formation of transient antibodies to protein is a common occurrence and is likely due to the formation of IgM or transient low affinity IgGs (Smith *et al*, 1997; Wabl *et al*, 1999). Transient positivity for anti-natalizumab antibodies led to a temporary diminution of natalizumab efficacy in this population, but efficacy was regained by 6 months when antibodies were no longer detected. Transient antibodies had no impact on safety. Persistently antibody-positive patients had detectable anti-natalizumab antibodies on two or more occasions separated by at least 42 days or had no follow-up samples taken after a single positive value. In each of the Phase 3 MS studies, 6% of patients developed persistently-binding antibodies against natalizumab. Patients persistently positive for anti-natalizumab antibodies experience a loss of efficacy and increase in certain infusion-related events.

3.9 SAFETY IN SUBGROUPS

Adverse events were examined by sex, race, body weight, concomitant disease, and geographic region to determine whether the 300 mg fixed dose of natalizumab was safe in these populations. There appeared to be no consistent pattern of risk associated with any of these intrinsic and extrinsic factors and natalizumab treatment. Increasing weight was associated with increased diarrhea in both MS and CD, while arthralgia, depression, and nausea may be more common in the heaviest CD subjects. Other events occurred most commonly in the highest and lowest extremes of body weight, although not consistently so. Also, there were no concomitant diseases that increased the risk of more serious events, such as hypersensitivity-like reactions, including a history of immunological disease. Natalizumab was not studied adequately in subjects over age 65, in subjects with renal and hepatic impairment, or in pediatric patients. The efficacy, safety, and appropriate dosing in these populations are not known.

In summary, the safety profile of natalizumab appeared to be similar in each of the subgroups examined.

3.10 CONSEQUENCES OF STOPPING THERAPY

The consequences of stopping natalizumab therapy were carefully evaluated in the Phase 2 study, MS231, which involved 213 patients who were randomized to receive 6 monthly infusions of placebo, 3 mg/kg natalizumab, or 6 mg/kg natalizumab. Patients were followed for 7 months after the last infusion. During that time, relapses and other adverse events were recorded, and MRI scans were performed 4 months and 7 months after the last dose of natalizumab. Comparisons were made between the placebo group and the two natalizumab dose groups. As expected, the proportion of patients experiencing relapse, as well as the frequency of relapses, rose in the natalizumab group to levels comparable to those in the placebo group after the cessation of study drug. Moreover, there was a gradual rise in the proportion of active MRI scans in the natalizumab group to levels comparable to that of the placebo group after the cessation of therapy. Thus, the cessation of natalizumab treatment leads to the loss of efficacy, but there is no evidence of an increase in disease activity beyond that which would have been expected had there been no treatment with natalizumab, i.e., rebound. Therefore, MS patients who discontinue natalizumab therapy do not have an increased risk for marked increase in disease activity.

3.11 DRUG INTERACTIONS

In Study 1802, administration of Avonex appeared to be associated with an increase in the serum concentrations of natalizumab in a small cohort where intensive pharmacokinetic sampling was performed. However, based upon a comparison of the mean post-hoc parameter estimates from the population pharmacokinetic analysis, steady-state clearance and half-life values differed between patients taking concurrent Avonex (Study 1802) and natalizumab monotherapy (Study 1801), but only by approximately 5%. The magnitude of these changes in clearance and half-life were not considered clinically significant. In addition, natalizumab was well tolerated when administered to 589 patients in combination with Avonex for up to 120 weeks in Study 1802. It is notable that the two reports of PML in the MS database occurred in patients receiving concomitant Avonex. Thus, the risk of PML with natalizumab treatment may be increased by

concomitant treatment with interferon β, though this could have occurred in two patients on combination therapy due to chance alone (p=0.23). More study would be required to ascertain the effect of interferon β on the risk of PML when used concurrently with natalizumab.

The safety of natalizumab in combination with GA was evaluated in Study 1803. In this study, natalizumab was administered over 6 months to patients who continued to receive 20 mg of daily GA. There were no interactions between GA and the pharmacokinetics or α4-integrin receptor saturation of natalizumab. However, this study was of insufficient size or duration to establish the long-term safety or efficacy in this population.

No data are provided on the efficacy, safety, and possible interactions with higher dose interferon preparations (Rebif, Betaseron/Betaferon).

Given the discussion above, the Sponsor is recommending that natalizumab be used as a monotherapy and is warning against combining natalizumab with other immunomodulatory and immunosuppressive agents, except for short courses of corticosteroids for the treatment of acute relapses.

3.12 POST-MARKETING SAFETY

Between the approval of natalizumab in the US in November 2004 and the time of voluntary suspension of marketing in February 2005, it is estimated that approximately 7,000 patients were treated with natalizumab, the majority of whom received between 1 and 3 doses. A detailed review of deaths, serious infections, malignancies (serious and non-serious), serious hypersensitivity reactions, serious infusion reactions, serious hepatic dysfunction, serious hematological events, serious cardiac events, serious CNS events, and serious psychiatric events was performed through 1 June 2005. The safety profile of natalizumab observed in the post-marketing setting is generally consistent with the adverse event profile observed in the clinical trial safety database and is consistent with the proposed natalizumab product labeling.

There have been no confirmed cases of PML or other opportunistic infections identified in the post-marketing setting. Many of the adverse reactions were hypersensitivity-like in nature. Reports of allergic reactions, mainly involving a rash that occurred with the second infusion, are consistent with adverse events seen in the integrated clinical trial safety database. Most of the infections reported in the post-marketing setting were consistent with typical community-acquired pneumonia. There was one case of herpes encephalitis, which resulted in death, and one case of herpes meningitis with full recovery as described above (Section 3.6.3.2).

The conclusions that can be drawn from the safety data received from post-marketing reports are limited by the short period of time that the drug was available, but do not raise any concerns about previously unknown risks of the use of natalizumab.

3.13 SAFETY SUMMARY

The safety of natalizumab has been evaluated in over 3,900 patients, accounting for more than 5,500 patient-years of exposure. In the placebo-controlled experience, 2,799 patients with MS

and CD are included, accounting for 3,336 patient-years of placebo-controlled exposure. Based upon these analyses, it is possible to make several conclusions regarding the overall safety of natalizumab:

- Other than PML, the safety profile following the completion of the Phase 3 studies in MS and CD is quite similar to that at the time of the initial approval in the MS indication.
- Common and serious adverse events were similar in natalizumab-treated patients and control patients and consistent with the current product labeling.
- Once-monthly infusions of natalizumab were well tolerated with few infusion-related effects.
- Approximately 4% of MS patients experienced a hypersensitivity reaction; of these patients, approximately 1% experienced a serious reaction.
- The overall incidence and rate of common and serious infections were similar in natalizumab-treated patients and control patients.
- Serious opportunistic infections, including PML, occurred uncommonly in natalizumab-treated patients. Opportunistic infections were mostly observed in patients with CD, in association with immunosuppressant use or other significant co-morbidities.
- A comprehensive safety evaluation of natalizumab-treated patients confirmed that there were a total of three cases of PML (two in patients with MS and one in a patient with CD), two of which were fatal. This represents an approximate incidence of PML of 1 per 1000 (95% CI: 0.2 to 2.8 per 1000).
- Approximately 6% of patients who received natalizumab in clinical studies developed persistent anti-natalizumab antibodies, which were associated with loss of efficacy and a higher incidence of infusion-related adverse events.

3.14 PATIENT SELECTION BASED UPON EFFICACY AND SAFETY

An important part of maximizing the benefit-risk profile of natalizumab is appropriate patient selection. Natalizumab may not be appropriate for all patients. Natalizumab has demonstrated efficacy in two significant patient populations:

1) treatment-naïve patients with mild to moderate disability (EDSS 0 to 5.0) with recent clinical disease activity (1 relapse in the year prior to study entry), and

2) patients with mild to moderate disability with continuing disease activity despite treatment with β-interferon (1 relapse in the year prior to study entry while receiving Avonex).

It is appropriate, therefore, that natalizumab be considered to treat these active MS patients. However, natalizumab should be used only as monotherapy. Given the available data, it is

unclear whether the risk of developing PML is increased when natalizumab is used with immunomodulators or immunosuppressants as compared with monotherapy. Likewise, it is unclear whether natalizumab when combined with these agents is more advantageous than natalizumab alone. Unless the efficacy of combining the therapies is directly compared to that of natalizumab monotherapy, and until the contribution of concomitant immunomodulators to the risk of PML in the setting of natalizumab use is clarified, physicians will be warned against the use of natalizumab in combination with immunomodulatory or immunosuppressive treatments.

There are a few additional patient groups where the use of natalizumab may not be justified, either because data are lacking or because the benefit/risk ratio is altered:

- *Patients without evidence of relapsing disease.* Patients without evidence of inflammatory activity clinically or by MRI, such as those with relatively "benign" inactive disease, or chronic-progressive forms of MS, were excluded from the Phase 3 trials and therefore may not be appropriate to receive natalizumab.

- *Patients with a single clinical event without features suggestive of MS.* Although natalizumab had a consistent effect in relapsing patients regardless of baseline disease activity, it has not been evaluated in these types of patients.

- *Patients who are clinically stable on current therapy (that is, patients who are relapse–free on one of the approved therapies).* Patients who appear to be responding well to one of the approved therapies may not be immediate candidates for natalizumab. However, if safety or tolerability concerns exist on current treatment, or imaging studies indicate active inflammatory sub-clinical disease, natalizumab treatment would be appropriate.

- *Patients who are immunocompromised from any cause, including use of immunosuppressant medications.* Immunocompromised patients have an independent risk factor for PML and other opportunistic infections. Therefore, these patients should not receive natalizumab.

- *Patients who have previously suffered a hypersensitivity reaction to natalizumab.* Re-dosing of natalizumab following a hypersensitivity reaction was not assessed in the Phase 3 program. Until these data are available, all patients with infusion-related hypersensitivity reactions, defined as urticaria with or without associated systemic symptoms, should be discontinued from further natalizumab.

- *Patients who develop persistent antibodies to natalizumab.* Persistent antibodies against natalizumab lead to a loss of efficacy and an increase in infusion-related side effects. Patients who develop antibodies should discontinue treatment with natalizumab due to decreased benefit potential and increased risk.

3.15 CONCLUSIONS

Through detailed safety analyses, we have identified PML as a rare, but significant, risk. In addition, serious non-PML opportunistic infections have been observed in natalizumab-treated patients, mostly in CD patients in association with concurrent immunosuppressant use or other significant co-morbidities. In addition, we have identified patient populations in whom the benefit-risk profile is less well defined who should not receive this treatment. The occurrence of these infections highlights the need for a comprehensive risk management program in the post-marketing setting focused on appropriate use conditions and assessment and minimization of the risk of PML and other serious opportunistic infections. This is part of the Risk Management Action Plan proposed in Section 4.

4 RISK MANAGEMENT PLAN

If TYSABRI is re-introduced in the US market, Biogen Idec and Elan will implement a comprehensive risk management plan. This plan is being developed in collaboration with the FDA and in accordance with FDA's Guidance on this topic. The TYSABRI risk management plan is designed to both minimize the risk of PML and to assess further the risk of PML and overall safety of TYSABRI.

The program has risk minimization and risk assessment components (Display 4-1) and consists of three key elements:

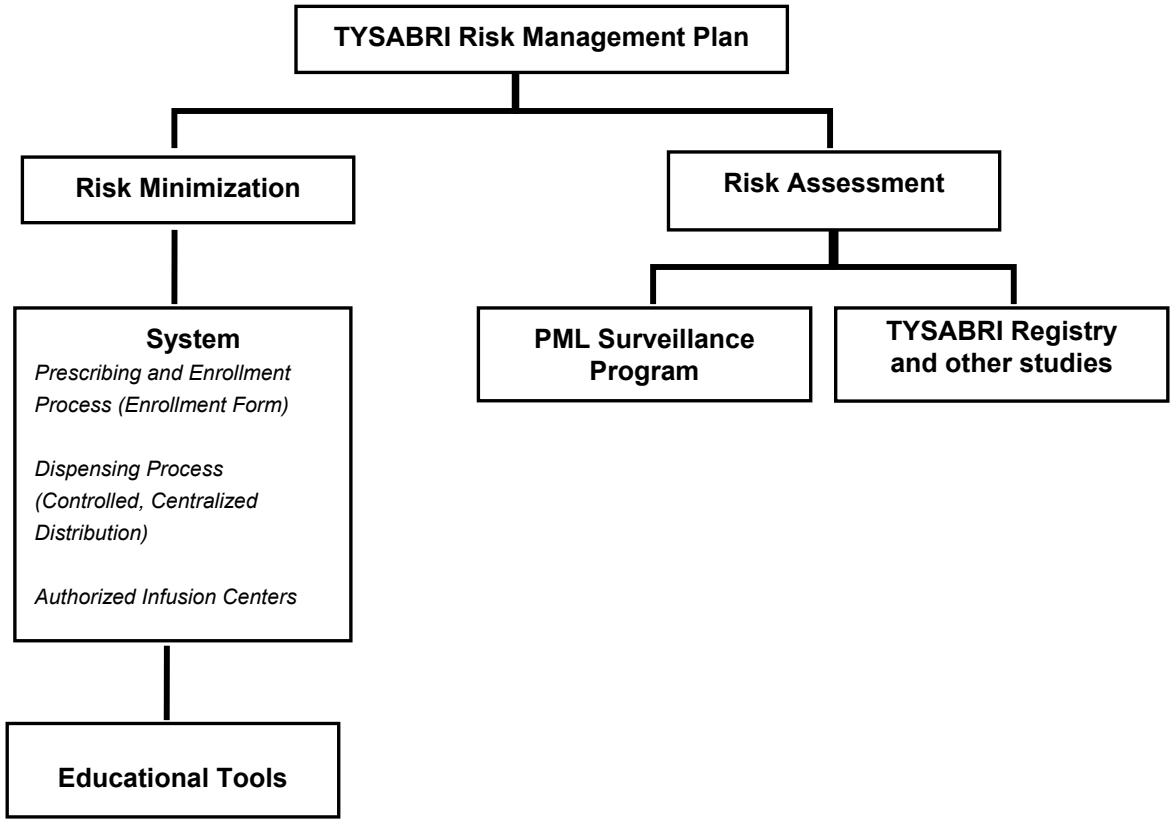
1) a Prescribing, Enrollment and Dispensing System

2) Educational Tools, and

3) a PML Surveillance Program, a large post-marketing safety registry, and other clinical studies.

Biogen Idec and Elan will continually assess the success of the risk management plan and the information that it generates, report the outcomes to FDA, and act promptly to revise and improve the plan, as necessary, in order to achieve its goals.

Display 4-1 The TYSABRI Risk Management Plan



4.1 RISK MINIMIZATION

The goals of risk minimization are:

- *To promote informed risk-benefit decisions regarding TYSABRI use in MS patients.* Prescribing physicians and their patients should know that TYSABRI is associated with an increased risk of PML and that TYSABRI is prescribed only for the treatment of relapsing MS.
- *To minimize the risk of PML.* Patients who are at risk of developing PML should be excluded from TYSABRI treatment. Thus, physicians should know that TYSABRI is contraindicated in patients who are immunocompromised and that concurrent use of TYSABRI with immunosuppressant or immunomodulatory agents is strongly discouraged.
- *To minimize death and disability due to PML.* Early detection and immune-reconstitution may improve outcome in PML. Thus, it is important that 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 any continuously worsening symptoms lasting over several days to their physician.

There are several unique aspects about the medical management of patients with MS and the administration of TYSABRI that allow for successful implementation of the proposed risk minimization plan.

1. *TYSABRI is prescribed by physicians who specialize in the care of patients with MS.*

In the US, patients with MS receive medical treatment by a relatively small group of physicians, primarily neurologists. Approximately 6,000 physicians treat 90% of patients with MS. This is in contrast to 170,000 family practitioners that treat primary care diseases in the US. Biogen Idec has a dedicated force of physicians and sales representatives that interact with neurologists and other healthcare professionals who care for patients with MS. Consequently, Biogen Idec can readily reach nearly all physicians who will prescribe TYSABRI.

Because PML is a disease of the central nervous system, the targeted prescribers of TYSABRI are also the best-qualified physicians to diagnose and manage PML. Neurologists have the expertise to monitor subjects for signs and symptoms indicative of PML and select appropriate diagnostic tests to diagnose a patient with PML.

2. *Patients with MS are knowledgeable about their treatment options.*

Patients with MS are generally a young, highly-motivated patient population. In a recent survey, 94% to 99% of patients with MS were aware of their treatment options, including β-interferons and GA (Biogen Idec, data on file). During the period when TYSABRI was available commercially, Biogen Idec found that 79% of patients with MS were aware of TYSABRI's introduction. Also, Biogen Idec has sought feedback from patients with MS and found that the

risk of PML with TYSABRI has been broadly disseminated in the MS community. Thus, the targeted patient population will want to learn more about the risks of PML with TYSABRI.

3. *Discussion of risks and benefits associated with MS treatment is routine in neurology practice.*

Prescribing a disease-modifying treatment for a serious, disabling disease such as MS is a carefully considered and deliberate decision. Based upon feedback from neurologists and MS patients, this decision usually involves a detailed discussion between the physician and patient about the risks and benefits of available therapies. Some neurologists already use an informed-consent form prior to initiating therapy with an immunomodulatory agent such as β-interferon or GA. The TYSABRI risk minimization strategy builds upon this existing decision-making process.

4. *TYSABRI is administered monthly by healthcare professionals in infusion centers*.

In contrast to therapies that are self-administered in the patient's home, TYSABRI is administered intravenously every month at an infusion center under the care and management of infusion nurses. This regulated, procedure-oriented dispensing environment allows for monthly monitoring of patients for potential symptoms suggestive of PML and for effective dissemination of information on TYSABRI that reinforces appropriate use.

The program has a Prescribing, Enrollment, and Dispensing System and Educational Tools designed to inform neurologists, infusion nurses, and MS patients about PML risk and to minimize the risk of PML and its health consequences. The system and tools build upon the unique aspects of the medical management of patients with MS and the administration of TYSABRI.

4.1.1 Prescribing, Enrollment, and Dispensing System

The Prescribing, Enrollment, and Dispensing System allows distribution of educational material to physicians, infusion nurses, and patients, and enforces appropriate use of TYSABRI. The system consists of two processes: a prescribing and enrollment process and a dispensing process.

4.1.1.1 Prescribing and Enrollment Process

The prescribing and enrollment process enrolls patients and physicians into the risk management program following submission of an enrollment form.

Prior to starting TYSABRI treatment, the physician will provide the patient with the Patient Information Leaflet (described in Section 4.1.2.2), will ask the patient to read it, and will discuss the information with the patient. Once the decision to use TYSABRI is made, the physician and patient will complete the enrollment form. The enrollment form includes a TYSABRI prescription and a Patient-Physician Acknowledgement. The physician and patient will sign the Patient-Physician Acknowledgment to document that they discussed and understood TYSABRI risks and benefits, including the risk of PML, and that the physician is prescribing TYSABRI for the treatment of relapsing MS. The enrollment form is faxed to Biogen Idec and the patient and

physician information are entered into the Biogen Idec database, thus initiating enrollment into the TYSABRI risk management program.

Use of the enrollment form is expected to be high. During the initial marketing period for TYSABRI, a strong majority of patients who received TYSABRI enrolled into a similar patient support program. Each enrolled patient is assigned a case-manager who can answer questions about TYSABRI, provide insurance coverage research, and match the patient to an appropriate infusion center. These services will be provided again upon TYSABRI's re-introduction and are another reason for patients and physicians to use the enrollment form. In addition, educational materials for TYSABRI will inform physicians of the need to use the enrollment form for all TYSABRI-treated patients and Biogen Idec and Elan sales representatives will be trained to reinforce the importance of using the form with all neurologists. Finally, neurologists and MS patients have provided feedback on the TYSABRI risk management program and strongly support the use of the enrollment form. With the re-introduction of TYSABRI, Biogen Idec and Elan will closely monitor compliance with the use of the enrollment form and expect that greater than 90% of patients and physicians will use the form to initiate TYSABRI therapy. Biogen Idec and Elan are working with FDA to determine the best way to assure high compliance with use of the enrollment form.

4.1.1.2 Dispensing Process

The dispensing process employs a new controlled, centralized distribution system to deliver TYSABRI only to authorized infusion centers. An infusion center will become "authorized" only after Biogen Idec and Elan have trained the infusion nurses at the center on the appropriate use of TYSABRI and the risk of PML. This training is compulsory for all infusion centers that will be administering TYSABRI. Biogen Idec and Elan will ship TYSABRI only to authorized infusion centers.

Specifically, Biogen Idec and Elan representatives will visit infusion centers and will train the infusion nurses on the risks and benefits of TYSABRI using the Package Insert, educational materials on the risk of PML with TYSABRI, and the Patient Information Leaflet. Infusion centers will be expected to distribute the Patient Information Leaflet to their patients. In addition, Biogen Idec and Elan representatives will also provide the infusion centers with a Patient Checklist that is to be completed by the infusion nurse for each patient prior to each monthly infusion. This Patient Checklist serves as a tool for the nurse to document prior to each infusion that the patient does not have symptoms suggestive of PML and that the patient remains eligible to receive TYSABRI. The Package Insert, Patient Information Leaflet, and Patient Checklist will also be included in each shipment of TYSABRI so that infusion centers will have a ready supply of these tools.

The controlled, centralized distribution of TYSABRI allows Biogen Idec and Elan to track all TYSABRI shipments, i.e., the location and number of vials shipped to each infusion center. Biogen Idec and Elan will ensure that TYSABRI is delivered only to authorized infusion centers prior to each shipment. In addition, product distribution data will be reconciled against the list of authorized infusion centers. Thus, Biogen Idec and Elan control shipment of TYSABRI only to

sites with infusion nurses who have been trained regarding the risks of TYSABRI and its appropriate use.

4.1.2 Educational Tools

Biogen Idec and Elan sought feedback from neurologists, infusion nurses, and MS patients to develop educational materials that would be useful, effective, and practical. Based upon this feedback, Biogen Idec and Elan have developed a number of tools that will educate healthcare providers, and thus their patients, about the potential risk for PML with TYSABRI treatment. These educational tools will be distributed directly to the infusion centers and physicians with subsequent dissemination to patients. Patients and healthcare providers can also access up-to-date information at Biogen Idec's website, www.TYSABRI.com, and through a toll-free phone-line to Biogen Idec's call center. In addition, Biogen Idec and Elan are proposing important revisions to the package insert.

4.1.2.1 Revised Package Insert

The revised package insert contains important new information on the safety of TYSABRI. This information is found in a prominent Boxed Warning, Indication, Contraindications, and additional Warnings. The Precautions and Adverse Reactions sections have also been revised. Key components are highlighted below:

- Boxed Warning:

  TYSABRI is associated with an increased risk of PML. PML causes death and disability.

  Warning about concurrent use with immunomodulators (e.g., β-interferon) and immunosuppressants (e.g., azathioprine).

  Healthcare professionals should be alert to any new signs or symptoms that may be suggestive of PML. TYSABRI dosing should be suspended immediately at the first signs or symptoms suggestive of PML and an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain should be performed. Cerebrospinal fluid analysis for JC viral DNA may also be useful for diagnosis of PML.

  TYSABRI is indicated *only* for the treatment of patients with relapsing forms of multiple sclerosis to delay the progression of disability and to reduce the frequency of clinical exacerbations.

- Indication:

  TYSABRI is indicated *only* for the treatment of patients with relapsing forms of multiple sclerosis to delay the progression of disability and reduce the frequency of clinical exacerbations. The safety and efficacy of TYSABRI beyond two years are unknown. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

- Contraindication:

  TYSABRI is contraindicated in patients who have or have had PML. TYSABRI should not be administered to patients who are immunocompromised, including those immunocompromised due to HIV, hematological malignancies, organ transplants, antineoplastic or immunosuppressive therapies.

- Additional Warnings:

  An MRI scan should be obtained prior to initiating therapy with TYSABRI because this may be helpful to differentiate PML from MS in patients with new signs or symptoms suggestive of PML.

  Concurrent use of antineoplastic or immunosuppressive agents may increase the risk of infections, including opportunistic infections.

- Adverse Reactions:

  Opportunistic infections (e.g., JC virus caused progressive multifocal leukoencephalopathy, pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis) in TYSABRI-treated patients.

4.1.2.2 Patient Information Leaflet

The Patient Information Leaflet is intended to provide information to patients with MS on the risks of TYSABRI treatment, including the risk of PML. In addition, the leaflet instructs patients to promptly report any continuously worsening neurological symptoms to their physician, thereby reinforcing the importance of early detection of PML. The Patient Information Leaflet will be widely disseminated. In addition to distribution to prescribers and infusion centers, the leaflet will be available on websites hosted by Biogen Idec and distributed to patient groups such as the National Multiple Sclerosis Society (NMSS).

4.1.2.3 Patient-Physician Acknowledgement

The Patient-Physician Acknowledgement is part of the enrollment form. It documents that the patient and prescribing physician have made an informed risk-benefit decision regarding using TYSABRI to treat relapsing MS. The tool also reinforces the importance of early detection of PML through clinical vigilance. Patients and physicians will sign the Patient-Physician Acknowledgement, send it to Biogen Idec, and keep a copy in the patient's chart.

By signing the Patient-Physician Acknowledgement, the physician acknowledges that he or she has read the full prescribing information for TYSABRI, is aware that TYSABRI is associated with an increased risk of PML, which causes death or disability, has discussed the risks and benefits of TYSABRI with his or her patient, and is prescribing TYSABRI for the treatment of relapsing MS. The physician also acknowledges that the patient is not immunocompromised, and

has instructed the patient to promptly report to his or her physician any continuously worsening symptoms that persist over several days.

By signing the Patient-Physician Acknowledgement, the patient acknowledges that he or she has read the Patient Information Leaflet, is aware that TYSABRI is associated with an increased risk of PML, which causes death and disability, has discussed the risks and benefits of TYSABRI with his or her physician, and understands that it is important to promptly report to his or her physician any continuously worsening symptoms lasting over several days.

4.1.2.4 Pre-Infusion Patient Checklist

Use of the Patient Checklist by infusion nurses is designed to minimize inappropriate use of TYSABRI and facilitate early detection of PML through regular, monthly assessments in infusion centers. Infusion nurses will be instructed to complete the Patient Checklist for each patient prior to each TYSABRI infusion. Using the checklist, the infusion nurse screens the patient for potential symptoms of PML. Specifically, the checklist prompts the nurse to ask the patient about continuously worsening neurological symptoms that have persisted over several days, e.g., new or sudden decline in thinking, eyesight, balance, or strength. If a patient answers NO to any question on the Patient Checklist, the nurse is instructed not to administer TYSABRI and to refer the patient to his or her physician. Based on feedback from infusion nurses, it is expected that the checklist will be easily integrated into the current set of infusion protocols used by infusion nurses.

The proposed concepts that will be included in the Patient Checklist are as follows:

- The patient will be receiving TYSABRI for the treatment of relapsing MS.
- The patient has NEVER been diagnosed with PML.
- The patient is NOT currently experiencing any continuously worsening symptoms that have persisted over several days. *Examples include: new or sudden decline in their thinking, eyesight, balance, or strength.*
- The patient is NOT known to have the following conditions: HIV, hematologic malignancy (e.g., leukemia, lymphoma), organ transplantation.
- The patient is NOT currently receiving treatment with an anti-neoplastic or immunosuppressant agent. *Examples include: azathioprine, cladribine, cyclophosphamide, methotrexate, mitoxantrone, mycophenolate mofetil, rituximab.*
- The patient has read the TYSABRI Patient Information Leaflet.

4.1.2.5 "Dear HCP" and "Dear Patient" Letters

Following re-introduction of TYSABRI, Biogen Idec and Elan will send "Dear HCP" letters to all neurologists and physicians who would potentially prescribe TYSABRI. The letter will describe the safety warnings and information in the revised label and the risk management program. The sponsors will also send a letter to patients who would potentially be prescribed TYSABRI (these

patients will be obtained from Biogen Idec's current database of MS patients). This "Dear Patient" letter will inform MS patients about TYSABRI's re-introduction and direct them to speak with their physicians to make an informed decision about its appropriateness as a treatment for themselves.

4.1.2.6 Additional Education

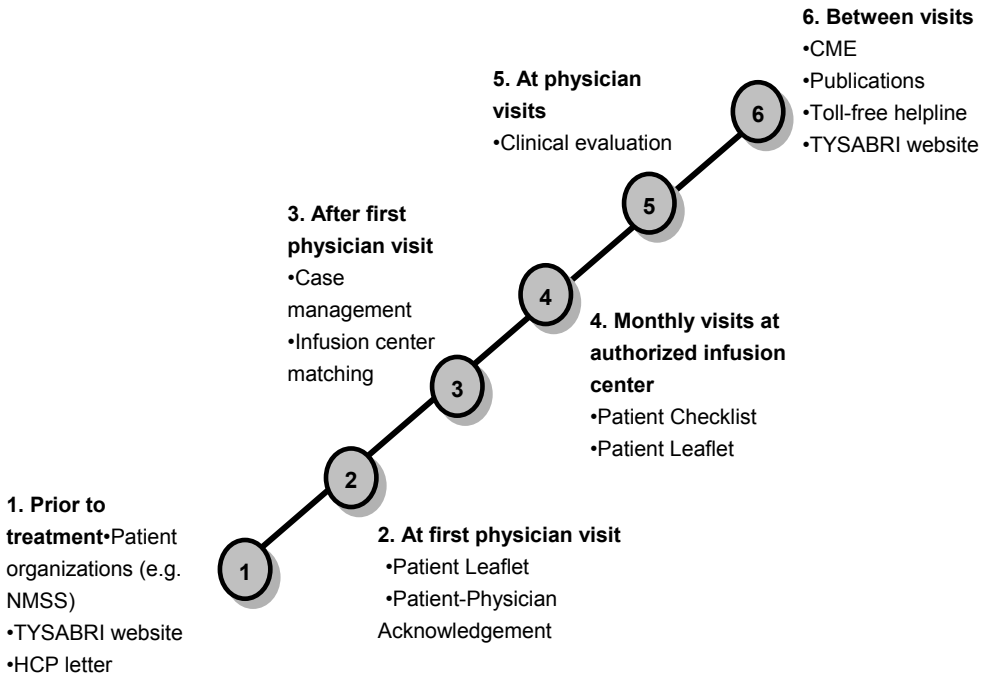
Additionally, Biogen Idec and Elan will support various other initiatives to provide educational materials about TYSABRI's PML risk and appropriate-use conditions, to neurologists and infusion nurses for use with MS patients.

- In collaboration with independent experts, Biogen Idec and Elan have developed an algorithm for the diagnosis of PML. This diagnostic algorithm will be published in a peer-reviewed journal and will be made available to physicians.
- When TYSABRI is re-introduced, Biogen Idec and Elan will develop press materials that will publicize the Dear HCP letter and its contents. This will facilitate broad dissemination of consistent messages regarding PML risk and appropriate-use conditions for TYSABRI.
- All neurologists in Biogen Idec's database, including physicians who have completed and submitted an enrollment form, will receive periodic educational mailings. Physicians will be expected to share this information with their patients.
- All patients and physicians will have access to Biogen Idec's TYSABRI website, www.TYSABRI.com, and a toll-free helpline to Biogen Idec's call center, where risk information about TYSABRI will be conveyed. The call center is staffed by trained Biogen Idec employees who will be prepared to answer patient questions related to TYSABRI. This toll-free help-line also provides patients and physicians access to health care professionals in Biogen Idec's medical information department who can also answer questions related to TYSABRI.
- Biogen Idec and Elan will support educational initiatives through the NMSS, and will facilitate the generation and dissemination of medical information on PML and TYSABRI through media such as review articles, seminars, and Continuing Medical Education (CME) programs directed at neurologists and infusion nurses.

4.1.3 Summary of Risk Minimization Plan

The key elements of the risk minimization plan are integrated within the risk minimization program as shown in Display 4-2. The risk minimization plan enables patients to receive information about the risk of PML and appropriate use of TYSABRI at multiple points: in the physician's office when the treatment decision is made, in his or her home, at monthly visits to the infusion center, and at follow-up visits to his or her physicians. The provision of tools at multiple points of care, including the point of prescribing and the point of infusion, continuously encourages appropriate-use of TYSABRI and reinforces awareness of the risk of PML.

Display 4-2 Integrated View of TYSABRI Risk Minimization Plan



In summary, Biogen Idec and Elan believe that the proposed plan will minimize the risk of PML in patients who will benefit from TYSABRI therapy. As designed, the program allows MS patients access to TYSABRI treatment while providing effective risk minimization.

4.2 RISK ASSESSMENT

The goals of risk assessment are:

- To determine the incidence and risk factors for PML with TYSABRI treatment.
- To further assess the overall safety profile of TYSABRI. This includes the safety profile beyond 2 years of dosing, the nature and incidence of opportunistic infections and malignancies, and the effect of TYSABRI on humoral and cell-mediated immunity.

The key program to assess the incidence and risk factors for PML is the PML Surveillance Program. In addition, Biogen Idec and Elan plan to conduct several studies, including a large post-marketing safety registry, to better characterize the overall safety in patients receiving TYSABRI treatment.

4.2.1 PML Surveillance Program

The PML Surveillance Program is designed to assess the incidence and risk factors for PML with TYSABRI treatment. The program is a comprehensive reporting and data collection system for any PML event that may occur in TYSABRI-treated patients. In contrast to passive reporting of events in the post-marketing setting, the PML Surveillance Program intensively stimulates the reporting of PML. The program pro-actively asks physicians via the enrollment form whether any of their TYSABRI-treated patients have developed PML. Physicians who answer yes are also asked whether they have reported the case to Biogen Idec.

Physicians will be enrolled into the PML Surveillance Program when they submit an enrollment form at initiation of TYSABRI treatment. If he or she does not complete any additional enrollment form for 6 months, then Biogen Idec will send this physician a mail-card that asks about the occurrence and reporting of any patients with PML as described above. If the physician fails to reply within a reasonable timeframe, then Biogen Idec will contact the physician by telephone to ask the same questions. Thus, physicians will be reminded at least every 6 months (through the enrollment form, and if needed, through mailings and direct telephone calls) to report any new case of PML to Biogen Idec.

For any report of PML, Biogen Idec will contact the physician for more detailed information about the patient, using a PML-specific questionnaire. Biogen Idec will request full clinical details as well as submission of source documentation (such as clinical findings, MRI, and CSF JCV results). A case of PML will be confirmed based on pre-defined criteria that have been developed in collaboration with external independent experts. In addition, if the diagnosis of PML is indeterminate, the Sponsors may submit the source documentation on the case to an external PML expert for an opinion of the diagnosis. Finally, a qualitative analysis of the case will be performed to identify any potential risk factors for PML development (e.g., prior or concomitant therapies, underlying co-morbidities, etc). Thus, any potential case of PML will be carefully evaluated.

Feedback from neurologists and MS patients confirms that obtaining a better understanding of the risk of PML with TYSABRI is an important goal. Thus, neurologists and MS patients are very motivated to participate in a PML risk assessment program such as the PML Surveillance Program. Furthermore, neurologists confirmed that if they had a case of PML in a TYSABRI-treated patient, they would report such a case to Biogen Idec as soon as possible, regardless of the reminders planned in the PML Surveillance Program. Thus, it is expected that every case of PML in TYSABRI-treated patients will be reported to Biogen Idec, even if the case occurs in the small minority of patients (and their physicians) who have not completed an enrollment form. This also means that a case of PML is likely to be reported to Biogen Idec in a timely fashion.

Biogen Idec and Elan will report all confirmed PML cases to the FDA on an expedited basis, i.e., within 15 days of receipt of the case.

In addition, cases of confirmed PML will be tabulated on a periodic basis (i.e., every 3 months after re-introduction) and provided to the FDA expressed as:

- cases per estimate of total population exposed (cases/persons exposed)
- cases per estimate of person-years of TYSABRI exposure
- a qualitative analysis of any confirmed cases of PML will be made to identify any potential risk factors for PML development (e.g., prior or concomitant therapies, underlying co-morbidities, etc).

The PML Surveillance Program will allow real-time benefit-risk assessment after re-introduction of TYSABRI; any meaningful change in the benefit-risk assessment would trigger prompt and appropriate action, including discussion with FDA.

4.2.2 TYSABRI Registry

The clinical trial safety database for TYSABRI is reasonably large and provides an assessment of safety with TYSABRI administered for 2 to 3 years. To obtain safety with long-term use in a real-world setting, Biogen Idec and Elan will conduct a large post-marketing safety registry.

The TYSABRI Registry will be a multi-national, observational cohort study that will enroll approximately 5,000 patients with MS on TYSABRI treatment and follow them longitudinally for up to 5 years. The primary objective of the TYSABRI Registry is to determine the incidence of serious infections, including serious opportunistic infections, in patients with MS treated with TYSABRI. The secondary objective will be to determine the incidence of malignancies with long-term use. The study will collect all serious adverse events. The sample size of 5,000 patients will allow the detection of rare adverse events that occur with an incidence of 0.06% with a 95% probability of success.

4.2.3 Safety of Re-Exposure to TYSABRI

In order to evaluate the safety of TYSABRI with re-exposure after an interval without treatment, Biogen Idec and Elan will conduct two multi-national, open-label studies. Approximately 1,500 patients with MS who previously received TYSABRI treatment during their participation in clinical studies will be enrolled.

4.2.4 Effect of TYSABRI on Immune Function

Biogen Idec and Elan will conduct a study to evaluate the effect of TYSABRI on humoral and cellular immunity to recall and neo-antigens. Both cellular (*ex vivo* proliferation responses) and humoral (specific serum immunoglobulin) immune responses to recall vaccine antigens (e.g., tetanus and pneumovax) and naïve antigens (KLH) will be studied with or without natalizumab treatment. Data from this study may provide information into potential immunological risk factors for PML with TYSABRI treatment.

4.2.5 Studies on the Epidemiology of PML

The epidemiology of PML in either the general population or in patients with MS has not been well characterized. Thus, Biogen Idec and Elan will conduct epidemiological studies to: (1) quantify the incidence of PML in the general population, as well as in MS and other autoimmune diseases, and (2) assess the impact of selected characteristics, risk factors, and other variables on the risk of developing PML. Two datasets will be studied: claims and eligibility data from the PharMetrics Patient-Centric Database and both electronic and hard copy medical record data from a large Midwestern health plan.

4.2.6 Non-Clinical Studies

Biogen Idec and Elan will initiate specific *in vitro* studies to investigate the effects of natalizumab interaction with specific cellular targets and functions with respect to JC virus infection and replication. In addition, the effects of short-term α4-integrin inhibition in rodent and guinea pig experimental autoimmune encephalomyelitis will be evaluated, specifically with respect to effects on immune function. These non-clinical studies, while exploratory, may provide insights into potential immunological risk factors for PML with TYSABRI therapy.

4.3 EVALUATION PLAN

Biogen Idec and Elan are committed to evaluating the effectiveness of the risk management plan for TYSABRI and reporting the results on a regular basis to the FDA. The following sources of data will be utilized: enrollment form data, PML Surveillance Program, TYSABRI Registry, Distribution data (vials shipped), and surveys of prescribing physicians, patients, and infusion nurses. The evaluation metrics and methods are outlined in Displays 4-3 and 4-4 below. The data in Display 4-3 will be provided to the FDA at 6 and 12 months after re-introduction of TYSABRI, and annually thereafter.

Biogen Idec will provide the FDA with Periodic Adverse Event Reports (PAERs) and Periodic Safety Update Reports (PSURs) on a regular basis, per regulatory requirements. The PAERs and PSURs will include adverse events (including events such as serious and/or opportunistic infections, malignancies, and hypersensitivity reactions) that may be spontaneously reported in the post-marketing setting. Data from the PML Surveillance program (i.e., description of any PML cases, analysis of risk factors, and PML occurrence rate) and serious adverse events that have occurred in the TYSABRI Registry will also be included in these periodic reports. These reports will be provided to the FDA every 3 months for the first 2 years after re-introduction, then semi-annually thereafter.

In conclusion, this evaluation plan will allow Biogen Idec and Elan to assess the effectiveness of risk minimization and risk assessment efforts in an ongoing fashion and to improve the plan, as necessary.

Display 4-3 Risk minimization evaluation: metrics and methods

Metric	Evaluation method
Prescribing physician knowledge and behavior regarding TYSABRI and PML	Prescribing physician survey
Patient knowledge regarding TYSABRI and PML	Patient survey
Infusion nurse knowledge and behavior regarding TYSABRI and PML	Infusion nurse survey
Availability and use of tools at infusion centers and physician offices	Prescribing physician survey Infusion nurse survey
Percentage of prescribing physicians who have completed Patient-Physician Acknowledgement(s)	Enrollment forms received by Biogen Idec and distribution data
Percentage of patients receiving TYSABRI who have completed a Patient-Physician Acknowledgement	Enrollment forms received by Biogen Idec and distribution data
Percentage of enrollment forms that have signed Patient-Physician Acknowledgement	Enrollment forms received by Biogen Idec
Percentage of vials shipped to authorized infusion sites	Distribution data
Proportion of TYSABRI prescriptions written concurrently with immunosuppressants/immunomodulators or to patients known to be immunocompromised	TYSABRI Registry

Display 4-4 Risk assessment evaluation: metrics and methods

Metric	Evaluation method	Expected date
PML cases and outcomes per estimate of persons/person-years of exposure, analysis of PML risk factors	PML Surveillance Program	Every 3 months for first 2 years, then semi-annually
Post-Marketing Safety	Post-Marketing Spontaneous Reports	PAER/PSUR* every 3 months for first 2 years, then semi-annually
Incidence of opportunistic infections and malignancies	TYSABRI Registry	Yearly Interim Clinical Study Reports
Safety with Re-Treatment	IND Annual Report for Re-Dosing Studies	Annually (final Clinical Study Report when studies completed)

*PAER=Periodic Adverse Event Report; PSUR= Periodic Safety Update Reports

4.4 CONCLUSION

Biogen Idec and Elan have developed a comprehensive risk management plan that encompasses both risk minimization and risk assessment. The plan is designed to promote informed risk-benefit decisions between physicians and patients regarding the use of TYSABRI, to minimize morbidity and mortality due to PML through early detection with clinical vigilance, and to minimize the risk of PML by treating only non-immunocompromised patients and strongly discouraging concurrent use with immunosuppressants or immunomodulators.

The risk management plan was designed specifically to take advantage of the unique aspects about the medical management of patients with MS and the administration of TYSABRI, i.e., TYSABRI is prescribed by neurologists and administered monthly in infusion centers under the supervision of healthcare professionals, and patients with MS are a very motivated patient population. The program includes enrollment of prescribers and patients and a controlled, centralized distribution of TYSABRI only to authorized infusion centers that Biogen Idec and Elan have trained on PML risk and appropriate use of TYSABRI. Through the use of multiple tools, the program facilitates the education of physicians, infusion nurses, and MS patients about the appropriate use of TYSABRI, the risk of PML, and the importance of early detection of PML through clinical vigilance. To help assure the use of the product only in MS, Biogen Idec and Elan's sales representatives will detail TYSABRI only to neurologists and other HCPs involved in the care of MS patients. In addition, Biogen Idec and Elan also plan several clinical studies to determine the incidence of, and risk factors for PML with TYSABRI treatment and to further assess the overall safety profile of TYSABRI.

The TYSABRI risk management plan strikes a balance between the need to minimize the risk of a rare, but serious, adverse event and provide TYSABRI's significant benefit to appropriate patients with MS, a disease of high unmet need, without placing unnecessary burden on neurologists, infusion nurses, and MS patients. Finally, Biogen Idec and Elan will continually assess the risk management plan and the information that it generates and, as needed, make modifications to improve its effectiveness.

5 BENEFIT-RISK CONSIDERATIONS

Most individuals diagnosed with MS suffer a relentlessly progressive disease that is characterized by unpredictable acute exacerbations, increasing physical disability, and cognitive impairment; these symptoms are often made worse by secondary neuropsychiatric complications. The burden and disability of MS are equal to or greater than that suffered by patients of other autoimmune diseases, such as RA and CD.

Approved therapies for broad use in relapsing forms of MS are effective in some patients, but over time, most treated patients will experience progressive disease activity. At best, the interferon products and GA reduce relapse rates by one-third; further, only Avonex and Rebif (both interferons) show an impact on disability progression. Indeed, as many as 75,000 individuals currently receiving available therapies in the US report ongoing symptoms of active disease.

Although the safety experience with the interferons and GA is generally acceptable, many patients find these products difficult to tolerate, resulting in a high rate of noncompliance with treatment regimens and therapy discontinuation. As such, the pool of patients who have stopped therapy - despite suffering active disease - is growing steadily and is currently estimated to exceed 50,000 in the US. Thus, as many as 125,000 patients in the US are in need of more effective or better tolerated therapies. The demand for better therapeutic options for MS patients is obvious and compelling.

The Sponsor responded to MS patients' need for newer options for relapsing MS by developing natalizumab. The FDA approved natalizumab in November 2004 for the treatment of relapsing forms of MS following priority review. At that time, patients and physicians viewed the efficacy, safety, and convenience profile of the product very favorably, as evidenced by the remarkably rapid adoption of the drug in the marketplace. Approximately 7,000 patients received at least one infusion within the first three months after approval. The great demand for this new product by a highly informed patient group and their physicians is a clear demonstration of the significant unmet need of MS patients for more and better therapies.

The approval of natalizumab was followed 3 months later by a safety signal to which the Sponsor immediately and effectively responded. After receiving notice of one confirmed and one possible case of PML in MS clinical trial patients who had received over 2 years of treatment with natalizumab, the Sponsor conferred immediately with FDA and swiftly opted to voluntarily withdraw natalizumab from the market and halt all dosing. The purpose of the suspension was to minimize any additional risk to treated patients, while undertaking an extensive investigation to understand the significance of these findings. A third case was identified a few weeks later in a CD patient misdiagnosed as having a malignant astrocytoma.

In collaboration with the FDA, other regulatory authorities, the NIH, and top PML experts, the Sponsor developed a clinical protocol designed to enable examination of all patients treated with natalizumab for the possibility of undiagnosed PML or other opportunistic infections. The protocol design included examination of brain MRI and plasma from most patients and cerebrospinal fluid from a significant minority to look for evidence of JCV replication.

Results of this extensive investigation are presented in detail within this document (Section 3.6.3.3). In summary, 3,389 patients (91% of all clinical trial subjects) were evaluated during this period, 3,116 of who had received natalizumab. Ultimately, the occurrence of PML was limited to the original three patients: two MS patients and one CD patient. We therefore estimate the risk of PML in natalizumab-treated patients to be 1 per 1,000 (95% CI 0.2 to 2.8 per 1,000). We do not yet know whether this estimate applies to any patient considering natalizumab therapy or to unique subsets of potential patients. The three patients who developed PML were either receiving concomitant treatment with an immunomodulator or were immunocompromised from prior immunosuppressant use (both MS patients received interferon β-1a and the CD patient was lymphopenic from prior immunosuppressant therapy). Our general knowledge of PML indicates that altered immune function is a critical risk factor for the development of this disease.

In parallel with the investigation described above, the Sponsor re-reviewed all existing natalizumab preclinical studies to look for subtle evidence of susceptibility to opportunistic infection; no signals were detected. In addition, the Sponsor completed the analysis of the 2-year efficacy and safety data from both Phase 3 MS trials (results detailed in Sections 2 and 3). In summary, the 2-year findings confirm and expand the 1-year results that formed the basis of the initial natalizumab priority review and accelerated approval. Excluding the occurrence of PML, 2-year safety data from both studies remained consistent with those described in the original package insert.

Natalizumab is an immunomodulatory agent that offers great benefit to patients with relapsing MS. Like other highly active drugs used to treat autoimmune diseases, it is not without risk. Although knowledge about the pathobiology of MS is lacking, it is clear that a component of the disease is driven by autoimmunity. Indeed, immunomodulating therapies have become the cornerstone of treatment for the majority of patients with autoimmune disorders such as MS, CD, and RA. Unfortunately, with the clinical efficacy of these agents comes the risk of significant mechanism-based side effects. The risks of medications that modulate immune function in order to treat serious chronic diseases have been well recognized over the past several years. Medicines such as the TNFα antagonists (e.g., infliximab, adalimumab, and etanercept) are potent modulators of immune function and are approved for numerous serious autoimmune diseases such as RA, CD, psoriasis, psoriatic arthritis, and ankylosing spondylitis. Although very effective, these agents are associated with serious adverse events, particularly infections that have been associated with significant morbidity and mortality.

To date, the aforementioned serious adverse events associated with other immunomodulatory agents have been managed by educating prescribers and patients about the potential risks, as well as continually investigating the risk with continued exposure. The efficacy of these products and the disabling nature of the diseases they treat necessitate that physicians and patients carefully consider the benefits and risks of treatment prior to treatment initiation. Physicians and patients must decide on a daily basis whether these treatments are right for them. The situation should be no different for natalizumab. Physicians and patients should have the opportunity to decide if natalizumab is right for them. The feedback that we have had to-date from neurologists and MS patients is that they want access to a more effective treatment for MS and are willing to have these discussions and make choices regarding the risks.

The Sponsor recognizes the responsibility to share our current knowledge regarding appropriate use conditions for natalizumab with patients and prescribers. The risk management plan described in Section 4, manages appropriate access to drug. The program is based upon revised product labeling that would clearly limit its use to relapsing MS patients, warn against use in combination with other immunomodulators, and describe newly identified risks of natalizumab treatment. The Sponsor will educate prescribers that natalizumab should not be used in immunocompromised patients and should only be used as a single disease modifying agent (i.e., monotherapy) and not in combination with other immunomodulatory or immunosuppressive treatments (except for short courses of corticosteroids for the treatment of acute relapses). In addition, the distribution of natalizumab will be limited to physicians fully informed about the risks of the drug so that both physicians and patients can make informed decisions regarding treatment. Furthermore, the risk management plan establishes a comprehensive program that enables the Sponsor to proactively recognize new safety signals and rapidly inform patients, physicians, and the FDA of important new findings. The Sponsor has exhibited the ability and desire to respond swiftly and effectively to safety signals and will continue to do so.

Natalizumab holds promise as a highly effective treatment for MS patients suffering from this disabling disease. The degree of efficacy and overall safety profile demonstrated in the clinical studies, combined with the ability to manage the risk for PML with the revised label and risk management plan, lead to a benefit-risk ratio that is favorable and should allow physicians and patients to consider natalizumab as a treatment. Like other immunomodulatory agents currently on the market with risks and benefits, natalizumab is a highly effective treatment that is not without risk. MS patients should have the opportunity to make informed choices as to whether natalizumab is right for them.

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