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MEDICAL REVIEW

CLINICAL REVIEW

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Established Name Natalizumab
Proposed Trade Name Tysabri
Therapeutic Class monoclonal antibody
Applicant Biogen Idec, Inc.

Priority Designation P

Formulation recombinant humanized IgG4 antibody to
 α 4-integrin
Dosing Regimen 300 mg intravenous infusion every 4 weeks
Indication treatment of relapsing forms of multiple
sclerosis
Intended Population relapsing multiple sclerosis

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This licensing application is for accelerated approval of natalizumab, (proposed trade name: Tysabri), for the treatment of patients with relapsing forms of multiple sclerosis (MS), to reduce the frequency of clinical exacerbations. Two multicenter, randomized, double-blind, placebo-controlled studies (Studies 1801 and 1802) provide the primary evidence of safety and efficacy. Both studies are two years in duration; however, this regulatory action is based on results achieved through approximately one year in the ongoing studies.

Study 1801 enrolled subjects with active relapsing-remitting MS (RRMS). Most of these patients had never received any of the currently approved MS therapies. Study 1802 enrolled subjects with clinically active RRMS, who had been receiving a standard MS therapy (Interferon β -1a) on a weekly basis during the year prior to study entry. In both investigations, subjects had experienced at least one clinical relapse during the year prior to study entry, providing evidence of clinically active disease.

Subpart E of the BLA regulations (21 CFR 601 subpart E) allows accelerated approval of new biologics that provide meaningful therapeutic benefit over existing treatment for serious or life-threatening illnesses, based on a surrogate endpoint that is reasonably likely to predict clinical benefit. This application provides evidence of efficacy for only one year of natalizumab administration, based on reduction in MS relapse rates. For MS therapies, a relapse endpoint may be accepted as evidence of effectiveness; however, the clinical meaningfulness of a decrease in the relapse rate through only one year is uncertain. Drugs currently approved for MS have each demonstrated evidence of a benefit at 2 years in order to gain marketing approval. However, the magnitude of natalizumab's treatment effect at one year is quite robust, and is deemed reasonably likely to predict a clinical benefit at two years. Therefore, the effect at one year can be considered as a surrogate for an effect at two years. The usual limitations of a surrogate must be borne in mind, in particular the difficulty in reliably predicting the magnitude of natalizumab's effect at two years. Completion of the ongoing studies is essential to the verification of the safety and efficacy observed at one year.

Accelerated approval requires that the new drug provide evidence of the potential to address an unmet medical need. Many MS patients continue to have exacerbations while taking one of the available first-line MS therapies. None of the currently available therapies have proven efficacy when used as an add-on therapy. Study 1802 provides evidence that natalizumab is effective as an add-on therapy for subjects who continue to have relapses while on a first-line therapy (Interferon β -1a). Therefore, natalizumab has the potential to address an unmet medical need.

The clinical review recommendation is for accelerated approval of natalizumab for the treatment of patients with relapsing forms of MS, to reduce the frequency of clinical exacerbations.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific risk management activities are recommended for the marketing of natalizumab.

1.2.2 Required Phase 4 Commitments

1. To conduct a pharmacokinetic study of at least 6 months duration to assess whether chronic administration of natalizumab in combination with glatiramer acetate results in a drug interaction that suggests the need for a dose adjustment of natalizumab.
2. 
3. To verify that the clinical benefit of reduction in exacerbations is sustained with continued natalizumab administration. This will be accomplished by completing the ongoing studies C-1801 and C-1802 through the planned two years and submitting the results along with appropriate labeling changes.
4. To further evaluate the safety of natalizumab and the efficacy of natalizumab on physical disability. This will be accomplished by completing the ongoing 2-year studies (C-1801 and C-1802) and submitting the study results, including all safety and efficacy data, for all study subjects through Week 128 or subject withdrawal. Appropriate labeling changes will be proposed as part of this submission.
5. To conduct a concurrently controlled pregnancy registry for women who become pregnant while exposed to natalizumab, to identify the pregnancy outcomes and postnatal health status of the children. This commitment includes submitting a revision to the label, once the design of the registry is finalized, that informs patients and physicians of the existence of the registry.
6. To conduct a study to measure the effects of at least a six-month course of natalizumab on immune responses in subjects with relapsing forms of MS that evaluates the effect of natalizumab on percentages of lymphocytes including CD3+, CD4+, CD8+, as well as B and NK cells, and the associated α 4-integrin expression and binding site saturation.
7. To conduct a study of the effect of natalizumab on neoantigen immunization with respect to interval from dosing and the potential for induction of tolerance and assessment of tolerance using a series of two booster immunizations post-natalizumab clearance. If such a study provides evidence that natalizumab has an effect on neoantigen immunization, the applicant commits to conducting a study of the effect of natalizumab on patient response to a neovaccination after withdrawal of natalizumab treatment.

8. To conduct a study of the effect of natalizumab on recall antigen responses in a chronic dosing situation, including the levels of antibody to the recall antigen and the ability of a booster immunization to raise antibody levels.
9. To use new binding and neutralizing assays to conduct a study of the development and general time course of immunogenicity at any level of titer, and the relationship of natalizumab immunogenicity to safety events.
10. Pending the development of a new assay for antibodies to natalizumab, to use the current assay to assess the immunogenicity of natalizumab by conducting a study of patients who are at least three months post-treatment, so that no natalizumab is present in serum to interfere with the assay. The applicant will analyze these immunogenicity data with consideration of the reasons for discontinuing natalizumab and the adverse event profile of the subjects.

1.2.3 Other Phase 4 Requests

There are no additional requests for clinical Phase 4 studies.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Natalizumab is a monoclonal antibody for intravenous (IV) administration. Natalizumab binds to a human integrin that is highly expressed on the surface of white blood cells. Natalizumab may produce its clinical effect in MS by interfering with the movement of inflammatory white blood cells from the blood vessels into the brain and spinal cord.

The applicant has studied natalizumab for the treatment of relapsing MS and Crohn's disease (CD). Studies in CD are ongoing. This application is for the treatment of MS, to decrease the frequency of relapses. Studies 1801 and 1802, the two pivotal efficacy and safety trials, randomized 942 and 1171 subjects, respectively, to receive either natalizumab or placebo for up to 28 months. The safety review considers a database of 1617 MS patients who have been exposed to natalizumab for a median duration of 20 months.

1.3.2 Efficacy

Studies 1801 and 1802 are the two Phase 3, multicenter, randomized, double-blind, placebo-controlled studies that provide the primary evidence of effectiveness for natalizumab in MS, and are the focus of this review. Both studies enrolled patients who experienced at least one clinical relapse during the prior year, thereby providing evidence of active disease. For each study, the primary endpoint was the annualized relapse rate at one year, comparing the natalizumab group to the placebo group.

Study 1801 enrolled primarily patients who had never received any interferon beta or glatiramer acetate. Patients were randomized 2:1 to receive natalizumab (n=627) or placebo (n=315) every four weeks for up to 28 months. Study subjects who received natalizumab experienced an annualized relapse rate of 0.25 relapses/patient-year, compared to 0.74 relapses/patient-year in the placebo group (p<0.001). This represents a relative reduction of 66%.

Study 1802 was an “add on” study that enrolled patients who had experienced one or more relapses despite treatment with Avonex[®] (Interferon β-1a) during the year prior to study entry. Patients were randomized (1:1) to receive natalizumab (n=589) or placebo (n=582) every four weeks for up to 28 months. All patients continued to receive Avonex[®] throughout the study. Subjects who received natalizumab and Avonex[®] experienced an annualized relapse rate of 0.36 relapses/patient-year, compared to 0.78 relapses/patient-year in the placebo group (p<0.001). This represents a relative reduction of 54%.

In both Phase 3 studies, the three prespecified secondary endpoints at one year were the increase in the proportion of relapse-free subjects, the reduction in the number of new or newly enlarging T2 lesions on brain magnetic resonance imaging (MRI), and the reduction in the number of gadolinium-enhancing lesions on brain MRI. Natalizumab administration was associated with a statistically persuasive effect on each of these endpoints in both Phase 3 studies. In both studies, the salutary effects of natalizumab were also consistent across the major subgroups.

The decrease in relapse rate associated with natalizumab alone (Study 1801) is approximately twice the magnitude of the effect observed with registration trials for the currently available first-line therapies (Avonex[®], Betaseron[®], Copaxone[®], and Rebif[®]) for the proposed indication. Natalizumab is the first drug to show efficacy when used as an add-on to a current first-line therapy (Study 1802). The final results of the ongoing two-year studies will be necessary to verify the efficacy of natalizumab. There are no studies providing a direct comparison of natalizumab to any of the current first-line therapies.

1.3.3 Safety

A total of 1617 MS patients, in both controlled and uncontrolled studies, have been exposed to natalizumab, with a median duration of exposure of 20 months. Natalizumab appears to cause hypersensitivity reactions, an increased risk of some infections, headache, depression, joint pain, and menstrual disorders. Hypersensitivity reactions are strongly associated with the development of antibodies to natalizumab. The infections were predominately mild respiratory tract infections, influenza, and urinary tract infections. Serious adverse events were uncommon. In Study 1801, the most frequent serious adverse events associated with natalizumab were infections (2.1% versus 1.3% with placebo, including pneumonia [0.6%]), hypersensitivity reactions (1.3%, including anaphylaxis/anaphylactoid reaction [0.8%]), depression (0.8%, including suicidal ideation, [0.5%]), and cholelithiasis (0.8%). Natalizumab's overall safety profile was similar in Studies 1801 and 1802, and appears favorable compared to the currently available first-line MS therapies (Avonex[®], Betaseron[®], Copaxone[®], and Rebif[®]). However, there are no studies that provide a direct comparison of the safety of natalizumab to any of the current first-line therapies. Review

of the final results of the ongoing two-year studies, along with postmarketing experience, will be necessary to better characterize the safety of natalizumab.

1.3.4 Dosing Regimen and Administration

The recommended dose of natalizumab is 300 milligrams by IV infusion every four weeks. Patients should be observed during the infusion and for one hour after the infusion is complete. The infusion should be discontinued if there are any signs or symptoms suggestive of a hypersensitivity reaction. These signs and symptoms include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain.

1.3.5 Drug-Drug Interactions

After multiple dosing, Interferon β -1a (Avonex[®] 30 mcg IM once weekly) reduced the clearance of natalizumab by 30%. Although serum natalizumab levels would be expected to increase with co-administration of Interferon β -1a, the similarity of the natalizumab-associated adverse event profile between Study 1801 (in the absence of Interferon β -1a) and Study 1802 (with co-administered Interferon β -1a) suggests that co-administration of an interferon does not necessitate a change in the natalizumab dose to maintain safety.

Results of studies in MS patients taking natalizumab and concomitant interferon β -1a or glatiramer acetate are inconclusive with regard to the need to adjust the dose of interferon or glatiramer acetate.

1.3.6 Special Populations

The safety and efficacy of natalizumab have not been adequately studied in patients with chronic progressive MS, renal insufficiency, hepatic insufficiency, age \geq 65, age $<$ 18, or in women who are pregnant or nursing. Considering the low incidence of MS below age 16, the studies necessary to demonstrate safety and efficacy in a pediatric population would be highly impractical. Therefore, FDA approved the applicant's request for a waiver of the requirement to perform studies in the pediatric population. Natalizumab should be used during pregnancy only if clearly needed.

2 INTRODUCTION AND BACKGROUND

Multiple sclerosis is a chronic, inflammatory, possibly autoimmune, demyelinating disease of the central nervous system. Multiple sclerosis is a common cause of neurological disability in young adults, primarily affecting people between 20 and 40 years of age, and affecting women approximately twice as often as men. The disease affects approximately 300,000 patients in the US, with an annual incidence of approximately 1 to 5 per 100,000 (National MS Society).

Experts in the field generally recognize three clinical forms of MS: relapsing-remitting, secondary progressive, and primary progressive (Lublin and Reingold, 1996). Relapsing-remitting MS is the presenting form in up to an estimated 80 to 85% of patients, and involves recurrent attacks of neurological symptoms and signs (relapses or exacerbations) involving multiple areas of the nervous system. Attacks occur at variable time intervals, ranging from months to years apart. These exacerbations or relapses are followed by variable degrees of recovery (remissions). The majority of subjects with RRMS develop secondary progressive MS (SPMS) in which periods of stable recovery give way to neurological decline over time. About 50% of patients with RRMS will develop SPMS within 10 years of onset; the proportion approaches 80% after 25 years (Runmarker and Anderson, 1993).

The predominant tool used to measure the accumulation of disability is the expanded disability scale score (EDSS), which is determined by assessing the Kurtzke Functional Systems in each of 6 neurological areas (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, and visual). EDSS scores range from 0 (normal) to 10 (death) in 1/2-unit steps. Patients are fully ambulatory through EDSS 4.5, after which progressive impairment in ambulation becomes the predominating factor in the EDSS.

Diagnosis, especially for inclusion in clinical trials, has been codified over the years by consensus of the field, and published as formalized criteria and categories (Poser et. al., 1983). Diagnosis generally requires confirming at least two lesions, which must have occurred in different parts of the CNS and at different times (demonstrating dissemination of disease activity in both time and space). "T1-weighted" MRI performed after the infusion of gadolinium (Gd) is believed to show cranial lesions of acute onset, the contrast agent leaking through the normally impermeable endothelial barrier. These lesions may resolve over a period of months. "T2-weighted" MRI lesions are believed to represent fixed, residual pathology. Magnetic resonance imaging has become a standard procedure in the diagnosis of MS. Magnetic resonance imaging demonstrates the MS lesions scattered throughout the brain. While MRI lesions are not pathognomonic for MS, the pattern of lesions can be strongly suggestive. More recently, diagnostic criteria that place additional emphasis on MRI imaging (McDonald et. al., 2001) have become popular to define the MS population for clinical trials.

2.1 Product Information

Natalizumab is a recombinant humanized IgG4 κ antibody produced in murine myeloma cells. Natalizumab binds to the α 4-subunit of the α 4 β 1 human integrin (also known as VLA-4), which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Natalizumab is a new biological entity that blocks the interaction of the integrin with vascular cell adhesion molecule-1 (VCAM-1), additional ligands such as osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab also blocks the interaction of α 4 β 7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions inhibits migration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. Natalizumab may also suppress inflammatory reactions in diseased tissues by inhibiting the interaction of α 4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. Therefore, natalizumab may suppress inflammatory activity at the disease site and inhibit migration of additional immune cells to inflamed tissues.

Natalizumab is formulated as a solution. Each 15 mL dose contains 300 mg natalizumab; 123 mg sodium chloride, USP; 17.0 mg sodium phosphate, monobasic, monohydrate, USP; 7.24 mg sodium phosphate, dibasic, heptahydrate, USP; 3.0 mg polysorbate 80, USP/NF, in water for injection, USP at pH 6.1. Natalizumab is supplied as a sterile, colorless, clear to slightly opalescent concentrate for IV infusion.

Biogen Idec and Elan Pharmaceuticals have been partners in the development of natalizumab as a treatment for MS. However, Biogen Idec is the specified applicant for this submission.

Clinical scale lots of natalizumab were used in the two Phase 3 clinical trials (1801 and 1802) that form the primary support for this application. However, only one modestly-sized clinical trial (1803) has included administration of the commercial scale natalizumab that the sponsor proposes to market for the treatment of MS (see Section 4.1, Sources of Clinical Data, and Section 2.5.5, New Commercial Material, of this review and Dr. Elena Gubina's CMC review of this application).

Natalizumab's proposed trade name is Tysabri. In the medical literature, this product has been referred to as either natalizumab or Antegren.

The applicant proposes that natalizumab be indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations.

The applicant's proposed recommended dose of Natalizumab is 300 mg IV — infusion,

The applicant states that the safety and effectiveness of Natalizumab have not been adequately studied in pregnant women, nursing mothers, patients aged 65 years and older, and patients below the age of 18.

2.2 Currently Available Treatment for MS

MS therapies can be broadly divided into two categories: those directed against the immune system and intended to inhibit the disease process, and those intended to reduce symptoms. In general, the former have been less successful than the latter; however, it is immune modulator approaches that are likely to provide major advances in effective therapy.

2.2.1 Immune Modulators Approved for Treatment of MS

There are currently five drugs approved in the United States for treatment of MS. Betaseron[®] (Interferon β -1b), Avonex[®] (Interferon β -1a), and Rebif[®] (Interferon β -1a), are interferons licensed for the treatment of relapsing forms of MS. Copaxone[®] (glatiramer acetate) is a non-interferon licensed for RRMS. Betaseron[®] is indicated for use in ambulatory RRMS patients to reduce the frequency of clinical exacerbations. Avonex[®] is indicated for the treatment of relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Rebif[®] is indicated for the treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Copaxone[®] is indicated for reduction of the frequency of relapses in patients with relapsing-remitting MS. These four products are the first and second-line treatments for MS, and each is administered by subcutaneous or intramuscular injection. Novantrone[®] (Mitoxantrone), a cancer chemotherapeutic agent, was approved in 2000 for patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS. Due largely to its cumulative dose-limiting cardiotoxicity, Novantrone[®] has been used in only a very small proportion of the MS population.

In clinical use, the interferon betas and glatiramer acetate have a variety of adverse effects, which vary for the different products. These adverse effects include injection site reactions, flu-like symptoms, fever, chills, headache, fatigue, asthenia, myalgia, and anorexia. Hematological (lymphopenia, neutropenia, thrombocytopenia, and anemia) and hepatic toxicities are known side-effects of interferon beta therapy. There is also concern because of the potential for interferon betas to cause depression.

It is estimated that approximately 350,000 patients globally are currently receiving treatment with one of the approved MS therapies (applicant's internal data). However, despite the demonstrated efficacy of these treatments and their widespread use, there is a substantial population of patients with relapsing MS who remain untreated for their disease. Many of these patients have disease with relatively little evidence of active inflammation clinically (relapses) or by MRI, and therefore choose not to begin treatment. Some patients have active relapsing MS but choose not to be treated because of fear of self-injection or potential adverse effects from the available treatments. Other patients have tried an existing therapy but discontinued treatment due to intolerance, adverse effects, or lack of efficacy.

Of those patients who do receive treatment, a substantial number continue to experience disease activity clinically and on MRI. This ongoing disease activity is expected because each of the approved medications produces only approximately a 30% reduction in relapse rate (Interferon

Study Group 1993, Jacobs et al, 1996; PRISMS Study Group, 1998; Johnson et al, 1995). Therefore, a substantial unmet medical need exists for MS treatments that offer more efficacy and are well-tolerated.

Although a variety of therapeutic strategies are widely used in clinical practice to manage continued disease activity while on treatment (e.g., switching therapy, changing dose and frequency of interferon, various combination treatments), these practices are largely empirical as there are no randomized, controlled trials to assess the efficacy or safety of these approaches. Therefore, there also exists a substantial unmet medical need for therapies that can be added to existing therapies to improve efficacy.

2.2.2 Other Immune Modulators and Immunosuppressants

Corticosteroids are used for treatment of acute exacerbations. Steroids can decrease the peak severity and duration of the acute exacerbations, but have not been proven to decrease the frequency of relapses or prevent the long term progression of disability.

Other immunosuppressants (e.g., azathioprine, cyclophosphamide, and methotrexate) have been studied for treatment of MS. However, their limited benefit and potential for significant side effects have prevented widespread use for MS.

Intravenous immunoglobulin (IVIG) infusions are believed by some investigators to be effective in treating MS, but are not widely used in the U.S., and do not have an approved indication for the treatment of MS.

2.2.3 Symptomatic Therapies

Numerous agents have been used for symptomatic benefit in MS. These include amantadine and pemoline for treatment of fatigue, baclofen (a muscle relaxant and antispasmodic), tizanidine and benzodiazepines to treat spasticity, urologic antispasmodics for bladder dysfunction, and a number of agents for neuropsychologic impairment and pain management, including benzodiazepines, antidepressants, and anticonvulsants. None of these agents slow the progression of the disease or influence the frequency of relapses.

2.3 Availability of Proposed Active Ingredient in the United States

Natalizumab is a new molecular entity that is not currently marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

Currently, no pharmacologically-related products are marketed. Accordingly, it is not possible to draw upon experience from pharmacologically related products.

Natalizumab is an immune-modulating agent; therefore, safety concerns include the potential for increased risks of infection and/or malignancy. Natalizumab is a biologic; therefore,

immunogenicity is a concern. Safety issues of infection, malignancy, and immunogenicity are discussed in Section 7 of this review.

Natalizumab is an IgG4 antibody that exists in two forms, as a bivalent antibody (two heavy chains and two light chains) and a monovalent antibody (one heavy chain and one light chain). Two formulations of natalizumab with differences in the proportion of bivalent versus monovalent antibody were found to be comparable in a clinical bioequivalence study (see CMC Review by Drs. Gubina, Kutza, and Zhang, and Clinical Pharmacology review by Dr. Mahmood). Theoretically, the monovalent natalizumab antibody may engage in scrambling with monovalent IgG4 antibodies to other antigens. Scrambling is the physical association of two monovalent IgG4 antibodies to different antigens to produce a functional bispecific antibody (Aalberse and Schuurman, Immunology, 2002). However, natalizumab administration in combination with other immunogenic MS therapies, including glatiramer acetate and all three currently approved beta-interferons, may provide an opportunity for scrambling between natalizumab monovalent antibodies and any IgG4 antibodies formed to the concomitant MS therapy. Particularly, antibodies to glatiramer acetate are primarily of the IgG4 type. However, the potential differential activity of natalizumab bivalent vs. monovalent antibody and the potential for natalizumab monovalent antibody to scramble with other monovalent IgG4 antibodies are theoretical concerns with unclear clinical implications. For additional discussion of these issues, see Dr. Lei Zhang's CMC review of this application.

2.5 Presubmission Regulatory Activity

2.5.1 Fixed Dosing Regimen

Natalizumab was administered using weight-adjusted dosing in Phase 1 and Phase 2 clinical trials in MS. Clinical trials later in the course of development, including the pivotal studies 1801 and 1802, used fixed dosing of natalizumab 300 mg IV every 4 weeks (see Section 4.1, Sources of Clinical Data). In a December 10, 2001 letter to the IND sponsor, FDA noted the change from weight-adjusted dosing to a fixed dose and advised the sponsor, "If this study [C-1801] or subsequent studies provide evidence that weight may influence either the safety or the efficacy of Natalizumab, then it may be necessary for you to obtain additional pharmacokinetic/pharmacodynamic data regarding Natalizumab, and/or conduct additional studies of the safety and efficacy of weight-adjusted dosing of Natalizumab for patients with multiple sclerosis." Explorations of natalizumab's efficacy and safety with respect to subject weight are a focus of this review.

2.5.2 Interaction of Natalizumab with Standard MS therapies

In a December 10, 2001 letter to the sponsor, FDA also expressed concern regarding the interaction of any new MS therapy with the standard MS therapies: "Substantial pharmacokinetic, pharmacodynamic, and safety data on the interaction of a potential new treatment with available standard therapies will be necessary in a license application." Largely

as a result of this advice, the add-on study with Avonex[®] (Study 1802) was designed and carried out.

2.5.3 Pediatric Waiver

On May 1, 2002, the applicant requested a pediatric waiver pursuant to 21 CFR 601.27(c). The FDA considered the low incidence of MS below age 16 and accepted the sponsor's certification that the studies necessary to demonstrate safety and efficacy in a pediatric population would be highly impractical. The FDA decision to approve the applicant's request was consistent with FDA precedent regarding other therapies for MS and was conveyed to the applicant in an August 2, 2002 letter.

2.5.4 Application for Accelerated Approval

The applicant has sponsored two ongoing Phase 3, randomized, double-blind, placebo-controlled studies (C-1801 and C-1802) which provide the primary basis for this license application (see Section 4.1, Sources of Clinical Data). Each Phase 3 study includes administration of natalizumab to MS subjects for up to 28 months. However, the IND sponsor pre-specified an analysis at approximately one year (see Section 6.1.3, Study Design, and Dr. Kallappa Koti's review of this application for a discussion of the timing of the "one-year" analysis) and pre-specified a primary endpoint based on the effect on relapse rate at the one-year analysis.

In review of previous applications for the treatment of MS, FDA has required data through two years of drug administration to support an indication for decreasing the frequency of clinical relapse (see review memorandum of Dr. Marc Walton). The applicant has applied for accelerated approval (see Guidance for Industry, Fast Track Drug Development Programs – Designation, Development, and Application Review, Center for Drug Evaluation and Research, July, 2004) based on data on the safety and efficacy of natalizumab through approximately one year of administration. The sponsor's basis for consideration of accelerated approval is the demonstration of an effect that addresses an unmet medical need, specifically the demonstration of clinical benefit when the agent is administered as add-on therapy to one of the currently approved agents (see Section 2.2.1, Immune Modulators Approved for Treatment of MS). To grant a license under accelerated approval, the FDA must also deem the one-year data as reasonably likely to predict a clinical benefit at two years. In effect, under accelerated approval, the effect on relapses at one year would serve as a surrogate for an effect on relapses at two years.

During a February 17, 2004 pre-BLA meeting, FDA agreed with the sponsor that, given the apparent magnitude of the treatment effect at one year, there was the potential for the data to serve as a surrogate for benefit at two years. The FDA also agreed that the potential to show benefit at two years, in combination with evidence suggesting that natalizumab addresses an unmet medical need, could support an application for accelerated approval (see review memorandum of Dr. Marc Walton).

2.5.5 New Commercial Material

During a February 17, 2004 pre-BLA meeting, FDA asked the sponsor to submit “data with regard to the comparability of the new commercial-scale product and the product used in the Phase 2 and Phase 3 clinical trials.” For further discussion of this issue, see Section 2.1, Product Information, of this review, the CMC Review by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang, and the Clinical Pharmacology review by Dr. Mahmood.

2.6 Other Relevant Background Information

Neither natalizumab nor any other anti-integrin is currently marketed anywhere in the world.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC Review concludes that the manufacture of natalizumab is well controlled and leads to a product that is pure and potent. However, there are limitations of the current assay for detection of antibodies to natalizumab. See CMC review by Drs. Gubina, Kutza, and Zhang, and Section 7.1.10, Immunogenicity, of this review.

3.2 Animal Pharmacology/Toxicology

The non-clinical toxicology review concludes that natalizumab is generally well tolerated in the animal models studied. The toxicities observed in animals were primarily extensions of the known pharmacologic activity of the drug. Non-clinical reproductive toxicology studies demonstrated that treatment with natalizumab has the potential to reduce fertility. See the Non-clinical Toxicology review by Dr. Barbara Wilcox.

The non-clinical pharmacology review concludes that toxicities of natalizumab in the reviewed pharmacology studies were limited to increases in circulating total leukocytes and differential lymphocyte, monocyte, eosinophil, and basophil counts. See the Non-clinical Pharmacology review by Dr. Anne Pilaro.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on data from clinical trials conducted by the applicant, Biogen Idec, in partnership with Elan Pharmaceuticals.

<u>Significant Submission(s) Reviewed</u>		<u>Document Date</u>
STN 125104/0	Original Submission	28-May-2004
STN 125104/0.001	Study 1803 Report Update	22-Jun-2004
STN 125104/0.002	Study 1803 Final Report	29-Jul-2004
STN 125104/0.003	Response to Clinical Information Request	03-Aug-2004
STN 125104/0.007	Response to Clinical Information Request	10-Sept-2004
STN 125104/0.011	Response to Clinical Information Request	21-Sept-2004
STN 125104/0.012	120-Day Safety Update	22-Sept-2004
STN 125104/0.027	Response to Clinical Information Request	05-Nov-2004
STN 125104/0.028	Revised Package Insert	05-Nov-2004
STN 125104/0.031	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.032	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.033	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.034	Response to Clinical Information Request	15-Nov-2004
STN 125104/0.036	Response to Clinical Information Request	16-Nov-2004

4.2 Tables of Clinical Studies

Natalizumab is being co-developed by Biogen Idec and Elan Pharmaceuticals for the treatment of RRMS and moderate to severe active CD. Table 1 summarizes the clinical trials initiated as part of development for the MS indication. The clinical trials in MS form the primary basis for this review. Clinical trials in CD and ulcerative colitis are described briefly in Table 2; however, they did not contribute materially to the evidence of effectiveness or safety for natalizumab in MS, and the data were considered primarily in terms of more serious safety events.

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Table 1: Clinical Development in Multiple Sclerosis

Study #	Goals	Population	Design	# of Doses	N	Natalizumab Dose	Result
Phase 1							
101	Safety, tolerability	Male normal volunteers	RD, DB, PC, DE	1	35	0.03 - 3.0 mg/kg	Tolerated
200	Safety, tolerability	RRMS, SPMS	RD, DB, PC, DE	1	28	0.03 - 3.0 mg/kg	Tolerated
224	Safety, PK	MS subjects receiving a beta-interferon	Open-label	1	38	3 and 6 mg/kg	Tolerated
221	PK, PD	RRMS, SPMS	RD, PC	1	39	1, 3, and 6 mg/kg	Tolerated, PK "dose-proportional"
Phase 2							
201	Preliminary efficacy - MRI	RRMS, SPMS	RD, DB, PC, 24-week duration	2	73	3 mg/kg	+ MRI
202	Preliminary efficacy - EDSS, MRI	RRMS, SPMS, acute exacerbation	RD, DB, PC, 14-week duration	1	180	1 and 3 mg/kg	+ MRI, - EDSS
231	Preliminary efficacy - MRI, EDSS, relapses	RRMS, SPMS	RD (1:1:1), DB, PC, DE, 6-month duration	6	213	3 and 6 mg/kg	+ MRI, - EDSS, + relapses
Phase 3							
1801	Confirmatory efficacy and safety - relapses, EDSS	RRMS	RD (2:1), DB, PC, 2-year duration	30	942	300 mg	See below
1802	Confirmatory efficacy and safety - relapses, EDSS	RRMS patients receiving a beta interferon	RD (1:1), DB, PC, 2-year duration	30	1196	300 mg	See below
Additional Clinical Trials							
1803	PK, interaction	RRMS patients receiving glatiramer acetate	RD (1:1), DB, PC, 6-month	6	110	300 mg	No PK/PD interaction
1804	Emergency use	5 y.o. girl, refractory MS	Open-label	10 (of 18 planned)	1	3 - 6 mg/kg	Died 5 months after discontinuing natalizumab
1805	PK, bioequivalence, compare formulations	Normal volunteers	Crossover	2	89	300 mg	Bioequivalent
1806	PK, bioequivalence, compare formulations	Normal volunteers	Crossover	2	86	300 mg	Bioequivalent
1808	Extension efficacy and safety	1801, 1802, 1803 completers	Open-label	Up to 24	144 (as of 7-04)	300 mg	Pending

RD = Randomized; DB = double-blind; PC = placebo-controlled; DE = dose-escalation; PK = Pharmacokinetics; PD = Pharmacodynamics

Table 2: Clinical Development in CD and Ulcerative Colitis (UC)

Study #	Goals	Population	Design	# of Doses	N	Natalizumab Dose
Phase 1						
CD201	Preliminary safety and efficacy	CD	RD, DB, PC	1	30	3 mg/kg
Phase 2						
CD202	Dose-finding; preliminary efficacy	CD	RD, DB, PC	1 to 2	244	3 and 6 mg/kg
CD251	Safety, tolerability	CD	Open-label	2	96	6 mg/kg
CD305	Safety, tolerability, PK	Adolescents with CD	Open-label	3	38	3 mg/kg
CD352	Safety, tolerability	Adolescents with CD	Open-label	Up to 24	26	3 mg/kg
CD306	Safety, tolerability	CD subjects receiving infliximab	RD, DB, PC	3	79	300 mg
Phase 3						
CD301	Confirmatory efficacy and safety	Moderate to severe CD	RD, DB, PC	3	904	300 mg
CD303	Confirmatory efficacy and safety	CD patients with clinical response in CD301	RD, DB, PC	Up to 12	428	300 mg
CD351	Extension efficacy and safety	CD251, CD301, CD303, CD306 completers	Open-label	Up to 24	589	300 mg
Additional Clinical Trials						
UC201	Preliminary safety and efficacy	UC	Open-label	1	10	3 mg/kg

RD = Randomized; DB = double-blind; PC = placebo-controlled; DE = dose-escalation; PK = Pharmacokinetics

4.3 Review Strategy

The primary focus of the efficacy review is the two Phase 3 studies in MS, Studies 1801 and 1802. These two studies are the only large, placebo-controlled studies of the efficacy of natalizumab at the proposed recommended dose, in the proposed target population. Both studies provide data through an average of one year. Study 231 (see Section 10.1.1, [Study 231](#)) was a randomized, double-blind, placebo-controlled study in MS, but used weight-adjusted dosing rather than the proposed recommended fixed dose, and administered a total of only 6 doses of study agent to each subject over 20 weeks. Study 231 was well-designed and was reviewed for evidence supportive of clinical efficacy.

The safety review is also based primarily on Studies 1801 and 1802, which provide the only placebo-controlled data in MS subjects who received the proposed recommended dose of

natalizumab for more than 6 months. Other MS studies and studies in other indications were reviewed for safety signals and included in an integrated summary of safety. However, almost all of these studies were limited in size, uncontrolled, or did not include exposure of subjects to the proposed recommended fixed dose of natalizumab for more than 6 months. Therefore, the design of these studies substantially limited their informativeness with regard to product safety. The major exception to these design limitations is CD303, a relatively large, randomized, double-blind, placebo-controlled study of the proposed recommended fixed dose of natalizumab administered to subjects with CD for up to 12 months. However, CD303 was ongoing at the time of this license application, and did not contribute substantially to the safety database.

Studies 1802 and 1803 were reviewed for evidence of an interaction between natalizumab and current standard therapies, a beta-interferon (1802) or glatiramer acetate (1803).

4.4 Data Quality and Integrity

The Division of Scientific Investigations conducted Bioresearch Monitoring Inspection (BIMO) audits of three study sites. Each site was selected because it enrolled a relatively large number of subjects into a proposed pivotal trial, either 1801 (Site #108), 1802 (Site #168), or 1801 and 1802 (site #125). These sites were also selected because their North American locations made them more accessible for audit than comparable sites on other continents. The BIMO clinical inspectors concluded that the data submitted in the BLA, as represented by these three sites, were valid and reliable.

4.5 Compliance with Good Clinical Practices

The investigators for both Study 1801 and Study 1802 obtained Ethics Committee (EC) and/or Institutional Review Board (IRB) approval for the protocol and written informed consents for subjects, in conformance with the International Conference on Harmonization (ICH) Tripartite Guideline on Good Clinical Practices (GCP), and/or 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312. Investigational sites in Europe, Australia, Canada, New Zealand, Israel, Switzerland, and Turkey also conformed to local practice and regulations. Prior to any participation in Study 1801 or 1802, each subject provided written informed consent in accordance with local practice and regulations.

During the course of Study 1802, the sponsor closed a single site in _____ due to protocol noncompliance. The sponsor excluded data from this site, which enrolled 25 subjects, from all efficacy analyses. However, the Center for Drugs Evaluation and Research (CDER) conducted sensitivity analyses to assess the impact of excluding this site on the study efficacy results (see Section 6.1.4.5.2.1, Exploration of Irregularities). Safety data from the site were included in the safety analyses.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry (Financial Disclosure by Clinical Investigators, CDER, March 20, 2001). Disclosable arrangements that might represent a conflict of interest and bias the investigator occurred in the two pivotal MS studies (Study 1801: sites 109, 110, 119, 125, and 730; Study 1802: sites 125, 144, 148, 158, 160, 176, 183, 197, 451, 465, 656, and 752). Studies 1801 and 1802 were double-blind studies designed to reduce the potential for investigators' bias to influence study results. CDER conducted sensitivity analyses to assess the potential impact of investigator bias at these sites (see Section 6.1.4.5.2.2, Financial conflicts of interest).

5 CLINICAL PHARMACOLOGY

Natalizumab binds to the $\alpha 4\beta 1$ integrin expressed on the surface of all leukocytes except neutrophils and blocks the interaction with the integrin's receptors. The receptors for the $\alpha 4$ family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium and the mucosal addressin cell adhesion molecule-1 (MadCAM-1) present on mucosal endothelial cells. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. *In vitro*, natalizumab also blocks $\alpha 4$ -mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). *In vivo*, natalizumab may further act to inhibit the interaction of $\alpha 4$ -expressing leukocytes with their ligand(s) in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells.

The specific mechanism(s) by which natalizumab exerts its effect(s) in multiple sclerosis have not been fully elucidated. In multiple sclerosis, lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and their counter-receptors present on vascular endothelial cells. The clinical effect of natalizumab in multiple sclerosis may be secondary to blockade of the molecular interaction of $\alpha 4\beta 1$ -integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain.

For additional discussion of the clinical pharmacology of natalizumab, see Dr. Iftexhar Mahmood's Clinical Pharmacology review of this application.

5.1 Pharmacokinetics

Following the repeat IV administration of a 300 mg dose of natalizumab to MS patients, the mean maximum observed serum concentration was $98 \pm 34 \mu\text{g/mL}$. Mean average steady-state natalizumab concentrations over the dosing period were approximately $30 \mu\text{g/mL}$. The mean

half-life of 11 ± 4 days was observed with a clearance of 16 ± 5 mL/hour. The distribution volume of 5.7 ± 1.9 L was consistent with plasma volume.

With co-administration of Avonex[®] (Interferon β -1a) 30 μ g IM once weekly, natalizumab clearance decreased by 30% and half-life increased by 30% following the sixth dose (at Week 20) of natalizumab as compared to the first dose.

Results of studies in MS patients taking natalizumab and concomitant beta interferon (Avonex[®] 30 μ g IM once weekly) or glatiramer acetate (Copaxone[®] 20 mg subcutaneous [SC] daily) are inconclusive with regard to the need for dose adjustment of beta interferon or glatiramer acetate.

In normal volunteers and in patients with MS, the C_{max} increased with the natalizumab dose and was linear between doses of 0.3 and 3 mg/kg. However, the area under the concentration time curve (AUC) did not increase proportionally with dose, and the clearance of natalizumab decreased with increasing dose. Therefore, the overall pharmacokinetics of natalizumab are nonlinear between doses of 0.3 and 3 mg/kg. Following a 300 mg fixed dose of natalizumab given every 4 weeks to patients with MS, C_{max} , half-life and $AUC_{(0-inf)}$ were comparable between the first and the sixth dose.

Pharmacokinetics of natalizumab in pediatric multiple sclerosis patients or those with renal or hepatic insufficiency have not been studied.

For additional discussion of natalizumab pharmacokinetics, including bioequivalence studies 1805 and 1806, see Dr. Iftexhar Mahmood's Clinical Pharmacology review of this application.

5.2 Pharmacodynamics

Natalizumab administration increases the number of circulating leukocytes (including lymphocytes monocytes, basophils, and eosinophils), due to inhibition of transmigration out of the vascular space. Increases in circulating leukocytes are maintained throughout the administration period; counts return to baseline levels when natalizumab is discontinued. Natalizumab does not affect the number of circulating neutrophils.

The available data are insufficient to assess whether antibodies to natalizumab have any impact on the pharmacokinetics of natalizumab (see Section 7.1.10, Immunogenicity).

For additional discussion of natalizumab pharmacodynamics, see Dr. Iftexhar Mahmood's Clinical Pharmacology review of this application.

5.3 Exposure-Response Relationships

Based on a pharmacodynamic model, natalizumab serum concentrations of approximately 2.5 – 3 μ g/mL would be required to maintain a minimum α 4-integrin saturation of 80%. In Study 231, approximately 90% of subjects in both dose groups (3 mg/kg and 6 mg/kg) had natalizumab

serum concentrations in excess of 2.5 mcg/mL four weeks following the last infusion. Studies 231 and CD202 provide evidence of no relationship between body weight and clearance. Also, both weight-adjusted doses administered in Study 231 resulted in similar activity, safety, and tolerability. Therefore, the sponsor abandoned weight-adjusted dosing, as administered in the Phase 1 and Phase 2 studies (see Section 4.2, Tables of Clinical Studies), in favor of a fixed 300 mg dose of natalizumab in the two subsequent Phase 3 MS studies, Studies 1801 and 1802 (see Section 2.5.1, Fixed Dosing Regimen). A 300 mg fixed dose does not exceed 6 mg/kg in subjects weighing more than 50 kg, and is not less than 3 mg/kg in subjects weighing less than 100 kg. In Study 1801, the administration of 300 mg natalizumab IV resulted in mean α 4-integrin saturation levels in excess of 90% immediately post-infusion and resulted in sustained (at Week 4 post-infusion) α 4-integrin saturation levels of approximately 70%.

The sponsor has not initiated concurrently-controlled studies of greater than six months in duration using a natalizumab regimen other than 300 mg IV every 4 weeks. However, data from Study 231 provides evidence that natalizumab administration is associated with an elevation of serum leukocytes that persists for at least 8 weeks following natalizumab administration (see Figure 1). In addition, natalizumab administration every 4 weeks is associated with approximately 70% saturation of α 4-integrin at trough (Week 4) natalizumab levels. Therefore, there is evidence suggesting that natalizumab may have sustained clinical activity with less frequent administration. The applicant has not investigated the safety and efficacy of less frequent administrations.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant proposes that natalizumab is indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations.

The sponsor has applied for accelerated approval of natalizumab for the above indication(s) based on results achieved after approximately one year of treatment in ongoing two-year clinical trials.

6.1.1 Methods

Two large, multicenter, Phase 3, randomized, double-blind, placebo-controlled studies (1801 and 1802) provide the primary evidence of effectiveness for natalizumab in MS, and are the focus of this review. In the clinical development of natalizumab (see Section 4.2, Tables of Clinical Studies), these two Phase 3 studies were the only placebo-controlled studies that administered the proposed recommended dose of natalizumab to subjects with MS for more than six months.

analyses, each protocol was amended to prespecify cut-off dates for clinical and MRI outcome data to be included in the 1-year analyses.

- The 1801 protocol was amended to prespecify a clinical data cut-off date of July 17, 2003 and an MRI data cut-off date of August 12, 2003. The July 17, 2003 cut-off date included 988 total subject-years of observation into the 1-year analyses and occurred after all subjects remaining in the study completed at least the Week 48 visit.
- The 1802 protocol was amended to prespecify a clinical data cut-off date of October 15, 2003 and an MRI data cut-off date of October 31, 2003. The October 15, 2003 cut-off date included 1268 total subject-years of observation into the 1-year analyses and occurred after 98% of subjects remaining in the study completed at least the Week 24 visit.

Therefore, for each of the two Phase 3 Studies, the 1-year analyses described in this review are not based on one year of data for each subject, but rather are based on analyses that consider different lengths of study for the different subjects. This review describes these analyses and endpoints as “1-year” as a convenient approximation.

6.1.2.1 Primary Endpoint for One-Year Analysis

The primary objective at 1 year was to determine whether natalizumab, when compared with placebo, was effective in reducing the rate of clinical relapses through 1 year. Annualized relapse rate was the protocol-specified primary endpoint, calculated using Poisson regression, adjusting for the number of relapses in the previous year, baseline EDSS, the presence of gadolinium enhancing lesions on T1-weighted MRI, and age. Subjects were censored at the time they added rescue treatment with an available alternative MS treatment, which was allowed per protocol once sustained progression was achieved.

The FDA assessed the use of the Poisson regression as statistically valid to classify each Phase 3 trial as either a success or failure based on the primary endpoint. However, CDER recognized that patients or physicians do not generally understand the Poisson regression. Therefore, CDER requested that the applicant provide additional analyses that calculate the mean annualized relapse rate for each study group based on individual relapse rates (number of relapses divided by number of years on study), and including all relapses that occurred during the study (i.e., including relapses that occurred following the initiation of an available alternative MS treatment). CDER efficacy analyses described in this review use this latter calculation of annualized relapse rate, without adjustment for age, baseline EDSS values, or baseline MRI findings.

6.1.2.2 Secondary Endpoints for One-Year Analysis

The secondary endpoints at 1 year were the following:

- 1) Reduction in the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, comparing the natalizumab group to the placebo group, using a pre-specified logit regression, adjusted for baseline number of T2 lesions (<9 versus ≥ 9 lesions). For this analysis, missing values were imputed using the mean number of T2-hyperintense lesions in the study population.
- 2) Reduction in the number of gadolinium-enhancing lesions on brain MRI scans, comparing the natalizumab group to the placebo group, using a pre-specified logit regression, adjusted for baseline number of gadolinium-enhancing lesions. For this analysis, missing values were imputed using the mean number of gadolinium-enhancing lesions in the study population.
- 3) Increase in the proportion of relapse-free subjects, comparing the natalizumab group to the placebo group, using a pre-specified logistic regression adjusted for the number of relapses in the one year prior to study entry. For this analysis, a subject was considered to have relapsed if either the subject withdrew from the study and did not experience a relapse prior to withdrawal, or the subject took alternative MS medications and did not experience a relapse.

The secondary endpoints were rank prioritized in the order presented above. If statistical significance ($p < 0.05$) was not achieved for any secondary endpoint, all secondary endpoint(s) of a lower rank were not considered statistically significant.

Analysis of all MRI scans was performed at a central facility, either _____ (Study 1801) or _____ (Study 1802). Prior to subject enrollment at an investigational site, the MRI reading center verified the investigational site's scanning technique by evaluating a test scan from an MS subject. Original MRI tapes or optical disk media were sent by courier to the MRI center for review. Technicians and physicians at the central reading center evaluated the images for study-specific MRI endpoints. These physicians and technicians were blinded to the subjects' treatment assignments.

6.1.3 Study Design

The two Phase 3 trials, Studies 1801 and 1802, are very similar in design. Both are large, multicenter, international, randomized, double-blind, placebo-controlled, two-arm, two-year studies of natalizumab compared to placebo in subjects with relapsing MS. The designs of these two studies meet the regulatory requirements for adequate and well-controlled studies (21 CFR 314.126) to provide a reasonable assessment of the benefit of natalizumab in MS. The design of Study 1801 is described below, followed by a description of important differences between Studies 1801 and 1802.

6.1.3.1 Design of Study 1801

6.1.3.1.1 Study 1801 – Design

Study 1801 is a multicenter, international, randomized, double-blind, placebo-controlled, two-arm, parallel-group study in subjects with RRMS to assess the efficacy and safety of natalizumab. Approximately 900 subjects were to be randomized (2:1) at the baseline visit to receive either 300 mg of natalizumab or placebo by IV infusion every 4 weeks for up to 116 weeks. The co-primary endpoints are annualized relapse rate at 1 year and disability progression at 2 years.

Subjects were randomized at the Baseline Visit (Week 0) after all eligibility criteria (including a baseline EDSS score of 5.0 or lower) were confirmed. The randomization was stratified by site, using a centralized randomization schedule to balance the treatment group assignments within sites. The initial administration of study agent was to occur on the day of randomization (Week 0 visit).

A number of precautions were taken to preserve blinding throughout the study, including the following:

- 1) Centralized randomization stratified by site.
- 2) Study drug was administered in a blinded fashion such that neither the subject, the investigational site personnel, nor Biogen Idec knew a subject's treatment assignment. Only the _____ which was responsible for the randomization, was aware of the treatment assignment. The medical monitors at _____ were responsible for handling unblinding requests related to medical emergencies.
- 3) All study personnel at each study center were to be blinded to treatment assignment. Physicians, nurses, subjects, and any study personnel performing subject assessments were not to be informed of the subject's treatment assignment except in the event of a medical emergency or as required by regulatory authorities.
- 4) Investigational site personnel were not allowed to review laboratory leukocyte data, including the differential (with the exception of the absolute neutrophil count), which were obtained after the Screening Visit. White blood cell data, including the differential (with the exception of the absolute neutrophil count), which were obtained after the Screening Visit were not to be sent to the sites; but instead were to be reviewed centrally by an Independent Medical Monitor (IMM). Investigational sites were to be contacted periodically by the IMM for subject information to determine if the values were clinically significant.

- 5) After Screening, MRIs were to be evaluated for non-MS pathology by physicians/technicians at the site who were blinded to the subjects' treatment assignments.
- 6) Each investigational site was to have four separate neurologists: a Treating Neurologist and a backup Treating Neurologist who oversaw subject management including the assessment and treatment of adverse events and new neurologic events and the review and sign-off of laboratory data, and an Examining Neurologist and a backup Examining Neurologist who conducted all EDSS evaluations at scheduled and, if necessary in the event of a relapse, at unscheduled visits. Analyses of all MRIs were performed by a central MRI reading center whose staff were blinded to treatment assignments.

The Examining Neurologist was not to be involved with any other aspect of subject care and management. The Examining Neurologist was not to serve as Treating Neurologist for any subjects at a study center. To ensure consistency across sites, Examining Neurologists were required to undergo a standardized training session on EDSS scoring prior to enrollment of subjects at their site. The backup Examining Neurologist was to conduct subject evaluations only if the primary Examining Neurologist was unavailable due to illness, vacation, or travel. All study centers were to attempt to maintain the same Examining Neurologist throughout the study. If an Examining Neurologist had to be replaced, the new Examining Neurologist was required to undergo a training session. The communication of new findings on the neurologic examination from the Examining Neurologist to the Treating Neurologist was permitted (because findings on the neurologic examination might be important in the routine care of the subject, e.g., medical management of relapses). The roles of Treating and Examining Neurologist (primary and backup) were not interchangeable even for different subjects. However, the Examining Neurologist could also act as the Examining Technician. The Examining Neurologist was to remain blinded to adverse events, concomitant medications, laboratory data, MRI data, and any other data that had the potential of revealing subject treatment assignments.

- 7) Absolute neutrophil count data were sent to the investigational sites to aid in management of the subject, but, as with other laboratory and clinical information, was not to be reviewed by the Examining Neurologist, the backup Examining Neurologist, the Examining Technician, or the backup Examining Technician.
- 8) Either the Examining Technician or the Examining Neurologist administered the components of the Multiple Sclerosis Functional Composite (MSFC) at screening, baseline, and throughout the study.

Of note, the use of separate treating and examining neurologists has become a critical element to provide for blinded assessment of clinical outcome measures for many MS clinical trials. For trials of interferon betas, this approach was essential because of adverse events that would likely lead to unblinding of the treating neurologist. For Studies 1801 and 1802, this same approach

was used, although there was no clear evidence from the Phase 1 and Phase 2 studies that natalizumab would cause adverse events that were likely to be unblinding. The major exception was the known pharmacodynamic effect of natalizumab on peripheral leukocyte counts, but the methods employed above to blind the study personnel to laboratory data should have been sufficient. Overall, the methods to preserve blinding were adequate.

All study management, investigational site personnel, investigators, and subjects directly involved in the study were to remain blinded to subject treatment assignment until the conclusion of the 2-year study, except if a subject experienced a medical emergency that necessitated unblinding the subject's treatment assignment.

Prohibited concomitant medications included any investigational product, including investigational symptomatic treatment for MS, any "alternative drug treatments directed towards the treatment of MS such as chronic immunosuppression," and any steroid therapy, except for protocol-defined treatment of relapse. Permitted concomitant medications included symptomatic treatments (e.g., treatments for spasticity, depression, or fatigue). The decision on whether or not to treat a relapse was at the discretion of the Treating Neurologist. The protocol-specified treatment for relapses was methylprednisolone 1000 mg IV QD or in divided doses, for either 3 days or 5 days, with the duration of treatment at the discretion of the Treating Neurologist. Subjects were not to begin corticosteroid treatment of a possible relapse until they had been examined by the Examining Neurologist. Retreatment of the same relapse was not allowed unless approved by the Advisory Committee.

Subjects who experienced significant disease progression as defined by the protocol (at least a 1.0 point increase on the EDSS from a baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks) were to be notified that they had experienced worsening of physical disability. These subjects were to be given the option to continue study drug and all follow-up visits per protocol or to add treatment with either IFN- β or glatiramer acetate. The subject was to document this decision by signing an addendum to the Informed Consent Form. All safety monitoring, study visits, clinical evaluations, and MRI evaluations were to continue as planned.

An Advisory Committee was formed to provide scientific and medical direction and to oversee the administrative progress of the study. The Advisory Committee was to meet at least monthly to monitor subject accrual and noncompliance with the protocol at individual investigational sites. The Advisory Committee determined whether the study should be stopped or amended for reasons other than safety.

A Safety Monitoring Committee (SMC) was formed to review the safety data and to advise the sponsor with regard to study discontinuation for safety reasons. The operating guidelines for the SMC were pre-specified and included scheduled meetings approximately 1 year and 2 years after enrollment began on Study 1801. Every month, the Study Director was to forward to the members of the SMC copies of enrollment numbers and incidence and available details on serious adverse events (SAEs). Details of SAEs that were unexpected and associated with the use of the drug were to be forwarded to SMC members as information became available. Any

information that was unblinded to treatment assignment was to be treated as confidential. Membership of the SMC consisted of independent medical and statistical personnel who were not allowed to participate as investigators in any natalizumab study sponsored by Elan Pharmaceuticals, Inc. or Biogen Idec.

6.1.3.1.2 Study 1801 – Study Agent Administration

Infusions of 300 mg natalizumab or placebo were to be administered every 4 weeks for up to 116 weeks.

The study agent was provided in 5 mL vials stored at 2 – 8°C. Study agent from 3 vials (a total of 15 mL) was injected into a 100 mL bag of 0.9% saline. The study agent in solution was then allowed to warm to room temperature prior to administration. The diluted study agent was administered by IV infusion over approximately 60 minutes. Study agent administration was to begin within 5 hours following study agent dilution in normal saline.

The study agent was administered in a clinical setting under the supervision of a physician. Each subject was monitored in the clinic for at least one hour following the completion of study agent infusion.

6.1.3.1.3 Study 1801 – Eligibility Criteria

6.1.3.1.3.1 Study 1801 – Inclusion Criteria

All subjects were required to meet all of the following criteria:

- 1) Male and female subjects between 18 and 50 years of age, inclusive
- 2) had a diagnosis of MS as defined by McDonald et al, criteria 1-4 (see Appendix 10.3, McDonald Diagnostic Criteria for MS)
- 3) had a baseline EDSS score between 0.0 and 5.0, inclusive (see Appendix 10.4, Kurtzke Expanded Disability Status Scale)
- 4) had a brain MRI scan demonstrating lesion(s) consistent with MS
- 5) had at least 1 medically documented clinical relapse within the 12 months prior to randomization. For the purpose of this inclusion criterion, a relapse was defined as neurologic signs and/or symptoms documented in the medical record and of sufficient duration to be determined by the investigator or the treating physician as consistent with an MS relapse. The January 11, 2002 protocol amendment clarified that the 12-month interval between the relapse and randomization was to start at the time of relapse onset.

6.1.3.1.3.2 Study 1801 – Exclusion Criteria

Patients were excluded from enrollment if any of the following exclusion criteria existed at the time of randomization:

- 1) Primary progressive, secondary progressive, or progressive-relapsing MS, as defined by Lublin and Reingold, 1996. These conditions require the presence of continuous clinical disease worsening over a period of at least 3 months. Subjects with these conditions may also have superimposed relapses, but are distinguished from relapsing-remitting subjects by the lack of clinically stable periods or clinical improvement. This definition of progressive MS was added by the January 11, 2002 protocol amendment.
- 2) MS relapse occurred, in the opinion of the investigator, within 50 days prior to randomization and/or the subject had not stabilized from a previous relapse, in the opinion of the investigator, prior to randomization.
- 3) A clinically significant infectious illness within 30 days prior to randomization.
- 4) History of, or abnormal laboratory results indicative of, any significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, and/or other major disease, which, in the opinion of the investigator, would preclude the administration of a recombinant humanized antibody immunomodulating agent for 116 weeks.
- 5) History of severe allergic or anaphylactic reactions or known drug hypersensitivity.
- 6) Unable to perform the Timed 25-Foot Walk, 9 Hole Peg Test (HPT) (with both upper extremities), and Paced Auditory Serial Addition Test (PASAT 3).
- 7) Abnormal blood tests, performed at the screening visit, which exceeded any of the limits defined below:
 - Alanine transaminase/serum glutamate-pyruvate transaminase (ALT/SGPT), or aspartate transaminase/serum glutamic-oxaloacetic transaminase (AST/SGOT) >3 times the upper limit of normal (ULN).
 - Total WBC count < 2,300/mm³.
 - Platelet count <100,000/mm³.
 - Creatinine >2 times the ULN.
 - Prothrombin time (PT) > ULN.

- 8) Treatment with cyclosporine, azathioprine, methotrexate, subcutaneous glatiramer acetate, interferon beta, intravenous immunoglobulin, plasmapheresis, or cytophoresis within 6 months prior to randomization.
- 9) History of treatment with either an interferon β for a total of at least 6 months, or glatiramer acetate for a total of at least 6 months.
- 10) Any prior treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, natalizumab, or any other therapeutic monoclonal antibody.
- 11) Treatment with mitoxantrone or cyclophosphamide within 1 year prior to randomization.
- 12) Treatment with oral glatiramer acetate within 3 months prior to Screening (added by the January 11, 2002 protocol amendment).
- 13) Treatment with IV corticosteroids, oral corticosteroids, 4-aminopyridine, or products related to 4-aminopyridine, within 50 days prior to randomization. 4-aminopyridine was added by the January 11, 2002 protocol amendment. Products related to 4-aminopyridine were added by the September 15, 2003 protocol amendment.
- 14) History of alcohol or drug abuse within 2 years prior to randomization.
- 15) Female subjects who were not postmenopausal for at least 1 year, surgically sterile, or who were not willing to practice effective contraception (as defined by the investigator) during the study. The rhythm method was not to be used as the sole method of contraception.
- 16) Nursing mothers, pregnant women, and women who planned to become pregnant while on study.
- 17) Participation in previous natalizumab studies (unless subject was on placebo). A clarification that placebo subjects who experienced adverse events during those studies may also be excluded was added by the January 11, 2002 protocol amendment.
- 18) Participation in any other investigational study within 6 months prior to randomization.

6.1.3.1.4 Study 1801 – Study Procedures

Screening studies, to be performed within 35 days prior to randomization, included baseline laboratory studies (urinalysis, hematology, chemistry profile), pregnancy test for women of childbearing potential, physical examination, EDSS examination, brain MRI with and without gadolinium, Multiple Sclerosis Functional Composite (MSFC; repeated 3 times within 35 days prior to randomization), and optional genetic testing.

The scheduling of all visits was calculated based on the baseline visit date. The protocol specified several types of clinic visits:

- 1) Study Drug Administration Visits (SDAVs) occurred at baseline and every 4 weeks (+/- 3 days) through Week 116. These visits included monitoring of adverse events and concomitant medications, a urine pregnancy test for women of childbearing potential, and study agent administration.
- 2) Clinical Evaluation Visits (CEVs) of two types:
 - a. Scheduled – at baseline and every 12 weeks (+/- 1 week) through Week 120; each Scheduled CEV included a physical examination, laboratory studies (urinalysis, hematology, and chemistry panel), anti-natalizumab antibody sample, and MSFC and EDSS examinations.
 - b. Unscheduled – Subjects were to telephone the Treating Neurologist within 48 hours of the onset of any new neurologic symptom that might indicate a relapse. An Unscheduled Visit was to be scheduled for within 72 hours of the suspected relapse. The Treating Neurologist determined whether a relapse may have occurred, and, if so, referred the subject to the Examining Neurologist. The Examining Neurologist performed an EDSS examination within 5 days of the suspected relapse.

A selected cohort of subjects also had PK/PD tests to measure natalizumab levels and α 4-integrin saturation of mononuclear cells, monthly for 3 months and then every 3 months to the end of the study. Limited PK and PD measures (WBCs and lymphocytes) were to be assessed in all subjects.

- 3) MRI Evaluation Visits (MEVs) occurred at baseline and Weeks 52 and 104 (+/- 4 weeks). The brain MRI scan was not to be performed during the 5 days following the administration of study drug or within 30 days of receiving a course of steroids.
- 4) An End of Study Visit was scheduled for Week 128, including physical examination, a urine pregnancy test for women of childbearing potential, laboratory (urinalysis, hematology, and chemistry panel), PK/PD sample for a selected cohort of subjects, anti-natalizumab antibody sample, and MSFC and EDSS examinations. These same procedures were applied for a premature study termination visit.

6.1.3.1.5 Study 1801 – Endpoints and Analysis Plan

The primary endpoint for the 1-year analysis, which serves as the basis for this application, was the effect of natalizumab compared to placebo on the annualized relapse rate. For this study, a relapse was defined 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. This determination of whether an event was associated with new objective neurological findings was based on the assessment by the Examining Neurologist. In order to be counted as a relapse, the onset of a relapse was required to be at least 30 days following the onset of the previous relapse. If the onset of a relapse was less than 30 days following the onset of the previous

relapse, the relapse was considered an extension of the previous relapse and was not counted as an additional event.

See Section 6.1.2, General Discussion of Endpoints for a discussion of the co-primary endpoints (Section 6.1.2.1, Primary Endpoint for 1-year Analysis) and secondary endpoints (Section 6.1.2.2, Secondary Endpoints for 1-year Analysis).

6.1.3.2 Design of Study 1802

The design of Study 1802 was very similar to the design of Study 1801. Major features of Study 1802 that were different from the design of Study 1801 were the following:

- 1) Target enrollment of approximately 1200 subjects;
- 2) 1:1 randomization to either natalizumab or placebo;
- 3) Inclusion criterion – subjects between 18 and 55 years of age, inclusive;
- 4) Inclusion criterion that all subjects must have received Avonex[®] for at least 12 months prior to randomization;
- 5) Exclusion criterion that subjects must not have received any interferon product other than Avonex[®] within 1 year prior to randomization;
- 6) Subjects were to receive 30 µg Avonex[®] by IM injection once a week, administered by either the subjects or their designees, throughout the study. Avonex[®] was not to be administered within 24 hours of the IV infusion of study drug.

6.1.4 Efficacy Findings

This efficacy review is based primarily on two Phase 3 studies, Studies 1801 and 1802 (see Section 4, Data Sources, Review Strategy, and Data Integrity and Section 6.1.3, Study Design). Study 1801 compares natalizumab to placebo; Study 1802 compares natalizumab to placebo as an add-on therapy to Avonex[®]. Both studies enrolled subjects with active RRMS, with activity defined by the occurrence of at least one relapse during the year prior to randomization. In Study 1801, 11% of subjects were enrolled at U.S. sites, whereas 62% of subjects in Study 1802 were enrolled at U.S. sites.

6.1.4.1 Subject Enrollment, Study 1801

Study 1801 included 99 investigators in North America, Europe, Australia, and New Zealand who enrolled and randomized a total of 942 subjects. Seventy investigators in Europe enrolled 697 subjects, 24 investigators in North America enrolled 213 subjects, and 5 investigators in Australia and New Zealand enrolled 32 subjects. Forty-one sites enrolled at least 10 subjects and

collectively accounted for 624 subjects, or 66% of the total population; 19 sites enrolled fewer than 5 subjects.

Of the 942 subjects enrolled in the study, 315 were randomized to receive placebo and 627 were randomized to receive natalizumab.

The first subject received the first dose on November 6, 2001. The cut-off date for the analysis was July 15, 2003; however data from subject 109-009 were included even though the subject's Week 52 visit occurred on July 17, 2003. In order to capture MRI data for the majority of subjects, MRI evaluations performed through August 12, 2003 were included in the database.

6.1.4.2 Subject Enrollment, Study 1802

Study 1802 enrolled and randomized a total of 1196 subjects. However, Site # _____ which enrolled 25 subjects, was closed by the sponsor due to protocol noncompliance. The data from Site # _____ were excluded from the applicant's efficacy analyses. The remaining 123 sites in North America, Europe, and Israel enrolled a total of 1171 subjects.

Seventy investigators in North America enrolled 724 subjects, 51 investigators in Europe enrolled 417 subjects, and 2 investigators in Israel enrolled 30 subjects. Fifty-five sites enrolled at least 10 subjects and collectively accounted for 815 subjects, or 70% of the total population; 30 sites enrolled fewer than 5 subjects.

Of the 1171 remaining subjects enrolled in the study, 582 were randomized to receive placebo plus Avonex[®], and 589 were randomized to receive natalizumab plus Avonex[®].

The first subject received the first dose on January 14, 2002. The cut-off date for data to be included in the one-year analyses was October 15, 2003; however, in order to include MRI data from the majority of subjects, MRI data from evaluations performed through October 31, 2003, were included in the one-year analyses.

Because Studies 1801 and 1802 were similar in design, the results of the two studies are presented together in this review.

6.1.4.3 Baseline Characteristics

Treatment groups in both studies were well-matched with regard to demographics and baseline disease characteristics (Table 3). The study subjects were predominantly female, consistent with the U.S. MS population at large. The study subjects were almost entirely Caucasian, with an under-representation of minorities relative to the U.S. MS population.

Table 3: Baseline Characteristics

	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex®	Natalizumab + Avonex®
N	315	627	582	589
Age (mean ± SD, years)	36.7 ± 7.8	35.6 ± 8.5	39.1 ± 7.6	38.8 ± 7.7
Age (median, years)	37	36	39	39
Age, 25 th , 75 th percentile, years	31, 43	29, 43	34, 45	33, 44
Female – N, (%)	211 (67)	449 (72)	420 (72)	442 (75)
Caucasian – N, (%)	296 (94)	602 (96)	542 (93)	551 (94)
African Ancestry – N, (%)	6 (2)	5 (<1)	22 (4)	17 (3)
Hispanic – N, (%)	6 (2)	8 (1)	9 (2)	12 (2)
Weight (mean ± SD, kilograms)	72.2 ± 16.0	71.8 ± 16.1	73.0 ± 16.9	72.5 ± 17.1
Weight (median, kilograms)	70.7	69.0	70.0	70.0
Weight, 25 th , 75 th percentile, kilograms	60.0, 81.0	60.0, 80.0	60.0, 83.0	60.0, 82.0
McDonald 1 – number of subjects (%)	261 (83)	528 (84)	532 (91)	538 (91)
Years since MS onset (median) (25 th , 75 th percentile)	5.9 (2.0, 11.0)	5.0 (2.7, 10.0)	8.0 (4.3, 13.8)	7.2 (4.1, 12.4)
Relapses – previous 3 years (median) (25 th , 75 th percentile)	2 (2, 3)	3 (2, 3)	3 (2, 4)	3 (2, 4)
Relapses – previous 1 year (median) (25 th , 75 th percentile)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Relapses – previous year = 0 (n, %)	6 (1.9)	6 (1.0)	1 (0.2)	0 (0.0)
Relapses – previous year = 1 (n, %)	180 (57.1)	368 (58.7)	365 (61.3)	398 (66.4)
Relapses – previous year = 2 (n, %)	102 (32.4)	197 (31.4)	179 (30.1)	157 (26.2)
Relapses – previous year = 3 (n, %)	20 (6.3)	43 (6.9)	39 (6.6)	32 (5.3)
Relapses – previous year = 4 (n, %)	5 (1.6)	9 (1.4)	10 (1.7)	8 (1.3)
Relapses – previous year ≥ 5 (n, %)	2 (0.6)	4 (0.6)	1 (0.2)	4 (0.7)
Months since most recent relapse (median) (25 th , 75 th percentile)	5.7 (3.8, 8.8)	5.6 (3.7, 8.3)	5.1 (3.3, 7.8)	5.1 (3.4, 7.6)
EDSS (median) (25 th , 75 th percentile)	2 (1.5, 3.0)	2 (1.5, 3.0)	2.5 (1.5, 3.5)	2 (1.5, 3.0)
Gadolinium-enhancing lesions (median) (25 th , 75 th percentile)	0 (0, 2)	1 (0, 2)	0 (0, 1)	0 (0, 1)
T2 lesions ≥ 9 – number of subjects (%)	298 (95)	595 (95)	528 (91)	920 (88)

Relative to the subjects in Study 1801, subjects in Study 1802 were slightly older, with a longer duration of MS, on average. This is consistent with the fact that subjects in 1802 had been maintained previously on Avonex®, whereas the majority of subjects in 1801 had never received a beta-interferon.

6.1.4.4 Study Conduct

The overall conduct of Studies 1801 and 1802 is outlined in Table 4. At the time of the one-year analyses, less than 15% of subjects enrolled in each study had discontinued study agent, and less than 8% of the subjects enrolled in each study had withdrawn. Subjects who discontinued study drug or withdrew from the study due to an adverse event are described further in the Safety Review, Section 7.1.3, Dropouts and Other Significant Adverse Events.

Table 4: Disposition of Subjects				
	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex [®]	Natalizumab + Avonex [®]
Randomized - N	315	627	582	589
Withdrew prior to dosing – N, (%)	3 (1)	0	0	0
Dosed – N, (%)	312 (99)	627 (100)	582 (100)	589 (100)
Completed 1 year in study – N, (%)	280 (89)	568 (91)	387 (66)	393 (67)
≥ 13 infusions - N (%)	285 (90)	583 (93)	451 (78)	456 (77)
Discontinued study drug – N, (%)	25 (8)	44 (7)	70 (12)	61 (10)
Discontinued due to adverse event – N, (%)	8 (3)	31 (5)	24 (4)	16 (3)
Deaths – N, (%)	0	0	1 (<1)	0
Withdrew from study – N, (%)	18 (6)	21 (3)	41 (7)	29 (5)
Withdrew due to adverse event – N, (%)	6 (2)	12 (2)	4 (<1)	7 (<1)
Took an alternative MS drug – N (%)	21 (7)	19 (3)	19 (3)	6 (1)

Three subjects randomized to receive placebo in Study 1801 withdrew from the study prior to receiving study treatment; all other subjects received at least 1 dose of study agent.

Protocol violations are summarized in Table 5. In each study, the frequency of protocol violations of each type is similar for the two treatment arms, adjusted for the number of subjects in each arm. These violations were minor, and would not be expected to affect the results directionally.

Table 5: Protocol Violations

Type of Violation	Study 1801				Study 1802			
	Natalizumab N = 627		Placebo N = 315		Natalizumab N = 589		Placebo N = 582	
	number of violations	number of subjects (%)						
Eligibility criteria violation	64	52 (8.3%)	33	27 (8.6%)	88	70 (11.9%)	88	67 (11.5%)
Missed, partial, or incorrect dosing	323	144 (23%)	145	77 (24.4%)	868	306 (52%)	918	310 (53.3%)
Prohibited concomitant medication	29	22 (3.5%)	17	11 (3.5%)	69	55 (9.3%)	72	53 (9.1%)
Outside acceptable visit window	1239	406 (64.8%)	692	218 (69.2%)	1423	418 (71%)	1504	430 (73.9%)
Efficacy evaluation not performed or not valid	104	73 (11.6%)	60	45 (14.3%)	189	113 (19.2%)	197	107 (18.4%)
Safety evaluation not performed or not valid	162	103 (16.4%)	95	53 (16.8%)	185	101 (17.1%)	213	120 (20.6%)
Missed study visit	38	25 (4%)	22	13 (4.1%)	39	29 (4.9%)	54	39 (6.7%)
Other	994	399 (63.6%)	529	208 (66%)	1633	407 (69.1%)	1790	418 (71.8%)
Not classified*	2	2 (0.3%)	0	0 (0%)	6	4 (0.7%)	9	7 (1.2%)
Total	2955	554 (88.4%)	1593	291 (92.4%)	4500	569 (96.6%)	4855	568 (97.6%)

* Events that were not classified were reviewed individually by CDER and were all deemed minor violations.

6.1.4.5 Efficacy Results – Primary Endpoint

6.1.4.5.1 Applicant's Analyses

For the 1-year analysis in Study 1801, annualized relapse rates were 0.261 (95% CI: 0.211, 0.323) and 0.805 (95% CI: 0.669, 0.969) in the natalizumab and placebo groups, respectively

($p < 0.001$). In Study 1802, the respective annualized relapse rates were 0.383 (95% CI: 0.325, 0.450) vs. 0.816 (95% CI: 0.721, 0.923) in the natalizumab plus Avonex[®] versus the placebo plus Avonex[®] groups ($p < 0.001$). The applicant's analyses use a Poisson regression to calculate the annualized relapse rate and consider relapses and time on study up to the time of initiation of an alternative MS drug. Relapse rates were adjusted for the number of relapses in the one year prior to study entry, baseline EDSS, presence of gadolinium-enhancing lesions on MRI, and age. The applicant's analysis results were confirmed by CDER.

Both 1801 and 1802 employed randomization stratified by center. However, the applicant assessed that inclusion of study center in the analysis model was not feasible due to the relatively large number of small centers. After extensive internal discussion, CDER informed the sponsor during a telephone call on October 28, 2003, that the primary analysis model need not include a term for the study center.

6.1.4.5.2 CDER Analyses

CDER performed exploratory analyses and calculated annualized relapse rates as the mean of the individual relapse rates for all subjects in a group. Relapse rates for individual subjects were calculated as the number of relapses divided by the number of days on study, multiplied by 365.25 days/year. Thus, all subjects contributed equally to the calculation of annualized relapse rate, irrespective of their time on study. CDER's calculations include all confirmed relapses, specifically including relapses on study after initiation of an alternative MS treatment. The results of CDER's analyses of the annualized relapse rates (Table 6), using a t-test, are very similar to the results from the applicant's analyses, using Poisson regression. For all CDER analyses, relapse rates are reported with units of $\text{person}^{-1} \cdot \text{years}^{-1}$.

	Study 1801		Study 1802	
	Placebo N = 315	Natalizumab N = 627	Placebo + Avonex [®] N = 582	Natalizumab + Avonex [®] N = 589
Mean	0.735	0.250	0.780	0.357
Standard Deviation	1.126	0.533	1.002	0.620
Median	0	0	0.685	0
Range	0-6.408	0-3.454	0-6.764	0-3.414

6.1.4.5.2.1 Exploration of Irregularities

Site # — With respect to the protocol non-compliance at Site # — (Study 1802), CDER conducted sensitivity analyses to assess the extent to which the exclusion of these data might affect the study results. CDER conducted a "worst case" analysis of the primary endpoint, imputing a relapse rate of 0 for each of the 13 placebo group subjects, and a relapse rate of 1 for each of the 12 natalizumab group subjects. Using this imputation scheme, treatment with natalizumab was associated with a 52% relative decrease in annualized relapse rate (0.763 vs.