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Peripheral and Central Nervous System (PCNS) Advisory Committee

Briefing Document

Biogen Idec

Biologics Marketing Application STN 125104 / 15

Natalizumab (Tysabri) for Multiple Sclerosis

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Tysabri Advisory Committee Briefing Document

Objective: This committee is convened to advise the Food and Drug Administration (FDA) regarding proposed regulatory actions with regard to natalizumab (trade name: Tysabri) as a treatment for multiple sclerosis (MS). Issues for discussion include, but are not limited to, the possible return of natalizumab to the market, the risk of progressive multifocal leukoencephalopathy, and a proposed risk management plan for natalizumab.

Sponsor(s): 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 the current submission.

Background

Multiple sclerosis

MS is a chronic, inflammatory, possibly autoimmune, demyelinating disease of the central nervous system (CNS). Multiple sclerosis is a common cause of neurological disability in young adults, primarily with initial diagnosis in 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 United States, 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 (RRMS) is the presenting form in approximately 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 are followed by variable degrees of recovery (remissions). The majority of subjects with RRMS develop secondary progressive MS (SPMS) in which periods of stability after exacerbation recovery give way to slow, continuing neurological decline. 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 status scale (EDSS) score, which is determined by assessing the Kurtzke Functional Systems in each of six 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 formal 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 space and time). "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 (MRI) has become a standard procedure in the diagnosis of MS. Magnetic resonance imaging may reveal 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 been used to define the MS populations for clinical trials.

Alternative Approved Treatments

In addition to natalizumab, there are five other drugs approved in the United States for the 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 approved for treatment of 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 the reduction of frequency of relapses in patients with relapsing-remitting MS. Each of the available first-line treatments (i.e., the interferon betas and glatiramer acetate) for RRMS produces approximately a 30% reduction in relapse rate (Interferon Study Group 1993; Jacobs et al, 1996;

PRISMS Study Group, 1998; Johnson et al, 1995). Each of these first-line treatments is administered by either subcutaneous or intramuscular injection, with dosing frequency ranging from once a day to once a week. Novantrone® (mitoxantrone) is indicated 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. Interferon beta administration is also associated with depression.

Although effective treatments are available, a substantial number of patients with relapsing MS remain untreated for their disease. Many of these patients have relatively little evidence of active inflammation clinically (relapses) or by MRI, and therefore choose not to begin treatment. Other patients have active relapsing MS but choose not to be treated because of fear of self-injection or potential adverse effect from the available treatments. Other patients have tried an approved treatment but discontinued treatment due to intolerance, adverse effects, or lack of efficacy.

Other Immune Modulators and Immunosuppressants

Corticosteroids are used for the 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 immune suppressants, such as azathioprine, cyclophosphamide, and methotrexate, have been studied for the 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.

Product

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. Natalizumab may also suppress inflammatory reactions in diseased tissues by inhibiting the interaction of 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. No pharmacologically-related products are marketed anywhere in the world.

Natalizumab is supplied as a sterile, colorless, and clear to slightly opalescent concentrate for IV infusion. 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.

Natalizumab Development

Biogen Idec, in collaboration with its partner Elan, studied natalizumab for the treatment of relapsing MS and Crohn's disease (CD). Two multicenter, randomized, double-blind, placebo-controlled studies (Studies 1801 and 1802) provided the primary evidence of safety and efficacy of natalizumab in RRMS. In both studies, subjects had experienced at least one clinical relapse during the year prior to study entry, providing evidence of clinically active disease. Most subjects in Study 1801 had never received any of the currently approved MS therapies and were randomized to placebo or natalizumab. Study 1802 enrolled subjects who had been receiving a standard MS therapy on a weekly basis during the year prior to study entry, and were randomized to continued Avonex plus placebo or continued Avonex plus natalizumab. Each study had two primary endpoints (pre-specified alpha of 0.025 for each endpoint for each study). For each study, the primary endpoint at one year was the annualized relapse rate, comparing the natalizumab group to the placebo group. The primary endpoint at 2 years was a comparison of the two study groups with regard to disability (EDSS) progression.

The end-year-1 results of these two studies were favorable, leading Biogen Idec to submit a marketing application for natalizumab in May 2004.

One-Year Study Results (Original Submission)

Study 1801 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 subjects who had experienced one or more relapses despite treatment with Avonex® (Interferon β-1a) during the year prior to study entry. 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%.

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 available first-line therapies (Avonex®, Betaseron®, Copaxone®, and Rebif®) for relapsing MS. Natalizumab is also the first drug to show efficacy when used as an add-on to a first-line therapy (Study 1802).

A total of 1617 MS subjects, in both controlled and uncontrolled studies, had been exposed to natalizumab, with a median duration of exposure of 20 months. Natalizumab appeared to cause hypersensitivity reactions, an increased risk of some infections, headache, depression, joint pain, and menstrual disorders. Hypersensitivity reactions were 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 appeared acceptable compared to natalizumab's apparent efficacy. Also, natalizumab did not appear to be seriously more risky than the available first-line MS therapies.

Natalizumab Regulatory History:

Original approval (11/23/04): FDA review of the marketing application led to the approval of natalizumab for the treatment of patients with relapsing forms of multiple sclerosis (MS), to reduce the frequency of clinical exacerbations.

Both Studies 1801 and 1802 (see "Natalizumab Development" above) were two years in duration; however, the original regulatory approval on November 23, 2004, was based on results (see above) achieved through approximately one year in the then ongoing studies. FDA approved natalizumab for marketing under Subpart E of the BLA regulations (21 CFR 601 subpart E). Subpart E allows accelerated approval of new biologics that provide meaningful therapeutic benefit over existing treatment for serious or life-threatening illnesses.

That original application provided evidence of efficacy, based on reduction in MS relapse rates, for only one year of natalizumab administration. 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 was quite robust, and was deemed reasonably likely to predict a clinical benefit at two years. Therefore, FDA accepted the effect at one year 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 was essential to verify that the efficacy observed at one year was sustained, and to further evaluate safety.

Withdrawal from Market (2/28/05): In February, 2005, Biogen Idec informed FDA of the occurrence of two cases of progressive multifocal leukoencephalopathy (PML; described in the Integrated Safety Review) in Study 1802 subjects who had received natalizumab in combination with an interferon beta. Following discussions between Biogen Idec and FDA, Biogen Idec voluntarily withdrew natalizumab from the market on February 28, 2005. During marketing of natalizumab between 11/23/04 and 2/28/05, approximately 7000 patients received up to three doses of natalizumab (details below).

Safety review: From March – August, 2005, Biogen Idec conducted a review of all subjects who received natalizumab during drug development. The objective of the review was to identify any additional cases of PML in order to better characterize the risk associated with natalizumab administration. The review identified one additional confirmed case of PML, in a subject in a Crohn's disease (CD) study, who had been exposed to a variety of immune-modulating agents. Therefore, natalizumab administration has been associated with PML in a total of three subjects, two with MS, and one with CD.

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

including hypersensitivity reactions, is a concern. Safety issues of infection, malignancy, and immunogenicity are discussed in the Integrated Safety Review.

Current Submission: On September 27, 2005, Biogen submitted the final study reports, including 2-year efficacy and safety data, from Studies 1801 and 1802 (see below). The pivotal trials, Studies 1801 and 1802, serve as the primary evidence of natalizumab's efficacy as a treatment for MS. These trials are the only large, randomized, placebo-controlled, double-blinded, Phase 3 studies of natalizumab of greater than 6 months duration in subjects with MS. Thus, they will be the focus of the Integrated Efficacy Review. The sponsor proposes that the available data confirms that natalizumab is effective in decreasing the incidence of relapses and that the progression of disability is delayed in natalizumab-treated patients with relapsing MS.

The sponsor also states that natalizumab has a favorable risk-benefit profile for some subjects with MS, and that, therefore, marketing should be resumed. To address the risk of PML, the sponsor has proposed a risk management plan (RMP; details below) to accompany the proposed return of natalizumab to the market. For the Integrated Safety Review, data from the clinical development programs in MS, Crohns's disease, and rheumatoid arthritis are considered. Specifically, for the common adverse events, serious adverse events, and for rare events such as malignancies, the placebo-controlled trials in both MS and active Crohn's disease (CD) subjects are pooled. This database consists of 1641 subjects with MS or CD in the placebo arms, and 2799 subjects with MS or CD in the natalizumab arms. The FDA has granted a priority review to this application, with a target decision date of March 29, 2006.

Questions to Advisory Committee

FDA requests that the Advisory Committee (AC) discuss the following questions. However, FDA also encourages the AC to discuss any other issues that the AC members believe are relevant to the current submission.

1. Has Biogen demonstrated natalizumab's efficacy on reduced frequency of relapses through two years, and fulfilled the commitment made under the Accelerated Approval regulations to verify the sustained clinical benefit?

2. Has Biogen demonstrated efficacy on reduced accumulation of physical disability?

3. Outside of PML, are there safety-related issues associated with use of natalizumab that you consider to be important considerations in making a risk-benefit assessment, including:
    a. Non-infectious disease risks?
    b. Non-PML infectious disease risks (e.g., opportunistic infections, herpes CNS infections)?

4. PML has been observed in the multiple sclerosis (MS) population only in patients concomitantly receiving Avonex, and in a patient with Crohn's disease who had a complex recent and prior history of immunosuppressive agent exposure. Do you believe that the natalizumab-associated risk of PML is entirely limited to patients concomitantly (or recently) exposed to a second immunosuppressive agent?

5. Are there additional data (or studies) that you recommend FDA obtain prior to determining whether natalizumab may return to the marketplace? If so, please describe the necessary data (or study).

6. If natalizumab returns to commercial distribution, are there specific subsets of the relapsing MS population for whom you would consider natalizumab use either reasonable or inappropriate? Please discuss, for example:

    a. Patients with MS who have not tried any of the other available first-line therapies (interferon beta or glatiramer acetate)
    b. Patients with MS who are above or below a specific level of disability or have some other specific disease-related criteria
    c. Patients with MS who have tried one (or more) of the other available therapies and have continued to have a specified frequency of relapses or rate of disability increase
    d. Patients with MS who have tried one of the available therapies and been unable to continue treatment due to intolerability of adverse effects
    e. Patients with MS who have received one of the available therapies and plan to continue that therapy while receiving natalizumab. Please discuss each of the available therapies (i.e. Avonex, Betaseron, Copaxone, Rebif, and Novantrone)

separately.

7. Considering the currently available data, please discuss whether natalizumab should be returned to the marketplace for at least some patients, taking into account the preceding discussion of specific populations. After discussion, please vote on this question.

8. If the answer to Question 7 above is in favor of return to commercial availability, and natalizumab returns to the marketplace at this time, please discuss what you consider to be the essential or non-essential features of an acceptable risk management plan. Please include in your discussion potential restrictions to patient availability such as:

    a. Patient registry with distribution restricted to only patients enrolled in the registry
    b. Restriction to only MS patients
    c. Restriction to only MS patients for whom natalizumab was deemed appropriate in the answer to Question 7

    And potential requirements for ongoing monitoring while receiving natalizumab, including, but not limited to:

    d. JC Virus assay in serum and/or cerebrospinal fluid
    e. MRI of brain
    f. Quantitative cognitive testing or brief cognitive screening questionnaire
    g. Periodic full neurologic exam or brief physical function questionnaire

9. For subjects who received natalizumab in clinical trials, and who have not received natalizumab for at least 1 year (or longer), do you recommend any further monitoring? If so, what monitoring procedures and what duration of monitoring do you recommend?

10. If the answer to Question 7 above is in favor of return to commercial availability, and natalizumab returns to the marketplace at this time, please discuss the following:

    a. If a patient discontinues natalizumab, what monitoring procedures and what duration of monitoring after discontinuation do you recommend?

    b. If a patient discontinues natalizumab and plans to initiate treatment with another

immune-modulating agent (e.g., an interferon beta or glatiramer acetate), do you recommend that the patient wait for some period of time before initiating the interferon beta or glatiramer acetate? If so, how long?

c. If a patient discontinues an immune-modulating agent (e.g., either an interferon beta or glatiramer acetate) and plans to initiate treatment with natalizumab, do you recommend that the patient wait for some period of time before initiating natalizumab? If so, how long?

11. The two PML infections observed in MS patients were both in patients receiving natalizumab and Avonex concurrently, suggesting the possibility that PML risk is greater in patients receiving concurrent treatment. Furthermore, while Study 1802 indicated that natalizumab added to Avonex provides additional benefit, it is unknown whether Avonex provides any additional benefit when added to natalizumab treatment. If, in the preceding discussion you have advised that use of marketed natalizumab be recommended only for monotherapy, please discuss if, and when, exploration of the safety and efficacy of concurrent use of natalizumab with Avonex, or any other interferon beta should be evaluated. Please include in your discussion the options of:

a) Never risk concurrent use
b) Evaluation of concurrent use in clinical trials only after the risk of PML or other infections in monotherapy is better quantified
c) Evaluation of concurrent use in clinical trials is acceptable at the present time
d) Any other approaches to improved understanding of the risk-benefit comparison of concurrent use you wish to recommend

Integrated Efficacy Review

Natalizumab was initially approved under Subpart E of the BLA regulations (21 CFR 601 subpart E) that allows for 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. At the time of the initial approval, the one-year results provided adequate evidence of a benefit on relapse rate in patients with relapsing remitting MS. For MS therapeutics, some may accept a relapse endpoint as proof of effectiveness, but the clinical meaningfulness of a decrease in relapse rate through only one year is not known. The other currently approved MS therapies have been required to show evidence of effectiveness at two years prior to approval for marketing. The accelerated approval of natalizumab after the one-year analysis was based on several factors, including the magnitude of the treatment effect at one year, the evidence of natalizumab's efficacy as an add-on therapy to other approved MS therapies, and the safety profile at the time of the initial filing.

The potential to use natalizumab as an add-on therapy was considered important for the initial accelerated approval because of the potential to address an unmet medical need. Specifically, many MS patients continue to have clinical exacerbations despite taking one of the available first-line MS therapies. None of the other approved therapies has shown a significant benefit as an add-on therapy for patients who continue to have these relapses despite treatment. Analysis of the one-year data suggested that natalizumab may offer this additional benefit as an add-on therapy, but the results of the two-year analysis are the subject of the current review.

Now, as primary evidence to support their BLA, the sponsor has submitted the final results of their two-year pivotal trials, Studies 1801 and 1802. The safety and efficacy results of each trial are described in the corresponding safety and efficacy integrated review sections.

Both pivotal studies were designed with separate one-year and two-year primary outcomes. The current submission is provided as evidence of the required clinically meaningful effect at two years (time to onset of confirmed progression of physical disability at 2 years) in support of conversion to a standard approval. The sponsor also is seeking a slightly broadened indication that includes delaying the progression of physical disability, as well as reducing the frequency of clinical exacerbations. Studies 1801 and 1082 are the only placebo-controlled, double-blinded

trials in subjects with MS that provide two-year efficacy data, and so they will be the focus of the two-year efficacy analysis.

Study 1801 was a monotherapy trial of natalizumab. In this double-blind, placebo-controlled, parallel-group study, subjects with relapsing MS were randomized to one of two treatment groups: Natalizumab 300 mg IV infusion every four weeks versus matching placebo infusion. The subjects were not on other MS treatments at the time of randomization.

The second pivotal trial, Study 1802, was not a natalizumab monotherapy study. Instead, the sponsor recruited patients with relapsing MS who had been taking Avonex (interferon β-1a) weekly injections for at least 12 weeks prior to randomization, but were considered to have an inadequate response to Avonex because they had suffered a clinical exacerbation within 12 months prior to randomization. Study 1802 had a similar design to Study 1801, but Study 1802 was an add-on study. Specifically, all subjects in the trial were on Avonex at study entry and throughout the trial. Study 1802 subjects were randomized to receive either natalizumab 300 mg IV infusions every four weeks, or matching placebo infusions.

Indication for Treatment of Multiple Sclerosis

The currently proposed indication is "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." Under the initial accelerated approval, the indication for natalizumab was for relapsing forms of multiple sclerosis to reduce frequency of clinical exacerbations. Now the sponsor is seeking to convert the accelerated approval to a standard approval and expand the labeled indication by including the delay of progression of physical disability.

General Discussion of Endpoints

Multiple sclerosis is a disease manifesting both clinical relapses and progressive disability. In the past, the FDA has approved MS therapies based on evidence of an effect on either the frequency of clinical relapses or the progression of disability. Also, the past approvals of MS therapies have been based on data from two-year trials, and the FDA has held that the clinical meaningfulness of an effect on relapse rate after only one year of study drug administration is unclear. In the case of natalizumab, the sponsor proposed submitting the one-year data for

accelerated approval under Subpart E, using the one-year relapse rate as a surrogate that could predict efficacy after two years of study agent administration. The pre-specified primary endpoint at two years for the pivotal trials, however, was not relapse rate, but the progression of disability at two years.

The progression of disability and the occurrence of clinical relapses in MS are both clinically meaningful aspects of the disease, and could be useful as primary outcomes for Phase 3 MS trials. However, both clinical relapses and progression of disability are subjective measures and susceptible to investigator bias. Several techniques were employed to reduce bias and preserve the blinding. These study design elements are described in more detail under the section, "Minimization of Bias."

The pivotal trials of currently approved agents have frequently used MRI outcomes as secondary endpoints, and blinding of MRI assessments can be readily accomplished by using a central reading center with blinded readers to interpret scans. Yet, the clinical significance of MRI outcomes is not clear, and so MRI outcomes have not been viewed by FDA as acceptable primary outcomes in pivotal MS trials.

The pivotal studies in this application were designed with two sets of objectives and endpoints: one for the first year and one for the second year. The primary endpoints are identical for Studies 1801 and 1802, but the data was analyzed at slightly different time points after the first year in each study, due to sample size requirements. The timing for data cut-off at one year and at two years was pre-specified. For the one-year analyses, cut-off was to occur after subjects had undergone an average of one year of observation, but the protocol was later amended to include specific cut-off dates for clinical and MRI data to be included in the one-year analysis. The sponsor identifies the available data collected at this point in each study as the "one-year analysis." In fact, these analyses were not conducted at the one-year point for each subject, but are based on analyses that consider different lengths of study for the different subjects. These analyses and endpoints are considered as "one-year" as a convenient approximation.

Cut-off for the analysis of the second year of data was also pre-specified. The primary efficacy endpoint for the second year was designed to look at the effects of natalizumab on the sustained progression of disability at two years, as measured by EDSS (Expanded Disability Status Scale) scores. The EDSS is a disability scale that has been widely used in MS clinical trials. The EDSS score is based on measurements of eight different areas of the nervous system, also known

as eight "functional systems." Each of the eight systems is graded based on the amount of impairment. The total score ranges from 0 (normal) to 10 (death due to MS).

The sponsor set the cut-off point for data collection by requiring that at least 75% of the subjects had been studied for 120 weeks for each pivotal trial. Both Study 1801 and 1802 each describe co-primary outcomes, including annualized relapse rate at one year and progression of disability at two years.

Pivotal Trial Designs – Study 1801 and Study 1802

The study designs of the two pivotal MS trials, Studies 1801 and 1802, were very similar and key components are described in the following sections. For most sections of the protocol, Study 1801 and 1802 are identical. For the purposes of this document, Study 1801 will be described first, and then the differences between Studies 1801 and 1802 will be described. For each study, additional details regarding the study design are available in Appendix 3: Study 1801 Protocol Summary (Study 1801) or Appendix 4: Study 1802 Protocol Summary (Study 1802).

Study 1801

Primary Efficacy Endpoint for Two-Year Analysis

The primary endpoint for the two-year analysis is time to onset of the progression of disability, as measured by at least a 1.0 point increase in baseline EDSS (if baseline was 1.0 or more) or at least a 1.5 point increase from baseline EDSS (if baseline EDSS was 0), sustained for 12 weeks.

The analysis of the primary endpoint at 2 years was performed using a Cox proportional hazards model. The model included terms for treatment and baseline EDSS. The three baseline factors included in the model were selected using a backwards selection procedure. This resulted in the inclusion of baseline Gd-enhancing lesions, baseline T2 lesions, and age at baseline into the model. Kaplan-Meier methodology was also used to estimate the percentage of subjects progressing by 2 years.

Secondary Efficacy Endpoints for Two-Year Analysis

The secondary endpoints for the two-year analysis, in order of decreasing importance, include

the following:

- the rate of MS relapses
- the mean volume of T2-hyperintense lesions
- the mean number of T1-hypointense lesions
- the progression of disability as determined by changes in the Multiple Sclerosis Functional Composite (MSFC) score

The MSFC (Cutter, 1999) is a scale with three components testing walking speed (Timed 25-Foot Walk), arm dexterity (9-Hole Peg Test), and cognitive functioning (Paced Auditory Serial Addition Test). Each component of the scale is scored separately and then a composite score calculated based on the average of the three component scores.

Analyses of the secondary endpoints were prioritized in order of importance. A closed testing procedure was used. If an endpoint did not achieve statistical significance, then all endpoints of a lower rank were considered to be not statistically significant.

Adequacy of Study Design

The sponsor has submitted the results of Studies 1801 and 1802 and evidence of efficacy of natalizumab for the treatment of MS. These trials are similar in design in that they are both large, Phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel group trials of natalizumab compared to placebo in subjects with relapsing MS. Study 1801 is designed as a monotherapy trial of natalizumab, while Study 1802 examines efficacy of natalizumab as an add-on therapy to Avonex. In Study 1801, approximately 900 RRMS subjects were randomized in a 2:1 fashion to receive natalizumab 300 mg or matching placebo administered as an IV infusion every four weeks for up to 116 weeks. The subjects were randomized and received their first infusion at their baseline visit (Week 0). The randomization was stratified by site using a centralized randomization schedule to balance the treatment group assignments within sites.

Several efficacy parameters were assessed, including MS relapses, brain MRI scans, EDSS scores, MSFC scores, and visual function tests. The MSFC and EDSS were measured every 12 weeks. The subjects underwent brain MRI scans at baseline and then every year. Also, MS relapses were assessed on an ongoing basis at unscheduled visits.

The designs of these two pivotal studies meet the regulatory requirements for adequate and well-

controlled studies (21 CFR 314.126) that are capable of providing a reasonable assessment of benefit of natalizumab in patients with MS. To begin, these studies are placebo-controlled. The study objectives in the trials are clear. The statistical analysis plan and outcomes were also pre-specified and make sense from a clinical viewpoint (see previous section for a discussion of appropriate endpoints). The original protocol and subsequent protocol amendments are clearly described. Irregularities in the data and protocol violations are also included in the study reports. Further, the designs of the trials permit a valid comparison with a placebo control to provide quantitative assessment of drug effect. The randomization technique is acceptable and helps to minimize bias. The sponsor has employed multiple techniques to maintain blinding and prevent bias in the trials. These techniques appear consistent with what has been accepted by the FDA for previous trials.

Entry Criteria

Study 1801 was conducted in relatively young subjects (ages 18-50 years) who had a definite diagnosis of MS by McDonald criteria, but were not then on other treatments for the disease. They also had to have a baseline EDSS score between 0.0 and 5.0 (inclusive), a baseline brain MRI with at least one lesion typical of MS, and a documented clinical relapse within the year prior to randomization. These criteria resulted in recruitment of subjects who were relatively recently diagnosed with MS (the median time since diagnosis was two years).

Study 1802: Key Differences in Design from Study 1801

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

- Target enrollment was approximately 1200 subjects
- 1:1 randomization to either natalizumab or placebo
- Inclusion criteria – subjects between 18 and 55 years of age, inclusive
- Inclusion criteria that all subjects must have received Avonex for at least 12 months prior to randomization. (Subjects were excluded from Study 1801 if they had ≥ 6 months exposure to Avonex.)
- Subjects were to receive 30 μg Avonex by IM injection once a week throughout the study. Avonex was not to be administered within 24 hours of the study drug infusion.
- Subjects had to have had at least one relapse in the prior 12 months while on Avonex.

- Exclusion criteria based on prior treatment – mycophenolate mofetil was not allowed within 6 months of randomization in 1802 (no restriction in 1801)
- The way that T1-hypointense lesions were counted in Study 1802 varied slightly from the method used in Study 1801, as per their respective protocols. In Study 1801, all T1-hypointense lesions were counted; however, in Study 1802, only the non-enhancing T1-hypointensities, or T1-black holes, were counted. Also, in Study 1802, individual lesion counts per slice were assessed rather than total number of lesions. Thus, a single lesion that traversed three MRI slices was counted three times in Study 1802 and once in Study 1801.

Efficacy Results

The two-year analyses of the pivotal trials, Studies 1801 and 1802, provide the primary evidence of natalizumab effectiveness for the treatment of MS. Therefore, the two-year results of Studies 1801 and 1802 are the focus of this review and are considered individually, and then compared.

Subject Disposition

In Study 1801, 942 subjects were randomized at 99 sites in North America, Europe, Australia, and New Zealand. Study 1802 enrolled a total of 1171 subjects who were randomized at 123 sites in North America, Europe, and Israel. If subjects discontinued the study drug, they were encouraged to remain in the trial and complete the evaluations. Therefore, some subjects discontinued study drug, but remained in the trial, while others withdrew from the trial after discontinuing the study drug. The following table summarizes the disposition of the subjects in the pivotal trials.

Table 1: Studies 1801 and 1802 - Subject Disposition

	Study 1801		**Study 1802**	
Number of Subjects (%)	***Placebo***	***Natalizumab***	***Placebo + Avonex***	***Natalizumab + Avonex***
Randomized	315 (100)	627 (100)	582 (100)	589 (100)
Withdrew prior to dosing	3 (<1)	0	0	0
Dosed	312 (99)	627 (100)	582 (100)	589 (100)
Completed study	281 (89)	575 (92)	487 (84)	516 (88)
Discontinued study drug	45 (14)	73 (12)	129 (32)	100 (17)
Lost to follow-up	3 (<1)	3 (<1)	3 (<1)	3 (<1)
Adverse event	11 (3)	38 (6)	39 (7)	45 (8)
Voluntary withdrawal	22 (7)	15 (2)	53 (9)	27 (5)
Non-compliance	0	3 (<1)	4 (<1)	6 (1)
Death	0	1 (<1)	0	0
Other	9 (3)	13 (2)	30 (5)	19 (3)
Withdrew from study	34 (11)	52 (8)	95 (16)	73 (12)
Lost to follow-up	5 (2)	7 (1)	5 (1)	4 (1)
Adverse event	7 (2)	15 (2)	14 (2)	17 (3)
Voluntary withdrawal	14 (4)	12 (2)	45 (8)	25 (4)
Non-compliance	0	4 (<1)	5 (1)	6 (1)
Death	0	2 (<1)	2 (<1)	0
Other	8 (3)	12 (2)	24 (4)	21 (4)

Studies 1801 and 1802 – Demography

The baseline demographic characteristics between subjects in Studies 1801 and 1802 were fairly balanced between treatment groups. The average age was approximately 36 in each group, and 95% of the subjects were white. In Study 1802, the women outnumbered the men by an approximate 3:1 ratio. The great majority of subjects were white (93%) and the average age was approximately 39 in each group. The following table summarizes the baseline demographic

characteristics of subjects in the pivotal trials.

Table 2: Studies 1801 and 1802 – Demography

	Study 1801		**Study 1802**	
Number of Subjects (%)	***Placebo***	***Natalizumab***	***Placebo + Avonex***	***Natalizumab + Avonex***
Randomized	315 (100)	627 (100)	582 (100)	589 (100)
Age (years)				
n	315	627	582	589
Mean	36.7	35.6	39.1	38.8
s.d.	7.81	8.46	7.64	7.67
Median	37.0	36.0	39.0	39.0
Min., Max	19, 50	18, 50	19, 55	18, 55
Gender				
Male	104 (33)	178 (28)	162 (28)	147 (25)
Women	211 (67)	449 (72)	420 (72)	442 (75)
Race				
Black	6 (2)	4 (<1)	22 (4)	17 (3)
White	296 (94)	603 (96)	542 (93)	55 (93)
Asian	3 (<1)	3 (<1)	4 (<1)	2 (<1)
Hispanic	6 (2)	7 (1)	9 (2)	13 (2)
Other	3 (<1)	6 (<1)	5 (<1)	7 (1)
Missing	1 (<1)	4 (<1)	0	0
Height				
n	311	624	575	586
Mean	196.61	169.69	168.51	167.66
s.d.	9.045	9.448	9.884	9.536
Median	168	169.0	168.0	168.0
Min., Max	137.0, 197.0	127.0, 200.0	127.0, 205.0	124.0, 202.0
Weight				
n	314	626	577	583
Mean	72.23	71.8	73.03	72.49
s.d.	16.015	16.121	16.909	17.097
Median	70.65	69.0	70.0	70.0
Min., Max	39.5, 145.0	42.0, 129.0	40.0, 149.0	39.5, 137.5

Studies 1801 and 1802 – Baseline Disease Characteristics and Prior Medication Use

The baseline disease characteristics of subjects in the pivotal trials were balanced between treatment groups within each study, but the subjects did vary slightly between trials. On average, the subjects in Study 1802 had a longer duration of disease and higher baseline EDSS score, but the number of pre-study relapses between groups was similar. Also, the diagnosis of MS for all subjects in the trials was based on the McDonald criteria (McDonald, 2001). The sponsor examined how many of these subjects would have fit the criteria for clinically definite MS by using the older Poser criteria, and found that 96% of the subjects in Study 1801 and 99% of the subjects in Study 1802 were diagnosed based on two or more relapses and one or more objective lesions, clinically or MRI. Thus, nearly all of the subjects would have satisfied Poser criteria (Poser 1983) for clinically definite MS. The prior MS therapies that had been administered from the time of diagnosis until entry into one of the pivotal trials were also examined for subjects in each trial. As part of the entry criteria, all subjects in Study 1802 had to have been on Avonex for at least 12 months prior to study entry. The next most commonly used treatments were interferon β-1b, steroids, glatiramer acetate, and azathioprine. Within each treatment group in Study 1802, the use of prior medications appeared balanced. Likewise, in Study 1801, the use of prior medications was also relatively balanced between treatment groups. In Study 1801, 31% of the natalizumab-treated subjects and 28% of the placebo-treated subjects had received MS therapies prior to entering the study. The most common therapy was steroids. Of the approved MS treatments, interferon β-1a, glatiramer acetate, and interferon β-1b were the most commonly used prior to entering Study 1801. The following tables summarize prior medication use and the baseline disease characteristics.

Table 3: Studies 1801 and 1802 - Prior Medication Use

Number of Subjects (%)	**Study 1801**		**Study 1802**	
	Placebo	***Natalizumab***	***Placebo + Avonex***	***Natalizumab + Avonex***
Number Randomized	315 (100)	627 (100)	582 (100)	589 (100)
Number of subjects who had taken any of the following treatments prior to study entry	87 (28)	196 (31)	582 (100)	589 (100)
Interferon beta-1a	11 (3)	23 (4)	582 (100) (a)	589 (100)(b)
Interferon beta-1b	6 (2)	11 (2)	54 (9)	57 (10)
Steroids	53 (17)	118 (19)	32 (5)	29 (5)
Glatiramer acetate	9 (3)	19 (3)	27 (5)	26 (4)
Azathioprine	10 (3)	21 (3)	25 (4)	22 (4)
IV immunoglobulin	3 (<1)	12 (2)	6 (1)	14 (2)
Other	12 (4)	24 (4)	36 (6)	25 (4)
(a) All took Avonex and 4 (<1%) took Rebif; (b) All took Avonex and 6 (1%) took Rebif				

Table 4: Baseline Disease Characteristics

Number of Subjects (%)	**Study 1801**		**Study 1802**	
	Placebo	***Natalizumab***	***Placebo + Avonex***	***Natalizumab + Avonex***
Number randomized	315 (100)	627 (100)	582 (100)	589 (100)
Time since symptom onset (years)				
n	315	627	582	588
Median	6	5	5	7
Min., max.	0, 33	0, 34	1, 34	1, 34
Time since MS diagnosis (years)				
n	315	627	582	588
Median	2	2	5	4
Min., max.	0, 23	0, 24	0, 30	0, 27
EDSS score				
0	18 (6)	31 (5)	19 (3)	24 (4)
1.0-1.5	94 (30)	179 (29)	143 (25)	145 (25)
2.0-2.5	103 (33)	208 (33)	203 (35)	214 (36)
3.0-3.5	36 (20)	130 (21)	126 (22)	125 (21)
4.0-4.5	28 (9)	60 (10)	72 (12)	68 (12)
5.0 and greater	9 (3)	19 (3)	19 (3)	13 (2)
n	315	627	582	589
Median	2.0	2.0	2.5	2.0
Min., max.	0.0, 6.0	0.0, 6.0	0.0, 5.5	0.0, 6.0
Number relapses within past 3 years				
n	315	627	582	586
Median	2	3	3	3
Min., max	1, 14	1, 24	1, 16	1, 13

Table 4 (continued): Baseline Disease Characteristics

Number of Subjects (%)	**Study 1801**		**Study 1802**	
	Placebo	***Natalizumab***	***Placebo + Avonex***	***Natalizumab + Avonex***
Number randomized	315 (100)	627 (100)	582 (100)	589 (100)
Number of relapses within past 12 months				
n	315	627	582	587
Median	1	1	1	1
Min., max	0, 5	0, 12	0, 5	1, 7
Time since most recent pre-study relapse (months)				
n	315	627	582	588
Median	6	5	5	5
Min., max	1, 13	1, 14	1, 16	0, 14
Number randomized	315 (100)	627 (100)	582 (100)	589 (100)
Number meeting McDonald criteria (%)				
1 (a)	261 (83)	528 (84)	532 (91)	538 (91)
2 (b)	40 (13)	72 (11)	44 (8)	46 (8)
3 (c)	10 (3)	18 (3)	3 (<1)	3 (<1)
4 (d)	4 (1)	9 (1)	3(<1)	2 (<1)

(a) 2 or more relapses, 2 or more objective lesions. (b) 2 or more relapses, 1 objective lesion, and dissemination in space by MRI or positive CSF and 2 or more MRI lesions consistent with MS or further clinical attack involving different site. (c) 1 relapse, 2 or more objective lesions, and dissemination in time by MRI or second clinical attack. (d) 1 (mono-symptomatic) relapse, 1 objective lesion, dissemination in space by MRI or positive CSF and 2 or more MRI lesions consistent with MS, and dissemination in time by MRI or second clinical attack.

Studies 1801 and 1802 – Two-Year Primary Efficacy Outcome (Disability Progression)

The primary outcome of the two-year analyses for both clinical trials was time to onset of

sustained progression in disability as measured by change in EDSS. The EDSS change had to be at least a 1.0 point increase from a baseline EDSS of at least 1.0 that is sustained for 12 weeks, or at least a 1.5 point increase from baseline EDSS of 0 that is sustained for 12 weeks. When a subject met the definition of sustained progression of disability, then this event was counted as part of the analysis of the primary outcome. Many subjects in each trial completed the study without a progression of disability. Thus, they were censored at the end of the study. The number of subjects whose disability progressed during the trial is small, but a statistical difference is seen between treatment groups. The treatment effect on progression of disability for the natalizumab group is more apparent in Study 1801 than in Study 1802, but again, statistical significance is achieved in both trials. The FDA reanalyzed the two-year primary endpoint in Studies 1801 and 1802 and the results were consistent with the sponsor's analyses. No significant irregularities in the data have been identified.

Determination of Disability Progression

According to the protocol, confirmation of disability progression could not occur within 30 days from onset of a relapse. EDSS was measured at unscheduled visits during suspected relapses, as well as scheduled visits every 12 weeks. Yet, progression could not be confirmed at an unscheduled visit. Instead, the subject was required to return for confirmation at a later date.

Two consecutive visits that were at least 12 weeks (84 days) apart qualified for defining sustained progression, but the actual visits may have been +/- 5 days from the scheduled visit, resulting in EDSS examinations that were less than 84 days apart. The minimum number of days apart for visits to confirm progression of EDSS was 74 days by protocol. Death due to MS was counted as progression. If a subject was in a tentative progression at the time of death, then the progression date was the start of the progression. Otherwise, the progression date was the date of death.

If a subject returned for confirmation of a tentative EDSS progression, but the EDSS value measured at the confirmatory visit was not at least as high as the minimum change required for progression, then the EDSS progression could not be confirmed. For example, is a subject with a baseline EDSS score of 0.0 was observed to have an EDSS score of 1.5 at the Week 36 visit, but an EDSS score of 1.0 at Week 48, then progression could not be confirmed at Week 48.

If a subject had an increase in EDSS score that met the criteria for progression, but then missed one or more visits to confirm the increase in EDSS, but later was tested and found to have the persistent increase in EDSS score, then the subject was considered to have progressed. Disability progression could also be confirmed at an early study withdrawal visit, as long as the subject was not also having a relapse.

In both trials, a statistically significant effect was seen on time to progression of sustained disability. However, a substantial issue in interpreting the results of these studies is the high rate of censoring.

Censoring Rules

Subjects were censored if they prematurely ended treatment. They were to remain in the study for follow-up, and follow-up was only terminated if they completely withdrew from the trial. Otherwise, follow-up ended on the last visit when subjects withdrew from the study.

Subjects without confirmed disease progression who took alternate MS medications, were censored at the time that they took the alternate MS medications. Confirmation of disease progression may have led some subjects to begin taking alternate MS medications.

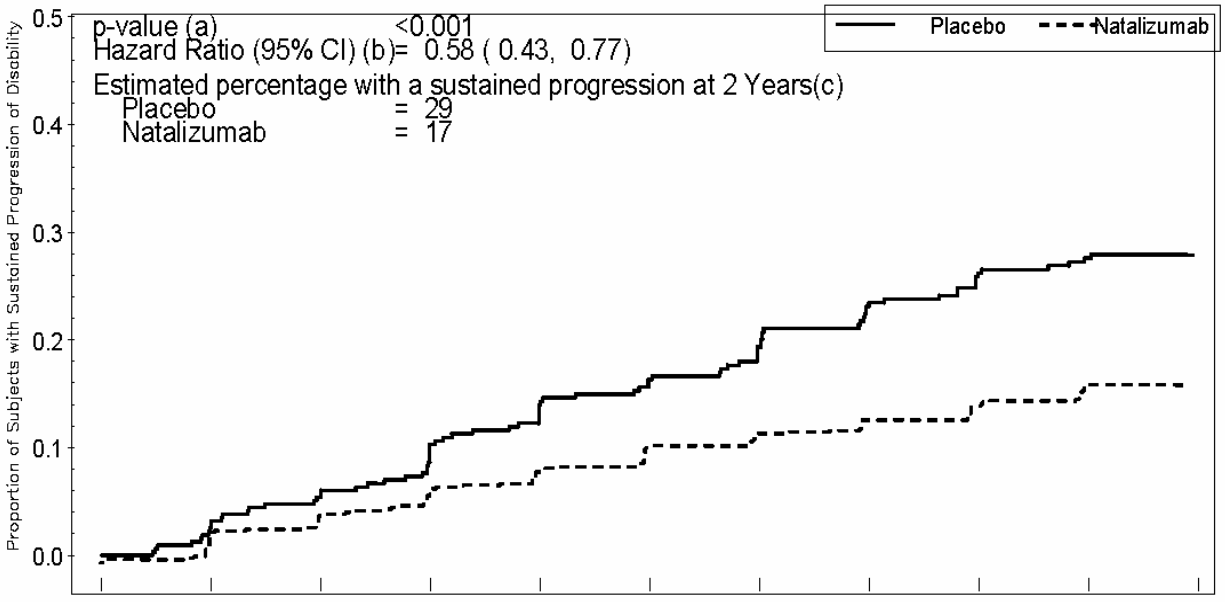
Study 1801 – Sponsor Analyses of Two-Year Primary Outcome

Study 1801 appears to win on the primary outcome, time to sustained progression in disability, at two years. The primary endpoint at 2 years was compared between treatment groups using Cox proportional hazards model. The model adjusts for baseline EDSS score and age. Baseline MRI findings were considered in the model, but excluded by backwards selection. The proportion of subjects progressing at two years was estimated using Kaplan-Meier methodology. Most subjects were censored because they finished the trial, but did not have sustained progression of disability, as measured by EDSS.

The Kaplan-Meier estimate of the percentage of subjects in the Intent-to-Treat (ITT) population who progressed by two years was 29% in the placebo group and 17% in the natalizumab group. Cox proportional hazards modeling, with adjustments for baseline

EDSS and age, revealed a hazard ratio of 0.58 (95% CI: 0.43, 0.77) indicating a 42% relative reduction in the risk of disability progression over the 2-year period of natalizumab treatment. The comparison between the treatment groups was highly statistically significant ($p<0.001$). The FDA reanalyzed the sponsor's data for primary efficacy outcome and the results were consistent with the sponsor's results. Figure 1: Time to Sustained Progression of Disability as Measured by Increase in EDSS of ≥1.0 from Baseline in ITT Population (taken from sponsor's figure 14.2-3 in final report of Study 1801)below illustrates the Kaplan-Meier results.

Figure 1: Time to Sustained Progression of Disability as Measured by Increase in EDSS of ≥1.0 from Baseline in ITT Population (taken from sponsor's figure 14.2-3 in final report of Study 1801)



Number of Patients at Risk

Placebo	315	296	283	264	248	240	229	216	208	200
Natalizumab	627	601	582	567	546	525	517	503	490	478

NOTE: Sustained progression of disability is defined as at least 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.

(a) Log Rank p-value.
(b) Hazard ratio (natalizumab/placebo) estimated from a Cox proportional hazards model adjusting for baseline EDSS and age (<40 versus >=40)
(c) Kaplan Meier estimate of the percentage of subjects expected to have sustained progression within 2 Years

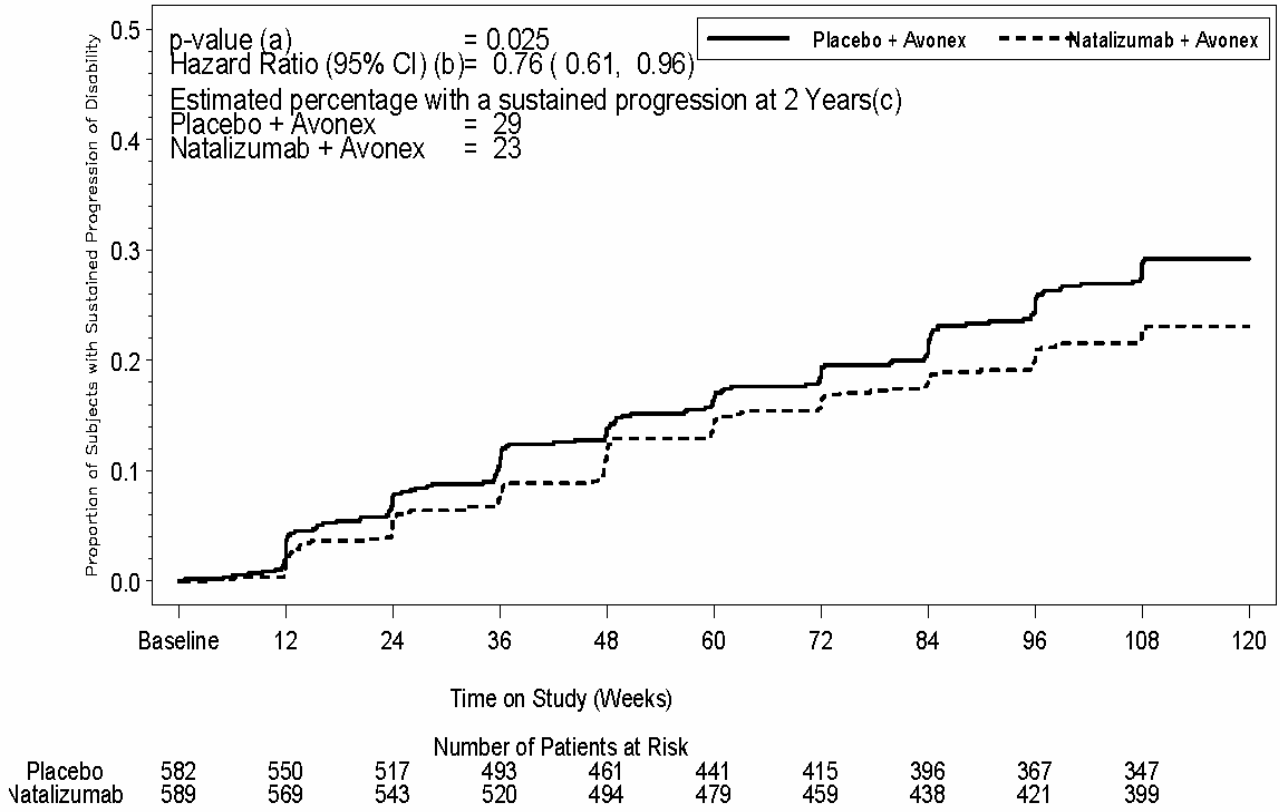
SOURCE: ANTEGREN\C-1801U2\TABFIG\F_SUS2YA.SAS DATE: 05APR2005

Study 1802 – Sponsor Analyses of Two-Year Primary Outcome

As in Study 1801, the primary endpoint at two years for Study 1802 was the time to onset of sustained progression in disability as measured by EDSS in the ITT population. In Study 1802 all subjects received Avonex concomitantly with the study treatment (natalizumab or placebo). Also, to be eligible for 1802, subjects must have been on weekly SC injections of Avonex for at least 12 months prior to randomization. They also had to have had a clinical relapse within 12 months prior to randomization while on Avonex. Thus, these subjects were viewed as having an incomplete response to Avonex, as well as active disease.

The results of the two-year primary outcome in Study 1802 also appear to be positive, but the treatment effect on disability progression is not as large as what was seen in Study 1801. According to the sponsor's analysis, the Kaplan-Meier estimate percentage of subjects progressing by two years was 29% in the placebo group, compared to 23% in the natalizumab group. A Cox proportional hazards model was constructed adjusting for baseline EDSS score. This model yielded a hazard ratio of 0.76 (95% CI: 0.61, 0.96) representing a 24% relative reduction in the risk of disability progression after treatment with natalizumab (p=0.024). FDA conducted an independent analysis of the primary outcome and the results corroborated the sponsor's analysis. The Kaplan-Meier results are illustrated in the following figure.

Figure 2: Study 1802: Time to Onset of Sustained Progression in Disability at 2 Years as Measured by Increases in EDSS (from the sponsor's figure 11.4-1 in the final report of Study 1802)



NOTE: Sustained progression of disability is defined as at least 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.

(a) Log Rank p-value.
(b) Hazard ratio (natalizumab/placebo) estimated from a Cox proportional hazards model adjusting for baseline EDSS
(c) Kaplan Meier estimate of the percentage of subjects expected to have sustained progression within 2 Years

SOURCE: ANTEGREN\C-1802U2\TABFIG\F_SUS2YA.SAS DATE: 18JUL2005

Studies 1801 and 1802 – Clinical Relapse Rate

Clinical relapse rate was the primary outcome for the first year data, and is the highest ranked secondary outcome for the two-year analyses.

Study 1801 – Sponsor's Two-Year Annualized Relapse Rate Analyses

Annualized relapse rate was the highest ranked secondary outcome for the two-year analyses. All data from all of the ITT subjects were included in the analysis of

annualized relapse rate up until they reached Week 104, took alternative medication for MS, or withdrew from the study. The placebo group contained 564.7 subject-years of data and the natalizumab group contained 1181.0 subject-years of data. The annualized relapse rate in the placebo group was 0.733 (95% CI: 0.619, 0.869) and the corresponding rate in the natalizumab group was 0.235 (95% CI: 0.193, 0.285). This difference of 0.498 represents a relative decrease of 68% in the annualized relapse rate for the natalizumab-treated group ($p<0.001$). FDA conducted analyses of the two-year annualized relapse rates in Study 1801, and the results are consistent with the sponsor's analyses. The following table summarizes the two-year annualized relapse rate in the ITT population.

Table 5: Study 1801 - Annualized Relapse Rate at Two Year in ITT Population (from sponsor's Table 11.4-8 of final report of Study 1801)

	Placebo	Natalizumab	Rate Ratio (95% CI) and p-value (a)
Number of subjects randomized	315 (100)	627 (100)	
Number of subjects with a relapse	169	173	
Number of relapses (b)			
0	146	454	
1	65	123	
2	63	36	
3	22	7	
≥4	19	7	
Total number of relapses	345	248	
Total subject-years followed	564.7	1181.0	
Unadjusted annualized relapse rate (c)	0.611	0.210	
Adjusted annualized relapse rate (95% CI) (a)	0.733 (0.619, 0.869)	0.235 (0.193, 0.285)	0.320 (0.256, 0.399) <0.001
Subject relapse rate (d)			
Mean	0.761	0.248	
Median	0.500	0.000	

NOTE: The analysis includes relapses and time on the study up to the time that alternative MS medication is added. (a) From Poisson regression, adjusted for the number of relapses in the one year prior to study entry, baseline EDSS (<=3.5 versus >3.5), presence of Gd lesions (present versus absent) and age (<40 versus ≥40). (b) Numbers in parentheses are percentages. (c) The total number of relapses that occurred during the study divided by the total number of subject-years followed in the study. (d) The number of relapses for each subject divided by the number of years followed in the study for that subject. Mean and median across all subjects are presented.

The sponsor indicates that the relapse rate over two years was lower than the relapse rate for the first year for each treatment group. This would indicate that the relapse rate the

second year was lower than the relapse rate the first year. This decrease in relapse rate from the first to second year is not unexpected as subjects with more treatment-resistant disease would be more likely to be censored earlier in the trial because they have stopped the study drug, have taken alternate MS therapies, or have dropped out of the study. As more subjects drop out of the trial, the proportion of subjects remaining who are less likely to experience a clinical relapse compared to those who are more likely, would increase. This would result in a lower relapse rate for each treatment group.

Study 1802 – Sponsor's Two-Year Annualized Relapse Rate Analyses

Annualized relapse rate was the highest ranked secondary outcome for the two-year analyses in Study 1802. All data from all of the ITT subjects were included in the analysis until they reached Week 104, took alternative medication for MS, or withdrew from the study. The placebo plus Avonex group contained 1057.6 subject-years of data and the natalizumab plus Avonex group contained 1117.2 subject-years of data. The annualized relapse rate in the placebo plus Avonex group was 0.749 (95% CI: 0.667, 0.842) and the corresponding rate in the natalizumab plus Avonex group was 0.336 (95% CI: 0.289, 0.390). This difference of 0.413 represents a 55% relative decrease in the annualized relapse rate for the natalizumab-treated group over two years ($p<0.001$).

Table 6: Study 1802 - Annualized Relapse Rate at Two Years in ITT Population (from sponsor's Table 11.4-8 of final report of Study 1802)

	Placebo + Avonex	**Natalizumab + Avonex**	**Rate Ratio (95% CI) and p-value (a)**
Number of subjects randomized	582 (100)	589 (100)	
Number of subjects with a relapse	365 (63)	230 (39)	
Number of relapses (b)			
0	217 (37)	359 (61)	
1	164 (28)	158 (27)	
2	105 (18)	41 (7)	
3	51 (9)	20 (3)	
≥4	45 (8)	11 (2)	
Total number of relapses	738	346	
Total subject-years followed	1057.6	1117.2	
Unadjusted annualized relapse rate (c)	0.698	0.310	
Adjusted annualized relapse rate (95% CI) (a)	0.749 (0.667, 0.842)	0.336 0.289, 0.390	0.448 (0.382, 0.525) < 0.001
Subject relapse rate (d)			
Mean	0.785	0.326	
Median	0.500	0.000	

NOTE: The analysis includes relapses and time on the study up to the time that alternative MS medication is added.

(a) From Poisson regression, adjusted for the number of relapses in the one year prior to study entry, baseline EDSS (<=3.5 versus >3.5), presence of Gd lesions (present versus absent) and age (<40 versus ≥40)

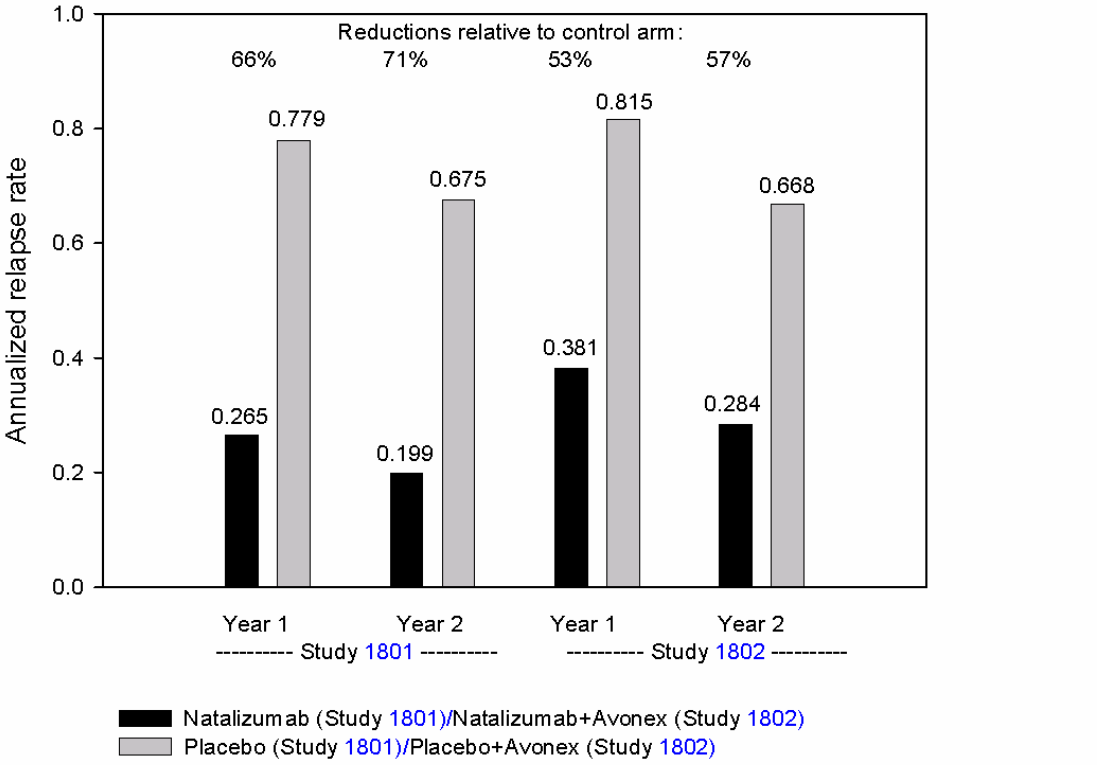
(b) Numbers in parentheses are percentages.

(c) The total number of relapses that occurred during the study divided by the total number of subject-years followed in the study.

(d) The number of relapses for each subject divided by the number of years followed in the study for that subject. Mean and median across all subjects are presented.

The sponsor indicates that the relapse rate over two years was lower than the relapse rate the first year for each treatment group. This indicates that the relapse rate the second year was lower than the relapse rate the first year. This decrease in relapse rate from the first to second year was also seen in Study 1801 in each treatment group, and is expected, as described above. FDA independently conducted analyses of the one- and two-year annualized relapse rate in Study 1802, and the results are consistent with the sponsor's analyses. The following figure shows the decrease in relapse rate over two years for each treatment group in Studies 1801 and 1802.

Figure 3: Annualized Relapse Rates in the First and Second Years in Phase 3 Studies (from Figure 5-1 in the sponsor's Summary of Clinical Efficacy in MS)



Annualized relapse rates following treatment with natalizumab were significantly reduced compared to placebo in all four analyses ($p<0.001$ in each analysis)

Study 1801 – Two-Year T2-Hyperintense Lesion Volume on Brain MRI Scan

The T2-hyperintense lesion volume was a secondary outcome in each pivotal trial. The T2 measurements were taken at baseline, Week 52, and Week 104. Changes in lesion volume were determined as both actual change and percentage change. The sponsor's

analysis indicates that at two years, the natalizumab treatment group had significantly reduced volume of T2-hyperintense lesions on brain MRI scans when compared to the placebo group. The average absolute volume of T2-hyperintense lesions appeared to decrease from baseline (Week 0) to one year (Week 52) in the natalizumab group, while it increased in the placebo group. Overall, the differences between treatment groups were significant at two years, compared to baseline. When one examines the differences between baseline (Week 0) and the end of year one (Week 52), compared to the differences seen between the end of year one (Week 52) and the end of year two (Week 104), it appears that the differences in treatment groups change slightly from year to year. Specifically, during the first year, there appears to be an actual decrease in the average volume of T2 lesions in the natalizumab group compared to the placebo group. During the second year, the natalizumab-treated group has a slight increase in T2 volume compared to the placebo-treated group at the end of the first year (Week 52). The average T2 volume during the second year of treatment increased much more in the placebo-treated group than the natalizumab-treated group, and the differences between the groups were significant.

The FDA did not reanalyze the sponsor's data for this secondary outcome. The following table summarizes the changes seen in T2-hyperintense lesion volume in the two treatment groups. In the table, a negative value is associated with a decrease in volume and a positive value is associated with an increase in volume.

Table 7: Study 1801 – Analysis of T2-Hyperintense Lesion Volume (mm^3) on Brain MRI Scans (from sponsor's Table 11.4-14 in the final repot of Study 1801)

	Placebo	Natalizumab	p-value (a)
Number Randomized	315	627	
Absolute volume at baseline (Week 0)			
n	315	627	
Mean	14962.3	15627.4	
Volume change from baseline to 1 year (Week 52)			
n	315	627	
Mean	740.9	-1323.7	<0.001
Volume change from 1 year (Week 52) to 2 years (Week 104)			
n	315	627	
Mean	2149.9	418.3	<0.001
Volume change from baseline to 2 years (Week 104)			
n	315	627	<0.001
Mean	2890.8	-905.4	
Percentage change from baseline to 1 year (Week 52)			
n	315	626	<0.001
Mean	43.5	8.1	
Percentage change from 1 year (Week 52) to 2 years (Week 104)			
n	315	626	
Mean	23.8	7.8	<0.001
Percentage change from baseline to 2 years (Week 104)			
n	315	626	
Mean	67.2	10.1	<0.001

(a) p-value for comparison between the treated and placebo groups, based on Friedmans ANCOVA (ranked data), adjusted for baseline T2 volume. Percentage change only calculated for subjects with baseline volume greater than 0.

Study 1802 – Two-Year T2-Hyperintense Lesion Volume on Brain MRI Scan

The T2-hyperintense lesion volume was a secondary outcome in each pivotal trial. The T2 measurements were taken at baseline, Week 52, and Week 104, and changes in lesion volume were determined as both actual change and percentage change. The sponsor's analysis indicates that at two years, the natalizumab treatment group had significantly reduced volume of T2-hyperintense lesions on brain MRI scans when compared to the placebo group. Overall, the difference between treatment groups at two years compared to baseline was significant. The average change in T2 volume lesion from baseline at two years was an increase of 557.8 mm^3 for the placebo plus Avonex group, while the average volume change in the natalizumab and Avonex group was -259.6 mm^3,a decrease in volume. The FDA did not reanalyze the sponsor's data for this secondary outcome. The following table summarizes the changes seen in T2-hyperintense lesion volume in the two treatment groups. In the table, a negative value is associated with a decrease in volume and a positive value is associated with an increase in volume.

Table 8: Study 1802 – Analysis of T2-Hyperintense Lesion Volume (mm^3) on Brain MRI Scans (from sponsor's Table 11.4-14 in the final repot of Study 1801

	Placebo + Avonex	**Natalizumab + Avonex**	**p-value (a)**
Number Randomized	582	589	
At baseline (Week 0)			
n	582	589	
Mean	8156.8	7817.8	
At 2 years (Week 104)			
n	582	589	
Mean	8714.6	7558.2	<0.001
Change from baseline to 2 years (Week 104)			
n	582	589	
Mean	557.8	-259.6	<0.001
Percentage change from baseline to 2 years (Week 104)			
n	580	589	
Mean	77.3	40.2	<0.001

(a) p-value for comparison between the treated and placebo groups, based on Friedmans ANCOVA (ranked data), adjusted for baseline T2 volume. Percentage change only calculated for subjects with baseline volume greater than 0.

Study 1801 – Two-Year T1-Hypointense Lesion Number on Brain MRI Scan

The T1-hypointense lesion number was the third ranked secondary outcome in each pivotal trial. The T1 measurements were taken at baseline, Week 52, and Week 104. For Study 1801, all new T1-hypointense lesions were counted, regardless of whether or not they enhanced with gadolinium. Gadolinium enhancement of T1-hypointense lesions may represent acute inflammation. Approximately half of acute T1-hypointense lesions evolve into chronic "T1-black holes." These T1-black holes are correlated with disability (Simon 2000).

Due to subject withdrawals and missing data, 862 of the 942 subjects randomized had baseline, one-year, and two-year scans for the analysis. After two years of treatment, the placebo-treated group had an average of 4.6 new T1-hypointense lesions, while the natalizumab-treated group developed an average of 1.1 new T1-hypointense lesions. This represented a 76% reduction of T1-hypointense lesions between treatment groups and was statistically significant ($p<0.001$). FDA did not re-analyze the raw data to confirm these findings. The following table summarizes the changes seen in T1-hypointense lesions during Study 1801.

Table 9: Study 1801 – Number of New T1-Hypointense MRI Lesions in the ITT Population (from sponsor's Table 11.4-16 of Study 1801 final report)

	Placebo	Natalizumab	p-value (a)
Number Randomized (%)	315 (100)	627 (100)	
Change from 0 to 1 year			
0	131 (42)	448 (71)	<0.001
1	64 (20)	104 (17)	
2	37 (12)	34 (5)	
3	21 (7)	20 (3)	
≥4	62 (20)	21 (3)	
n	315	627	
Mean	2.3	0.6	
Change from 1 to 2 years			
0	118 (37)	513 (82)	<0.001
1	77 (24)	72 (11)	
2	42 (13)	16 (3)	
3	22 (7)	7 (1)	
≥4	56 (18)	19 (3)	
n	315	627	
Mean	2.3	0.4	
Change from 0 to 2 years			
0	84 (27)	396 (63)	<0.001
1	39 (12)	97 (15)	
2	52 (17)	67 (11)	
3	21 (7)	25 (4)	
≥4	119 (38)	42 (7)	
n	315	627	
Mean	4.6	1.1	
s.d.	7.28	3.25	
Median	2.0	0	
Min., max.	0, 60	0, 54	

(a) P-value for comparison between the treated and placebo groups, based on logit regression

Study 1802 – Two-Year T1-Hypointense Lesion Number on Brain MRI Scan

The T1-hypointense lesion number was the third-ranked secondary outcome in Study 1802. The T1 measurements were taken at baseline, Week 52, and Week 104. The way that T1-hypointense lesions were counted in Study 1802 varied slightly from the method used in Study 1801, but both analyses were conducted according to protocol. In Study 1801, all T1-hypointense lesions were counted; however, in Study 1802, only the non-enhancing T1-hypointensities, or T1-black holes, were counted. Also, in Study 1802, individual lesion counts per slice were assessed rather than total number of lesions. Thus, a single lesion that traversed three MRI slices was counted as three lesions in Study 1802, whereas it would have been counted as one lesion in Study 1801.

After two years of treatment, the placebo-treated group had an average of 4.1 new T1-hypointense lesions, while the natalizumab-treated group developed an average of 2.3 new T1-hypointense lesions. This represented a 44% reduction of T1-hypointense lesions between treatment groups over two years, and the results was highly statistically significant ($p<0.001$). FDA did not re-analyze the raw data to confirm these findings. The following table summarizes the changes seen in T1-hypointense lesions during Study 1802.

Table 10: Study 1802 - Number of New T1-Hypointense MRI Lesions in the ITT Population (from sponsor's Table 11.4-16 of final report of Study 1802)

	Placebo	Natalizumab	p-value (a)
Number Randomized (%)	582 (100)	589 (100)	
Change from 0 to 1 year			
0	346 (59)	402 (68)	<0.001
1	48 (8)	44 (7)	
2	69 (12)	78 (13)	
3	26 (4)	12 (2)	
≥4	93 (16)	53 (9)	
n	582	589	
Mean	2.0	1.1	
Change from 1 to 2 years			
0	286 (49)	355 (60)	<0.001
1	78 (13)	63 (11)	
2	82 (14)	84 (14)	
3	25 (4)	17 (3)	
≥4	111 (19)	70 (12)	
n	582	589	
Mean	2.1	1.3	
Change from 0 to 2 years			
0	173 (30)	247 (42)	<0.001
1	81 (14)	85 (14)	
2	57 (10)	69 (12)	
3	74 (13)	65 (11)	
≥4	197 (34)	123 (21)	
n	582	589	
Mean	4.1	2.3	
s.d.	7.04	3.64	
Median	2.0	1.0	
Min., max.	0, 78	0, 29	

(a) P-value for comparison between the treated and placebo groups, based on logit regression, adjusted for the number of baseline T1 lesions.

Study 1801 – Changes from Baseline MSFC at 2 Years

The MSFC is based on three components that measure arm, leg, and cognitive function. A z-score is created for each component and then the scores are averaged to create a composite z-score. The subjects had MSFC scores measured every 12 weeks during the trial. The sponsor has summarized the scores from baseline to 2 years for each component score, as well as the composite score in the ITT population. For this scale, positive changes in the scores indicate an improvement from baseline, while negative changes indicate worsening from baseline. The average change from baseline to 2 years in the MSFC composite was an increase of 0.04 in the natalizumab group, and a decrease of 0.16 in the placebo group, a difference that was statistically significant. A statistically significant change was also seen for each component score of the MSFC in Study 1801.

The FDA did not reanalyze any of the MSFC data that was measured as a secondary outcome to estimate progression of disability. The MSFC has been used in several MS clinical trials; however, it is not accepted by the FDA as a validated primary outcome for the purposes of labeling an effect on disability progression. The results from the sponsor's analysis of the MSFC are presented in tabular form below.

Table 11: Study 1801 - Change in Baseline to 2 Years in MSFC (from sponsor's table 11.4-21 from final report of Study 1801)

Number Subjects (%)	Placebo	Natalizumab
Number Randomized	315 (100)	627 (100)
MSFC Z-score		
Mean	- 0.16	0.04
s.d.	0.717	0.714
Median	- 0.04	0.09
Min., max.	- 5.9, 1.0	- 10.9, 2.3
		p<0.001 (b)
Timed 25-foot Walk Z-score		
Mean	- 0.50	- 0.20
s.d.	1.730	1.908
Median	- 0.15	- 0.05
Min., max.	-18.4, 1.1	- 32.7, 8.5
		p<0.001 (b)
9HPT Z-score		
Mean	- 0.13	0.09
s.d.	0.714	0.611
Median	- 0.03	0.13
Min., Max.	- 3.8, 2.5	-3.4, 1.9
		p<0.001 (b)
PASAT 3 Z-score		
Mean	0.13	0.22
s.d.	0.629	0.532
Median	0.10	0.2
Min., max.	- 1.9, 3.2	- 2.5, 2.7
		p=0.005 (b)

(a) Z-scores were calculated based on a reference population mean of 5.328 (s.d. 2.005) for the Timed 25-Foot Walk, a mean of 0.05 (s.d. 0.010 for the 9HPT, and a mean of 50.824 (s.d. 10.304) for PASAT 3. (b) P-value assessing the difference between treatment groups from Friedman's analysis of covariance (ranked data), adjusted for baseline score.

Study 1802 – Changes from Baseline MSFC at 2 Years

The MSFC was measured at baseline and then every 12 weeks. The average composite z-score change from baseline to 2 years was an increase of 0.05 for the natalizumab group and a decrease of 0.10 in the placebo group, a difference that was statistically significant. A positive change from baseline indicates improvement. The natalizumab group was significantly better than placebo for the Timed 25-Foot Walk and the 9HPT. The difference between treatment groups for the PASAT 3 was not statistically significant, but trended in favor of natalizumab. FDA did not re-analyze these data to confirm the results; however, the sponsor's reported scores are summarized in the following table.

Table 12: Study 1802 - Change in Baseline to 2 Years in MSFC (from sponsor's table 11.4-21 from final report of Study 1802)

Number of Subjects (%)	Placebo + Avonex	Natalizumab + Avonex
Randomized	582 (100)	589 (100)
MSFC Z-score		
Mean	- 0.10	0.05
s.d.	0.766	0.485
Median	- 0.02	0.04
Min., max.	- 9.7, 2.1	- 3.0, 6.3
		p<0.001
Timed 25-foot Walk Z-score		
Mean	- 0.38	- 0.09
s.d.	1.892	1.026
Median	- 0.11	- 0.05
Min., max.	-27.6, 4.1	- 8.3, 16.6
		p<0.001
9HPT Z-score		
Mean	- 0.07	0.07
s.d.	0.628	0.605
Median	- 0.06	0.06
Min., Max.	- 3.7, 5.7	-2.6, 5.0
		p<0.001
PASAT 3 Z-score		
Mean	0.13	0.17
s.d.	0.688	0.630
Median	0.10	0.10
Min., max.	- 3.6, 3.4	- 3.0, 3.2
		p=0.159

(a) Z-scores were calculated based on a reference population mean of 5.328 (s.d. 2.791) for the Timed 25-Foot Walk, a mean of 0.05 (s.d. 0.010 for the 9HPT, and a mean of 50.824 (s.d. 10.304) for PASAT 3.

Other Considerations for Efficacy

The development of persistent anti-natalizumab antibodies during the pivotal trials appears to be associated with decreased efficacy. The sponsor has analyzed the results of the antibody-positive subjects, the results of which are briefly described below. Other considerations for efficacy include the persistence of efficacy, particularly after stopping natalizumab. Also, the sponsor has conducted multiple additional analyses on the primary, secondary, and tertiary outcomes in the pivotal trials. These additional analyses are not deemed critical for the purposes of the PCNS AC meeting.

Anti-natalizumab Antibody Development and Efficacy

The administration of biological therapeutics, such as natalizumab, can lead to the formation of antibodies that are directed against the therapy. These antibodies may change the efficacy and safety profile of the therapeutic agent. In the pivotal trials, 1801 and 1802, the sponsor measured antibodies to natalizumab at baseline and then every 12 weeks.

Antibody Development in Study 1801

In Study 1801, 57 subjects (9%) had detectable antibodies to natalizumab on the screening ELISA assay at least one time during the trial. Most of the subjects who became antibody-positive (82%) did so by Week 13. Another 12% converted by Week 24, and 4% by Week 36. Another subject had a single positive sample at Week 60, but was otherwise antibody negative throughout the rest of the trial. Of the 57 subjects who did have positive antibodies, 20 (35%) had a transiently positive response. The remaining 37 subjects, or 6% of the total population, developed persistently binding antibodies to natalizumab, and these were detectable at two or more time points.

Antibody Development in Study 1802

In Study 1802, the results were similar to Study 1801 in that 70 natalizumab-treated subjects (12%) had a positive antibody response on at least one occasion during the trial. Of these, 96% were detected by Week 12, with the remaining three subjects becoming antibody-positive by Week 24. Overall, 38 (6%) of the subjects developed persistently positive antibodies to natalizumab during the study.

Antibody Effect on Efficacy

To determine if the antibody development had an effect on efficacy, the sponsor re-analyzed the primary and secondary outcomes by subdividing the subjects into four groups: placebo subjects, natalizumab subjects who never tested positive for antibodies, natalizumab subjects with transiently positive antibody tests, and natalizumab subjects with persistently positive antibody tests. The sponsor notes that the development of persistently positive anti-natalizumab antibodies did appear to decrease the treatment effect in both Study 1801 and 1802. The presence of transiently positive antibodies did not have as much of an effect. FDA did not reanalyze the data to confirm these results; however, the sponsor's findings are summarized in the following table.

Table 13: Phase 3 Studies: Primary and Secondary Endpoints at Two Years by Screening Anti-natalizumab Antibody Status (from sponsor's table 5-3 from the Summary of Clinical Efficacy in Multiple Sclerosis) – Page 1 of 2

	Study 1801				**Study 1802**			
	Placebo	**300 mg natalizumab**			**Placebo + Avonex**	**300 mg natalizumab + Avonex**		
		Antibody negative (a)	**Transiently positive antibody (b)**	**Persistently positive antibody (c)**		**Antibody negative (a)**	**Transiently positive antibody (b)**	**Persistently positive antibody (c)**
Number Evaluated	315 (100)	568 (100)	20 (100)	37 (100)	582 (100)	515 (100)	32 (100)	38 (100)
Primary Endpoint:								
Est. proportion with progression at 2 years (d)	0.29	0.17	0.17	0.34	0.29	0.24	0.19	0.20
Secondary Endpoints:								
Adj. annualized relapse rate	0.732	0.224	0.158	0.476	0.752	0.314	0.373	0.654
Average relapse rate (e)	0.671	0.205	0.259	0.472	0.749	0.307	0.385	0.582
Change from baseline to 2 years in T2-hyperintense lesion vol.								
Mean	2890.8	-998.5	-4533.1	1766.5	557.8	-261.2	313.3	-550.3
s.d.	15068.43	11863.40	32211.41	7191.07	3874.79	3376.63	1901.82	7105.94

Table 13 (continued): Phase 3 Studies: Primary and Secondary Endpoints at Two Years by Screening Anti-natalizumab Antibody Status (from sponsor's table 5-3 from the Summary of Clinical Efficacy in Multiple Sclerosis) – Page 2 of 2

	Study 1801				**Study 1802**			
	Placebo	**300 mg natalizumab**			**Placebo + Avonex**	**300 mg natalizumab + Avonex**		
		Antibody negative (a)	**Transiently positive antibody (b)**	**Persistently positive antibody (c)**		**Antibody negative (a)**	**Transiently positive antibody (b)**	**Persistently positive antibody (c)**
Number Evaluated	315 (100)	568 (100)	20 (100)	37 (100)	582 (100)	515 (100)	32 (100)	38 (100)
Change from baseline to 2 years in number of T1-hypointense lesions	4.6	1.0	0.06	2.5	4.1	2.3	3.1	1.9
Mean	7.28	3.27	0.70	3.51	7.04	3.67	4.36	2.65
s.d.								
Change from baseline to 2 years in MSFC	-0.16	0.06	-0.14	-0.18	-0.10	0.06	-0.02	-0.08
Mean	0.717	0.704	1.137	0.561	0.766	0.497	0.418	0.356
s.d.								

NOTE: Numbers in parentheses are percentages. **(a)** Defined as <0.5 μg/mL at all post-baseline visits. **(b)** Defined as ≥0.5 μg/mL at only one post-baseline visit prior to the last visit. **(c)** Defined as ≥0.5 μg/mL at two or more post-baseline visits ≥42 days apart or ≥0.5 μg/mL at the last post-baseline visit. **(d)** Calculated using the Kaplan-Meier product limit method. **(e)** The number of relapses for each subject divided by the number of years followed in the study for that subject. Mean across all subjects is presented.

Integrated Safety Review

The integrated safety review is based primarily on the experience with natalizumab in the multiple sclerosis (MS) and Crohn's disease (CD) development programs. The review will begin with a description of exposure to natalizumab in the clinical development program, a summary of demographic data for the two primary data pools, and a discussion of the natalizumab-associated risk of progressive multifocal leukoencephalopathy (PML). An overview of deaths, other serious adverse events, adverse events that led subjects to discontinue treatment, common adverse events, and laboratory abnormalities that occurred during treatment with natalizumab will follow. Selected safety topics will then be addressed in more detail. The risk for infections, malignancies, anti-natalizumab antibody formation, hypersensitivity reactions, depression, and menstrual disorders during treatment with natalizumab will be discussed. The Integrated Safety Review will conclude with a brief discussion of the sponsor's proposed risk minimization plan (RiskMAP).

Description of Data Sources and Summary of Exposure to Natalizumab

Total exposure to natalizumab at doses proposed for clinical use in the MS and CD programs combined conforms to ICH exposure guidelines and is considered adequate.

1,617 subjects have been exposed to natalizumab in placebo-controlled studies of MS. Total person-years exposure to natalizumab in MS placebo-controlled trials was 2,910 person-years. 1,155 subjects were exposed to natalizumab for at least 6 months and 1,123 subjects were exposed to natalizumab for at least one year.

1,522 subjects have been exposed to natalizumab in the short-term acute treatment and long-term maintenance treatment CD studies that were included in the integrated safety database. 1,182 subjects received natalizumab in the subset of placebo-controlled CD studies, in which subjects received 1-3 natalizumab infusions every four weeks.

Total person-years exposure in CD studies included in the integrated safety database was 1,591 person-years. 714 CD subjects were exposed to natalizumab for at least 6 months and 516 for at least one year.

The following tables summarize exposure to natalizumab by duration of exposure and by the number of doses received for placebo-controlled studies in MS, placebo-controlled studies in CD, and short- and long-term CD studies.

Table 1-7 Number of doses received

	Placebo-Controlled Treatment Studies of Active CD		Short- and Long-Term Dosing in CD	Placebo-Controlled Studies in MS	
	Placebo	Natalizumab	Natalizumab	Placebo	Natalizumab
Number of Subjects Dosed	506 (100)	1182 (100)	1522 (100)	1135 (100)	1617 (100)
Number of Doses					
1	56 (11)	152 (13)	172 (11)	85 (7)	176 (11)
2	95 (19)	184 (16)	182 (12)	43 (4)	66 (4)
3	355 (70)	846 (72)	259 (17)	10 (<1)	10 (<1)
4	0	0	113 (7)	7 (<1)	9 (<1)
5	0	0	81 (5)	11 (<1)	9 (<1)
6	0	0	55 (4)	130 (11)	190 (12)
7- 9	0	0	108 (7)	16 (1)	21 (1)
10-12	0	0	45 (3)	24 (2)	13 (<1)
13-15	0	0	39 (3)	25 (2)	24 (1)
16-18	0	0	55 (4)	13 (1)	11 (<1)
19-21	0	0	58 (4)	21 (2)	11 (<1)
22-24	0	0	74 (5)	10 (<1)	13 (<1)
25-27	0	0	146 (10)	13 (1)	20 (1)
28-30	0	0	64 (4)	727 (64)	1043 (65)
31-33	0	0	40 (3)	0	1 (<1)
34-36	0	0	19 (1)	0	0
37-39	0	0	12 (<1)	0	0

NOTE: Numbers in parentheses are percentages
SOURCE: ANTEGREN\SU2_MS\TABFIG\MS_CD_LT_NUMDOSE.SAS DATE: 29JUN2005

Table 1-8 Duration of Exposure

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	Placebo-Controlled Treatment Studies of Active CD		Short- and Long-Term Dosing in CD	Placebo-Controlled Studies in MS	
	Placebo	Natalizumab	Natalizumab	Placebo	Natalizumab
Number of Subjects Dosed	506 (100)	1182 (100)	1522 (100)	1135 (100)	1617 (100)
Total Duration (Weeks)					
Mean	10.4	10.6	44.4	87.5	86.0
s.d.	2.79	2.52	44.02	46.21	48.31
Median	12.0	12.0	20.0	119.9	119.9
Min.,Max.	4, 15	4, 15	4,193	4,127	4,126
Weeks of Exposure					
1 to <4	0	0	0	0	0
4 to <8	79 (16)	140 (12)	209 (14)	91 (8)	184 (11)
8 to <12	146 (29)	384 (32)	201 (13)	38 (3)	63 (4)
12 to <16	281 (56)	658 (56)	225 (15)	10 (<1)	5 (<1)
16 to <20	0	0	105 (7)	8 (<1)	9 (<1)
20 to <24	0	0	68 (4)	33 (3)	49 (3)
24 to <28	0	0	56 (4)	107 (9)	152 (9)
28 to <34	0	0	60 (4)	10 (<1)	13 (<1)
34 to <40	0	0	33 (2)	7 (<1)	9 (<1)
40 to <46	0	0	32 (2)	12 (1)	4 (<1)
46 to <52	0	0	17 (1)	11 (<1)	6 (<1)
52 to <64	0	0	39 (3)	25 (2)	23 (1)
64 to <76	0	0	58 (4)	12 (1)	10 (<1)

NOTE: Numbers in parentheses are percentages
SOURCE: ANTEGREN\SU2_MS\TABFIG\MS_CD_LT_EXPO_DUR.SAS DATE: 29JUN2005

Duration of Exposure
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	Placebo-Controlled Treatment Studies of Active CD		Short- and Long-Term Dosing in CD	Placebo-Controlled Studies in MS	
	Placebo	Natalizumab	Natalizumab	Placebo	Natalizumab
76 to <88	0	0	62 (4)	21 (2)	13 (<1)
88 to <102	0	0	86 (6)	10 (<1)	14 (<1)
102 to <116	0	0	151 (10)	33 (3)	33 (2)
116 to <130	0	0	60 (4)	707 (62)	1030 (64)
130 to <144	0	0	29 (2)	0	0
144 to <158	0	0	20 (1)	0	0
158 to <172	0	0	6 (<1)	0	0
>= 172	0	0	5 (<1)	0	0

Approximately 1600 subjects who received natalizumab in placebo-controlled studies 1801, 1802, and 1803 continued to receive natalizumab in open-label Study 1808. Two hundred and one healthy volunteers, 10 subjects with ulcerative colitis, and approximately 300 subjects with rheumatoid arthritis have also been exposed to natalizumab.

Exposure by Dose

Early clinical development of natalizumab exposed subjects to weight-adjusted dosing ranging from 0.03 – 6 mg/kg. Fixed dosing of 300 mg was used for later Phase 2 and Phase 3 studies. 1271 subjects with MS were exposed to natalizumab at the fixed 300 mg dose proposed for clinical use every four weeks in studies 1801, 1802, and 1803.

In the majority of short- and long-term CD studies, subjects received at least one fixed dose of 300 mg natalizumab. In the remaining studies, weight-based doses of 3 mg/kg or 6 mg/kg were given. Approximately 85% (1302) of subjects in CD studies received at least one fixed dose of 300 mg natalizumab.

Data Pools

The sponsor used the pools of studies listed below for their safety data presentations.

- Placebo-controlled studies in MS (1617 natalizumab-treated subjects and 1135 placebo-treated subjects)
- Short-term-placebo-controlled studies of active CD (1182 natalizumab-treated subjects and 506 placebo-treated subjects)

- Short- and long-term dosing in CD studies (1522 natalizumab-treated subjects)
- Placebo-controlled studies of MS and CD combined (data from this pool were presented only for selected adverse events

Data from the studies listed below were not integrated into any of the above pools. Data regarding serious adverse events are presented separately for subjects who participated in these studies.

- Open-label MS Studies MS224, 1804, and 1808
- CD studies CD354 and CD306
- Healthy volunteer studies HV101 1805, and 1806
- Ulcerative colitis Study UC201
- Rheumatoid arthritis studies RA201 and RA2

The analysis of safety data from the first two pools listed above (placebo-controlled MS studies and the short- and long-term CD studies) is the focus of this integrated safety review.

Demographics

1182 subjects received natalizumab in the placebo-controlled CD studies pooled for this review. The median age was 36 years. 95% of subjects were white; 57% of subjects were women. Demographic data and baseline disease characteristics for subjects in the MS placebo-controlled studies are summarized in the table below.

Table 1-9 Placebo-controlled studies of MS: demographic and baseline disease characteristics

	Placebo	Natalizumab
Number of Subjects Dosed	1135 (100)	1617 (100)
Age (years)		
17 and under	1 (<1)	0
18-29	159 (14)	284 (18)
30-39	414 (36)	589 (36)
40-49	459 (40)	602 (37)
50-64	100 (9)	141 (9)
65 and over	2 (<1)	1 (<1)
75 and over	0	0
Median	39.0	39.0
Min.,Max.	17, 70	18, 65
Gender		
Male	338 (30)	425 (26)
Female	797 (70)	1192 (74)
Race		
White	1045 (92)	1504 (93)
Black	42 (4)	36 (2)
Other	47 (4)	73 (5)
Missing	1 (<1)	4 (<1)
Weight (kg)		
Median	70.00	69.00
Min.,Max.	39.5, 149.0	37.0, 140.0
Disease Duration (yrs)		
n	1125	1587
Median	7.7	7.2
Min.,Max.	0, 54	0, 42
Baseline EDSS		
<1.0	39 (3)	58 (4)
1.0, 1.5	242 (21)	338 (21)
2.0, 2.5	347 (31)	491 (30)
3.0, 3.5	247 (22)	344 (21)
4.0, 4.5	156 (14)	215 (13)
5.0, 5.5	50 (4)	72 (4)
>=6.0	52 (5)	99 (6)
Median	2.50	2.50
Min.,Max.	0.0, 8.0	0.0, 8.0

In both the MS and CD studies, patients older than 50 and black patients were not well represented. Men comprised the minority of subjects in the MS trials, which reflects the disease demographics. Men comprised a greater percentage of the CD trial population, which reflects the even distribution of CD among men and women.

Patients younger than 18 were not included among natalizumab-treated subjects in MS

placebo-controlled trials and comprised only 2% (38) of subjects in all CD trials. The data submitted in this BLA are insufficient to support conclusions regarding the safety of natalizumab in patients younger than 18.

Demographics and baseline disease characteristics were well-balanced between natalizumab- and placebo-treated subjects in both the MS and CD trials.

Overall, the demographics of subjects treated with natalizumab in CD and MS trials are adequate for the purposes of analyzing the safety of natalizumab for the treatment of patients with relapsing forms of MS. Although the number of non-Caucasian subjects exposed to natalizumab in clinical trials is small, the known characteristics of natalizumab and MS do not suggest that the safety profile of natalizumab would be appreciably different in the non-Caucasian population.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive Multifocal Leukoencephalopathy is an infrequent disorder characterized by progressive demyelination of central nervous system white matter. There is no known effective treatment for PML, and PML usually results in death. The disease typically affects individuals with suppressed immune systems, such as patients with cancer, those who have undergone organ transplantation, or those with acquired immune deficiency syndrome (AIDS). PML is not typically observed in patients with MS, even in those patients taking approved MS therapies.

PML is thought to be caused by recrudescence of a common human polyomavirus, JC Virus (JCV). The initial JCV infection usually occurs in childhood and is asymptomatic. Then, the virus remains latent in the kidneys and lymphoid organs until immune suppression allows reactivation. The symptoms of PML vary and may include mental deterioration, vision loss, speech disturbances, ataxia, paralysis, coma, and death. Given the appropriate clinical picture, the diagnosis of PML is usually confirmed by the presence of JCV in brain biopsy tissue or in the cerebrospinal fluid.

PML Cases

There are three confirmed cases of PML associated with natalizumab treatment. These cases have been reported in the literature (see Kleinschmidt-DeMasters 2005, Langer-

Gould 2005, and Van Assche 2005), and copies of the articles are included in this briefing package. The three confirmed PML cases are summarized briefly below.

PML Case 1 *(reported by Kleinschmidt-DeMasters)*

A 46 year-old woman with RRMS was participating in Study 1802 (Avonex add-on study) when she died from PML. The patient's symptoms of MS began in 1999 and she initiated treatment with Avonex in February 2000. She began receiving natalizumab 300 mg IV every 4 weeks on April 12, 2002, and received her last dose on January 18, 2005. She received a total of 37 natalizumab infusions. She also thrice received methylprednisolone intermittently for 5 days at a time March 16-20, 2002, December 15-19, 2004, and January 5-9, 2005. Her PML symptoms began in November 2004 with increased difficulty with eye-hand coordination and problems with her speech. Her symptoms progressively worsened. She was treated with methylprednisolone twice (as above) because she was initially thought to have worsening MS. MRI changes atypical for MS were seen in mid-December 2004, and she received the last natalizumab treatment in January 2005. She continued to decline and had a positive CSF JCV DNA in February 2005. She died later that month. Autopsy confirmed PML.

PML Case 2 *(reported by Langer-Gould)*

A 46 year-old man with RRMS who was in Study 1802, on Avonex, received a total of 28 natalizumab infusions. A routine MRI in October 2004 revealed a new atypical frontal lobe lesion, but the patient was asymptomatic at that time. This lesion was later identified as PML, but was not immediately recognized as such. He was noted to have atypical behavior during a doctor's visit in September 2004. By mid-December he developed worsening symptoms, and repeat MRI revealed new lesions consistent with PML. Natalizumab was stopped in mid-December. JCV DNA in serum and CSF in February were positive, as was a brain biopsy for PML. Avonex was stopped in February 2005. He continued to decline despite being treated with multiple medications. He eventually stabilized and improved, but remains severely disabled.

PML Case 3 *(reported by Van Assche)*

A 60 year-old Crohn's disease patient who had been treated intermittently with natalizumab and immunosuppressive agents died from what was initially thought to be an astrocytoma, but was later determined to be PML. He had a significant history of immunosuppressive use. Beginning in March 2002, he received three doses of

natalizumab given concomitantly with azathioprine. He then entered the placebo arm of the trial, and stopped natalizumab. He was on placebo and azathioprine until November 2002, when he had to stop the azathioprine due to pancytopenia. He was off immunosuppressive agents altogether until February 2003 when he began open-label natalizumab infusions. In July 2003, after his fifth consecutive natalizumab dose (eight total doses), he presented with a 1 week history of cognitive decline. A brain MRI revealed a frontal lesion for which he underwent partial resection and was diagnosed with anaplastic astrocytoma. He was treated with steroids and anticonvulsants, but died in December 2003. The sponsor re-evaluated the pathology slides and found that the subject actually had PML. Also, retrospective analysis of stored serum samples from the patient demonstrated detectable JCV DNA two months before clinical presentation. The serum JC DNA increased in number over the time leading up to clinical presentation.

Risk of PML with Concomitant Natalizumab Administration

After the discovery of three cases of PML in subjects who received natalizumab, the sponsor worked with the FDA to design a new study to assess the incidence of PML associated with natalizumab administration. The primary objective was to re-examine subjects who had received natalizumab in an effort to look for additional cases of PML or other atypical infections. The study included a comprehensive evaluation of patients for clinical signs or symptoms, MRI, or laboratory findings suspicious for PML. Also, CSF and plasma samples to assess for JC viremia were collected from asymptomatic natalizumab-treated patients from past trials. The samples were then compared to samples taken from a control group that consisted of naïve MS patients, patients with non-inflammatory neurological diseases, and patients without neurological disease. The sponsor also collected CSF and plasma samples to determine whether serum JCV testing might be useful as a surveillance to predict the occurrence of PML. A brief description of the study is provided below.

Methods

Study Population

The sponsor considered all past natalizumab trials and decided to include subjects who had participated in Studies 1801, 1802, 1803, or 1808. These trials were selected for re-examination because they were the most recent and largest studies with the longest

duration. In most of the other trials, subjects received only one or two doses. The exception was Study MS231 in which 132 subjects were randomized to receive six doses of natalizumab followed by 6 months of observation once the drug was removed. The last subject to finish MS231 did so in May 2001. Given the time since exposure and the safety profile during the trial, the sponsor opted not to re-examine these subjects because they deemed the risk of finding PML or atypical infections in these subjects was extremely low. The new study was called the Dose Suspension MS Safety Assessment (DSMSSA), and a similar but smaller trial was conducted for subjects with Crohn's disease (CD) or rheumatoid arthritis (RA) who had received natalizumab in a past clinical trial. The Dose Suspension CD/RA Safety Assessment is not described in review; however, its design is similar to the Safety Assessment trial in MS subjects. Also, a summary of natalizumab exposure for both trials is described below in section, "Natalizumab Exposure." Of note, there were no additional cases of PML identified in either of the Safety Assessment trials.

All subjects who had not yet entered Study 1808 (open-label extension trial for subjects in 1801, 1802, or 1803) because of a previous study withdrawal or a current participation in a Phase 3 natalizumab trial, were immediately enrolled into DSMSSA. All subjects who previously withdrew from one of the four trials, or were at sites that closed or withdrew from the study, were contacted and asked to join DSMSSA. All subjects who participated in DSMSSA were required to see their treating neurologist or an investigator as soon as possible after February 28, 2005.

Clinical Evaluation

All subjects in DSMSSA were required to undergo a comprehensive evaluation by a study investigator at a Dose Suspension Visit (DSV). Specifically, subjects were asked detailed questions about their recent medical history and underwent a comprehensive physical and neurological examination. The investigators also assessed the subjects for neuropsychiatric and cognitive changes, as well as cortical findings, such as aphasia, apraxia, neglect, cortical sensory loss, or cortical blindness. The reason for this approach is that the sponsor believes that such findings are atypical for MS patients, but may be seen in early cases of PML. The sites used standardized worksheets, which the sponsor has submitted. The worksheet is seven pages long, and page 4 includes the following table for investigators to complete such that a "Complete Neurological Exam" is

documented.

Table 14: Excerpt from Dose Suspension Visit Source Worksheet (page 4)

Complete Neurological Exam:

	Normal	Abnormal/	New or Worsening Condition?	Date/Time of Onset or Worsening	Description of Abnormalities
Mental Status exam (including cognitive or neuropsychiatric changes, aphasia, apraxia, and other cortical modalities.)					
Cranial Nerve exam (including visual fields,cortical blindness)					
Motor Exam (including neglect, cerebellar signs, parkinsonism)					
Sensory (including primary and cortical modalities)					
Reflexes					

MRI Evaluation

Prior to any of the subjects undergoing an MRI, standard diagnostic criteria for determining PML lesions from MS lesions were discussed and agreed upon by consensus. All subjects were asked to undergo MRI scanning of the brain, including T1-weighted images with and without gadolinium, T2-weighted and proton density images, and FLAIR. The scans were first evaluated at the investigative sites, and then were sent to the central reading centers associated with the original studies (e.g. Study 1802). If a neuroradiologist at an investigative site was concerned about an MRI, he/she contacted the central reading center and requested an expedited review or an independent review by

the central neuroradiologist and the Independent Adjudication Committee (IAC). Any MRI with ambiguous lesions was compared to previous scans, and approximately 35% of the scans required comparison to an earlier scan.

CSF and Plasma Collection

All subjects who had clinical signs or symptoms, or had an MRI suspicious for PML, were required to undergo lumbar puncture (LP) for CSF JCV testing. All other subjects were strongly encouraged to undergo testing. Two CSF samples from each subject were sent to NIH and two were kept at ViraCor for possible retesting. Also, all subjects were asked to submit plasma for testing JC viral load. For each subject tested, two plasma samples were tested at ViraCor and two were stored there for possible retesting.

CSF Analysis

The CSF samples were analyzed in two separate labs at the NIH. One was the lab of Dr. Stephen Fisher in the Division of Laboratory Medicine (DLM) and utilized high throughput automated testing for an initial rapid read. The second lab was that of Dr. Eugene Major in NINDS, and he used a manual, more sensitive assay. The test results were compared to each other and to control samples obtained from the Karolinska Institute. The reading of the NINDS lab was considered final since it was more sensitive. There were no cases where JCV was detected in ViraCor or DLM lab and not detected in the NINDS lab.

Plasma Analysis

All plasma samples were analyzed by ViraCor. For samples tested by ViraCor that were read as positive, a second sample was analyzed by NINDS. The NINDS analyst was blinded to which samples were positive at ViraCor.

MS and Other Neurological Disease Control Samples

A total of 411 control CSF and plasma samples were obtained from the Karolinska Institute in Sweden. Of these, 401 CSF and 320 plasma samples were from natalizumab-naïve MS subjects, subjects suspected of having MS, subjects who presented with a clinically isolated syndrome, and subjects with other neurological disorder (OND).

Serum Testing from Previously Reported PML Cases

For the three confirmed PML cases, the serum had been drawn at baseline and then every 12 weeks to evaluate for anti-natalizumab antibodies. These samples were also evaluated in the NINDS labs.

Independent Adjudication Committee (IAC)

The IAC reviewed each suspected case of PML and suspicious post-marketing reports from subjects. The IAC consisted of three voting members who were independent experts in diagnosis and management of PML and/or virology of the JC virus. The members included Dr. Eugene Major from NINDS, Dr. David Clifford from Washington University in St. Louis, and Dr. Tarek Yousry from the Institute of Neurology at Queen Square, London. The sponsor also had three members from its staff participate as non-voting members. The non-voting members were excluded from closed IAC sessions.

Results

The sponsor conducted an exhaustive review of cases and testing of many subjects who received natalizumab in the trials. There were no additional cases of natalizumab-associated PML discovered during that review.

Study Participation

A total of 2248 MS subjects were eligible for the dose suspension assessments (DSMSSA). Investigators were asked to contact all subjects who participated in Studies 1801, 1802, 1803, or 1808, inform them of the PML cases and ask them to participate in 1808. If subjects refused participation in 1808, then they were asked to undergo a neurological examination and an MRI. Sites had to document at least three attempts to contact subjects. A total of 2046 (91% eligible) participated in the assessments. Of the non-participants, 84 had previously received natalizumab in the Phase 3 studies, while six had received natalizumab only during 1808 (they had been on placebo during the Phase 3 trial). The sponsor provides an analysis of what happened to each subject from the previous trials. The sponsor also provided the following table that summarizes the reasons for exclusion from DSMSSA.

Table 15: DSMSSA Study Participation

	Never Dosed With Natalizumab	Previous Natalizumab	Placebo Then Natalizumab
Number of Subjects	289	1283	676
Number Included in the DSV Analysis	177 (61)	1199 (93)	670 (99)
Number Excluded in the DSV Analysis	112 (39)	84 (7)	6 (<1)
Reason for Exclusion			
• Closed Site-non-responsive, subject status unconfirmed	24 (8)	21 (2)	0
• Closed Site- subject status confirmed	11 (4)	7 (<1)	0
• Deceased	2 (<1)	4 (<1)	0
• Lost to follow-up	12 (4)	20 (2)	2 (<1)
• No informed consent	2 (<1)	2 (<1)	0
• Not applicable (confirmed PML)	0	1 (<1)	0
• Declined	55 (19)	21 (2)	4 (<1)
• Missing	6 (2)	8 (<1)	0

NOTE: Number in parentheses are percentages

As of August 1, 2005, 2009 study subjects (99.1%) underwent neurological examination and 1966 (98%) completed a dose suspension MRI scan. CSF was available from 329 (16%) subjects and plasma samples were obtained from 1139 (56%) of participating subjects. For the analysis, the sponsor divided the subjects into four groups, and these included: subjects never dosed with natalizumab (previously received placebo Avonex, or glatiramer acetate); subjects who received natalizumab at some point during Studies 1801, 1802, or 1803, but had not received natalizumab in the three months prior to the Dose Suspension Visit; subjects who received natalizumab during the previous trials and

had also received natalizumab within the 3 months prior to the Dose Suspension Visit; and subjects who received placebo during Phase 3 trials, but then received commercial natalizumab or natalizumab during Study 1808.

Natalizumab Exposure

The sponsor tabulated the number of natalizumab infusions administered to the MS patients who participated in the DSMSSA (Appendix 5: Natalizumab Drug Exposure in Subjects Included in the DSMSSA and the MS patients who did not participate in the DSMSSA (Appendix 6: Natalizumab Drug Exposure in Subjects Excluded in the DSMSSA (from Studies 1801, 1802, or 1803). The number of infusions is then stratified by whether subjects received natalizumab during Studies 1801, 1802, or 1803 ("Previous natalizumab group"), or whether subjects received placebo during the Phase 3 studies, ("Placebo/Avonex/GA [glatiramer acetate] then natalizumab group").

The number of subjects in the "Previous natalizumab group" totaled 1199, and of these subjects, 1130 received 12 or more natalizumab doses; 1053 subjects received 24 or more natalizumab doses; and, 279 subjects received 36 or more natalizumab doses. Of the MS subjects excluded from the DSMSSA trial, 33 subjects received 12 or more doses; 14 subjects received 24 or more natalizumab doses; and, one subject received 36 or more natalizumab doses. This distribution is summarized in the following table.

Table 16: Natalizumab Drug Exposure in Subjects Included in and Excluded from the DSMSSA Trial

	Number of Natalizumab Doses*						
	<12	≥ 12	≥18	≥24	≥30	≥36	Total
MS Subjects Included in DSMSSA							
Previous natalizumab group	69	1130	1097	1053	997	279	1199
Placebo/Avonex/GA then natalizumab group	649	21	0	0	0	0	670
MS Subjects Excluded from DSMSSA							
Previous natalizumab group	51	33	24	14	8	1	84
Placebo/Avonex/GA then natalizumab group	6	0	0	0	0	0	6

* From Studies 1801, 1802, or 1803

The sponsor conducted similar analyses for the Dose Suspension in CD/RA Safety Assessment trial (DSCDRASA). The sponsor included the number of natalizumab doses received by each subject in the DSCDRASA. They stratified the results by the number of "natalizumab-only" doses administered and the number of natalizumab doses administered concomitantly with other immunosuppressive agents, listing each agent separately (Appendix 7: Natalizumab Drug Exposure in Subjects Included in the DSCDRASA. A similar table was compiled for the subjects who were excluded from the DSCDRASA (Appendix 8: Natalizumab Drug Exposure in Subjects Excluded from the DSCDRASA. The most commonly used immunosuppressive agents included steroids, azathioprine, and methotrexate. A total of 1220 subjects with CD or RA who were dosed with natalizumab were included in the DSCDRASA. Of these, 266 received natalizumab only and 954 received natalizumab with a concomitant immunosuppressant.

Of the subjects in the DSCDRASA who received natalizumab without concomitant

immunosuppressants, 119 received 12 or more doses of natalizumab; 63 received 24 or more doses of natalizumab; and 5 received 36 or more doses of natalizumab. Of the subjects who received natalizumab and immunosuppressive agents, 380 received 12 or more natalizumab doses; 222 received 24 or more natalizumab doses; and 13 received 36 or more natalizumab doses. The sponsor conducted a similar analysis of subjects who were excluded from the DSCDRA. The number of subjects was very small and the reader is referred to (Appendix 8: Natalizumab Drug Exposure in Subjects Excluded from the DSCDRASA for more information. The following table summarizes the natalizumab exposure in MS or RA subjects included in the DSCDRASA.

Table 17: Natalizumab Drug Exposure in Subjects Included in the DSCDRASA Trial

	Number of Natalizumab Doses*						
	<12	≥ 12	≥18	≥24	≥30	≥36	Total
Natalizumab only group	147	119	95	63	19	5	266
Natalizumab and concurrent immunosuppressant/steroids	574	380	332	222	63	13	954

The sponsor conducted analyses to determine how many subjects underwent different components of the Safety Assessment trials. The components included neurological exam, MRI exam, JCV plasma testing, and CSF testing. Subjects in the DSMSSA were separated into two groups based on whether they had previous natalizumab exposure (i.e. natalizumab only), or exposure to placebo, Avonex or glatiramer acetate, followed by exposure to natalizumab. For the "Previous natalizumab," or natalizumab only group, it appears that most of the subjects cluster between 29-39 natalizumab doses for all four components of the Safety Assessment trial (Appendix 9: DSMSSA Evaluations Conducted in Subjects with Previous Natalizumab Exposure. However, the opposite distribution appears to be the case for subjects who received placebo, Avonex, or GA followed by natalizumab administration. For these subjects, most of the testing conducted during the safety assessment trials were in subjects who had received <12 natalizumab doses (Appendix 10: DSMSSA Evaluations Conducted in Subjects with Placebo/Avonex/G.A. then Natalizumab Exposure. In the DSCDRASA trial, subjects with CD or RA were analyzed by treatment group (natalizumab alone versus natalizumab with concomitant immunosuppressive agent) to determine how many subjects in each natalizumab dose group underwent each of the four safety assessments. The analysis is summarized in Appendix 11: DSCDRASA Evaluations in

Subjects with Natalizumab Exposure and +/- Immunosuppressant Agents .

Demographics

The sponsor provided a tabular summary of the demographics of study subjects. The baseline characteristics were well-balanced between the groups, but subjects in Studies 1802 and 1803 were slightly older than those in 1801.

Summary of Physical Examinations

The sponsor provided a summary of the physical examinations, and noted that the examination results appeared to be similar in all groups, except for head and neck findings. Subjects with recent exposure to natalizumab appeared to have higher rates of Head-Eyes-Ears-Nose-Throat (HEENT) abnormalities than those with distant exposure to natalizumab (3-4% v. <1%). This appears to be due primarily to higher rates of nasopharyngitis, which was previously described as being related to natalizumab exposure.

Summary of Neurological Examinations

In general, there were no major differences in the neurological examinations. Subjects who had ever been exposed to natalizumab tended to do better on FSS and EDSS scores.

Summary of MRI Evaluations

A comparison to previous scan was required in approximately 35% of the cases. Of the cases reviewed, 13 were referred to the IAC from the Central Reader Center for a second opinion regarding a suspicious brain lesion on MRI scan. Of these 13, nine were from subjects with short-term recent exposure to natalizumab. These nine subjects had received placebo during the Phase 3 trials. Of the 13 cases referred to the IAC, none had non-neurological physical examination abnormalities, but four had new neurological abnormalities on examination. None of the 13 subjects referred were found to have detectable JC virus in their plasma or CSF.

PCR Evaluations for JC viral DNA

As of August 1, 2005, 329 CSF samples (16% of participating population) were analyzed for JC viral DNA. The majority were obtained from subjects with recent exposure and many (196) of those had over two years continuous dosing. Of all the CSF samples tested, seven revealed a low number of JCV DNA copies in a single reaction in the NINDS lab. However, the NINDS lab could not confirm this finding upon retesting, and the findings were also not confirmed by the DLM lab, either. Apparently, the quantities were near the assay's lower limits of detection, and the official reading on these seven samples was "not detected." Thus, all 329 samples were read as negative.

Plasma samples from 1139 subjects were analyzed for JCV DNA. Any sample that tested positive at ViraCor lab was then sent to NIH for retesting in the NINDS lab. Over 200 random negative samples from ViraCor were sent for testing at NINDS. At the cut-off time, only two samples had tested positive and of these, one was initially negative at ViraCor (subjects 123-005 and 181-101). Subject 123-005 had received 35 infusions as part of Studies 1801 and 1808, and subject 181-101 had received eight infusions as part of Study 1808. Neither subject had clinical or radiographic findings suggestive of PML. Also, neither subject had CSF samples available for analysis. After the sponsor's pre-specified data analyses cut-off date, three additional subjects tested positive for JCV DNA in the plasma. Again, these three had no clinical signs or symptoms of PML, and their neurological and radiographic examinations were negative. Subjects 520-108 and 520-111 had both received placebo and Avonex in Study 1802, and subject 454-111 received 28 infusions in Study 1802. The latter subject had CSF tested for JCV DNA, and it was negative.

In the control samples (from Karolinska Institute), there were five CSF samples that tested positive on first test in the NINDS lab, but negative on the confirmatory test. They were read as negative. No single diagnosis was associated with the "false-positive" result.

Deaths

There have been 17 deaths in the natalizumab development program. Thirteen of these deaths occurred in natalizumab-treated subjects and four occurred in placebo-treated subjects.

In MS placebo-controlled studies, there were two deaths among subjects who received natalizumab (2/1617; 0.12%) and three deaths among subjects who received placebo (3/1135; 0.26%). There were three additional deaths among subjects who received natalizumab in open-label MS studies.

In CD placebo-controlled studies, there were two deaths in the natalizumab group (2/1182; 0.17%) and no deaths in the placebo group. There were four additional deaths in CD extension studies.

In the RA placebo-controlled study RA 201, there was one death in the placebo group and one death in the natalizumab group. There was one additional death in the open-label Study RA251.

The causes of death in all natalizumab-treated subjects are summarized below:

- Alcohol poisoning: 49 year old woman (MS Study 1801) with a history of anxiety died as a result of alcohol poisoning (autopsy-confirmed) 23 days after her 25th natalizumab infusion.
- Malignant melanoma: 38 year old man (MS Study 1801) died of metastatic malignant melanoma approximately two years after receiving five natalizumab infusions. He had noticed a lesion on his left shoulder at the time of his first or second natalizumab infusion. The lesion was ultimately diagnosed as malignant melanoma
- PML: 46 year old woman (MS Study 1808) died of PML after 37 natalizumab infusions.
- PML: 60 year old man (CD351) died of PML (initially misdiagnosed as anaplastic astrocytoma) after receiving eight natalizumab infusions; he was also taking azathioprine and had been treated with azathioprine, oral budesonide, corticosteroids, and infliximab during his 28 year history of Crohn's disease.
- MS progression: 5 year old girl (compassionate-use protocol 1804) died of respiratory distress secondary to progression of MS approximately 5 months after her tenth natalizumab infusion.
- Suicide: 27 year old man (MS Study 1808) committed suicide 23 weeks after his 31st natalizumab infusion.
- Carbon dioxide asphyxiation: 42 year old man (CD301) died as a result of work-

related, accidental, carbon dioxide asphyxiation after one natalizumab infusion (cause of death confirmed by police reports and autopsy).

- Multi-organ system failure: 49 year old woman (CD301) with a history of nephrotic syndrome pre-dating natalizumab treatment was hospitalized 20 days after her third natalizumab infusion with a severe CD exacerbation requiring hemicolectomy. Post-operative complications included sepsis and multi-organ system failure, leading to death.
- 73 year old man (CD351) died of multi-organ system failure after duodenal ulcer perforation requiring laparotomy. His hospital course was complicated by peritonitis and pulmonary aspergillosis. He had received a total of 10 natalizumab infusions.
- Multi-organ system failure: 69 year old man (CD351) with a history of nonalcoholic steatohepatitis died of multi-organ system failure while hospitalized with recurrent hepatic encephalopathy, acute renal failure, anemia, and pneumocystis carinii pulmonary infection. He had received 34 natalizumab infusions.
- Acute MI: 67 year old man (CD351) died of acute myocardial infarction complicated by left ventricular rupture, hemopericardium, cardiac tamponade, and cardiogenic shock. These events occurred 2 months after his 22nd natalizumab infusion.
- Respiratory failure: 53 year old woman (RA201) died of hemoptysis and respiratory failure during attempted placement of a central venous line while in the hospital being treated for *E. coli* urosepsis. Her death occurred approximately 20 days after her third natalizumab infusion. Intrapulmonary arterial hemorrhage was suspected as the cause of the massive hemoptysis.
- Rheumatoid pulmonary disease: 59 year old women (RA251) died of end-stage rheumatoid pulmonary disease (per autopsy) one month after her first natalizumab infusion.

Deaths in the Post-marketing Setting

Five deaths have been reported among the 7000 patients who are estimated to have received natalizumab between its approval and market suspension. The causes of death in four of these cases were suicide, ovarian cancer, herpes encephalitis, and motor vehicle accident. In the fifth case, the exact cause of death was not specified but occurred during

hospitalization for treatment of a urinary tract infection.

Other Serious Adverse Events

The overall incidence of serious adverse events (SAEs) in natalizumab-treated subjects compared to placebo-treated subjects was increased in CD but not in MS placebo-controlled studies. Immune system disorders, reproductive and breast disorders, cholelithiasis, and hypersensitivity reactions were all reported as SAEs more frequently in natalizumab-treated subjects than in placebo-treated subjects in both MS and CD placebo-controlled studies.

MS Studies

In placebo-controlled MS studies, reports of serious adverse events (SAEs) were more frequent in placebo-treated subjects than in natalizumab-treated subjects. 15.5% (251) of natalizumab-treated subjects experienced at least one SAE compared to 18.9% (214) of placebo-treated subjects.

The most frequently reported SAEs in MS placebo-controlled studies were nervous system disorders (particularly MS relapse) and infections. MS relapse was reported as a serious adverse event more frequently in placebo-treated subjects (9.0%) than in natalizumab-treated subjects (4.7%). Serious infections, which occurred in 2.4% of natalizumab-treated subjects, are discussed in more detail below in the special safety concerns section devoted to infections.

The following table summarizes the incidence of serious adverse events that occurred in at least 0.1% (2) of natalizumab-treated subjects and occurred more frequently in natalizumab-treated subjects than in placebo-treated subjects. The table is arranged according to decreasing frequency in natalizumab-treated subjects.

Table 18: Serious Adverse Events Occurring in ≥0.1% of Natalizumab-treated Subjects and More Frequently than in Placebo-treated Subjects; MS Placebo-controlled Studies

Serious Adverse Event	Natalizumab (n=1617); % (no.)	Placebo (n=1135); % (no.)
All infections and infestations	2.4% (39)	2.2% (25)
All injury, poisoning and procedural complications	1.7% (28)	0.9% (10)
All gastrointestinal disorders	1.2% (19)	0.8% (9)
All immune system disorders	0.8% (13)	0.2% (2)
All reproductive system and breast disorders	0.7% (12)	0.5% (6)
All Urinary Tract Infections (UTIs)	0.6% (10)	0.5% (6)
Cholelithiasis	0.6% (9)	0.3% (3)
Anaphylactic/anaphylactoid reaction	0.4% (7)	0.2% (2)
All renal and urinary disorders	0.4% (7)	0.3% (3)
All pneumonias	0.4% (6)	0.2% (2)
Appendicitis	0.4% (6)	0.3% (3)
All blood and lymphatic system disorders	0.3% (5)	0.2% (2)
Fall	0.3% (5)	<.1% (1)
Hypersensitivity NOS	0.2% (4)	0
Abdominal pain NOS	0.2% (4)	0
Ovarian cyst	0.2% (4)	0
Viral infection NOS	0.2% (3)	0
Dehydration	0.2% (3)	<.1% (1)
Overdose NOS	0.2% (3)	0
Road traffic accident	0.2% (3)	<.1% (1)
Infection NOS	0.1% (2)	<.1% (1)
Sinusitis NOS	0.1% (2)	<.1% (1)
Thrombocytopenia	0.1% (2)	0
Grand mal convulsion	0.1% (2)	<.1% (1)

Table 19 (continued): Serious Adverse Events Occurring in ≥0.1% of Natalizumab-treated Subjects and More Frequently than in Placebo-treated Subjects; MS Placebo-controlled Studies

Serious Adverse Event	Natalizumab (n=1617); % (no.)	Placebo (n=1135); % (no.)
Appendicitis perforated	0.1% (2)	0
Colitis NOS	0.1% (2)	0
Gastritis NOS	0.1% (2)	0
Cholecystitis NOS	0.1% (2)	0
Rash NOS	0.1% (2)	<.1% (1)
Urticaria NOS	0.1% (2)	<.1% (1)
Localized osteoarthritis	0.1% (2)	<.1% (1)
Cervical dysplasia	0.1% (2)	0
Asthenia	0.1% (2)	0
Fatigue	0.1% (2)	0
Alcohol poisoning	0.1% (2)	<.1% (1)
Closed head injury	0.1% (2)	0
Head injury	0.1% (2)	<.1% (1)
Hip fracture	0.1% (2)	0
Post procedural pain	0.1% (2)	0
Thermal burn	0.1% (2)	0

The following SAEs occurred in at least four natalizumab-treated subjects and exhibited a natalizumab-associated relative risk vs. placebo of at least 2: immune system disorders, cholelithiasis, anaphylactic/anaphylactoid reactions, pneumonia, falls, hypersensitivity, abdominal pain, and ovarian cyst.

The overall incidences of and natalizumab-associated relative risks for SAEs were similar in the Phase 3 Studies 1801 and 1802.

CD Studies

In the placebo-controlled short-term CD studies, SAEs were reported marginally more frequently in natalizumab-treated subjects than in placebo-treated subjects. 14.9% (176) of natalizumab-treated subjects and 14.0% (71) of placebo-treated subjects experienced at least one SAE.

The most commonly reported SAEs among natalizumab-treated subjects were gastrointestinal disorders and infections. The most frequently reported gastrointestinal disorder SAEs appeared to be Crohn's disease exacerbations. However, all gastrointestinal disorders and serious Crohn's disease-related events, however, were reported more frequently in placebo-treated subjects than in natalizumab-treated subjects. Gastrointestinal disorders were reported as an SAE for 9.7% of natalizumab-treated and 9.9% of placebo-treated subjects. Crohn's disease was reported as an SAE for 5.8% of natalizumab-treated and 8.3% of placebo-treated subjects.

The incidence of serious infections was similar in placebo- and natalizumab-treated subjects (2.6% in placebo group and 2.4% in natalizumab group).

The following table summarizes the incidence of SAEs that occurred in at least 0.2% (2) of natalizumab-treated subjects and occurred more frequently in natalizumab-treated subjects than in placebo-treated subjects. The table is arranged according to decreasing frequency in natalizumab-treated subjects.

Table 20: Serious Adverse Events Occurring in ≥0.2% of Natalizumab-treated Subjects and More Frequently than in Placebo-treated Subjects; CD Placebo-controlled Studies

SAE	Natalizumab (n=1182); % (no.)	Placebo (n=506); % (no.)
All	14.9% (176)	14.0% (71)
Intestinal obstruction NOS	0.8% (9)	0.6% (3)
Small intestinal obstruction NOS	0.8% (9)	0.4% (2)
All neoplasms	0.7% (8)	0.2% (1)
All nervous system disorders	0.5% (6)	0.2% (1)
Intestinal stenosis NOS	0.5% (6)	0
All hepatobiliary disorders	0.4% (5)	0
All blood and lymphatic system disorders	0.4% (5)	0
All immune system disorders	0.4% (5)	0.2% (1)
All cardiac disorders	0.4% (5)	0
All renal and urinary disorders	0.3% (4)	0.2% (1)
All reproductive system and breast disorders	0.3% (4)	0
Cholelithiasis	0.3% (4)	0
Anemia NOS	0.3% (4)	0
Vomiting NOS	0.3% (4)	0
Abdominal abscess NOS	0.3% (3)	0.2% (1)
Hypersensitivity NOS	0.3% (3)	0
All respiratory, thoracic, and mediastinal disorders	0.3% (3)	0.2% (1)
Abdominal adhesions	0.3% (3)	0
Intestinal fistula	0.3% (3)	0
Arthralgia	0.3% (3)	0
Meningitis viral NOS	0.2% (2)	0
Urinary tract infection NOS	0.2% (2)	0
Lung adenocarcinoma NOS	0.2% (2)	0

Table 21 (continued): Serious Adverse Events Occurring in ≥0.2% of Natalizumab-treated Subjects and More Frequently than in Placebo-treated Subjects; CD Placebo-controlled Studies

SAE	Natalizumab (n=1182); % (no.)	Placebo (n=506); % (no.)
Pulmonary embolism	0.2% (2)	0
Gastrointestinal haemorrhage	0.2% (2)	0
Nausea	0.2% (2)	0
Peritonitis	0.2% (2)	0
Small intestinal perforation NOS	0.2% (2)	0
Nausea	0.2% (2)	0
All skin and subcutaneous tissue disorders	0.2% (2)	0
All injury, poisoning, and procedural complications	0.2% (2)	0
All surgical and medical procedures	0.2% (2)	0

Similar SAEs were reported for natalizumab-treated subjects in the long-term CD trials. There was one additional reported serious anaphylactic reaction in a controlled trial.

Studies not in Integrated Safety Database

The SAEs that occurred in studies not included in the safety databases were similar to those that occurred in the studies included in the MS and CD pooled databases.

Post-Marketing Setting

The following SAEs other than nervous system disorders, malignancies, and infections (the latter two are discussed in detail below) have been reported in the post-marketing setting: hypersensitivity reactions (13 cases); pancytopenia (2); leukopenia (1); cardiovascular events (9); suicide (1); suicidal ideation (2); depression (2).

Adverse events associated with dropouts

Placebo-controlled MS Studies

Adverse events leading to discontinuation occurred in 5.8% (93) of subjects receiving natalizumab and in 4.8% (54) of subjects receiving placebo.

Urticaria was the most frequently reported adverse event leading to discontinuation of natalizumab; 20 subjects (1.2%) discontinued natalizumab due to urticaria compared to 0.4% (4) of placebo-treated subjects.

The other events most frequently leading to discontinuation in natalizumab-treated subjects were hypersensitivity (led to discontinuation in 0.4% of natalizumab group vs. 0 in placebo group), anaphylactic or anaphylactoid reactions (0.4% vs. 0), and nausea (0.3% vs. 0). All other adverse events led to discontinuation of natalizumab in three subjects or fewer.

Per study protocol, subjects were required to discontinue study drug if they developed urticaria, anaphylaxis, angioedema, serum sickness, or biopsy-proven vasculitis.

CD Studies

In placebo-controlled studies of active CD, adverse events leading to discontinuation occurred in 9.1% (108) of subjects receiving natalizumab and in 11.3% (57) of subjects receiving placebo.

Crohn's disease was the most frequently reported adverse event leading to discontinuation of natalizumab, although placebo-treated subjects discontinued study drug due to this adverse event more frequently. 3.8% (45) of natalizumab-treated subjects discontinued treatment due to Crohn's disease compared to 7.9% (40) of placebo-treated subjects.

The other events most frequently leading to discontinuation in natalizumab-treated subjects that led to discontinuation more frequently than in placebo-treated subjects were urticaria (led to discontinuation of 0.8% of natalizumab group vs. 0.2% of placebo group), dyspnea (0.3% vs. 0), flushing (0.3% vs. 0), nausea (0.3% vs. 0.2%), pruritus

(0.3% vs. 0.2%), hypersensitivity (0.3% vs. 0), infusion-related reaction (0.3% vs. 0), rigors (0.3% vs. 0), and tremor (0.3% vs. 0). All other adverse events led to discontinuation of natalizumab in two subjects or fewer.

Adverse events that led to study drug discontinuation in long-term CD trials were similar to those identified in the short-term placebo-controlled CD trials.

Common Adverse Events

96.0% (1552) of natalizumab-treated subjects and 97.3% of placebo-treated subjects experienced at least one adverse event in the pool of placebo-controlled MS studies. The most common adverse events experienced by natalizumab-treated subjects were headache (39.2% vs. 38.4% of placebo group), multiple sclerosis relapse (32.1% vs. 54.8% of placebo group), nasopharyngitis (29.5% vs. 30.0% of placebo group), and fatigue (27.5% vs. 26.9% of placebo group).

87.4% (1033) of natalizumab-treated subjects and 85.2% (431) of placebo-treated subjects experienced at least one adverse event in the pool of placebo-controlled CD studies. The most common adverse events experienced by natalizumab-treated subjects were headache (30.8% vs. 24.3% of placebo group), nausea (16.2% vs. 15.0% of placebo group), and nasopharyngitis (13.2% vs. 9.7% of placebo group).

Review of all adverse events experienced by at least 1% of subjects in MS and CD placebo-controlled trials did not identify new safety signals that were not apparent during the initial BLA review that preceded natalizumab's approval in 2004 or are not discussed elsewhere in this integrated safety review.

Other Less Common Adverse Events

Natalizumab has been associated with a variety of adverse events, many of which are described in other sections of this Integrated Review of Safety. The combined safety database source tables for the placebo-controlled studies in MS and the placebo-controlled treatment studies of active Crohn's disease (from sponsor's safety source table S4-1) were reviewed for significant adverse events that may not be described elsewhere in this review or in current natalizumab labeling. This database includes 1641 subjects in the placebo-treatment group and 2799 subjects in the natalizumab group. Of these, 1535

(93.5%) in the placebo group and 2585 (92.4%) in the natalizumab group experienced an adverse event. This review did not yield any new concerning safety signals that had not been reported previously or are not described elsewhere in this integrated safety review.

Laboratory Findings

Hematology

A known pharmacodynamic effect of natalizumab is an increase in circulating leukocytes, except neutrophils. This effect was seen in subjects taking natalizumab and appears to be reversible once the medication is stopped. The FDA was concerned about the potential for natalizumab to decrease red blood cells and cause anemia. This effect was seen in the natalizumab group but does not appear to be a significant safety issue. The effect on red cells appears to be reversible. No significant safety signals associated with platelet counts or prothrombin were identified.

Liver Function Tests

Review of the liver function testing revealed no new safety concerns.

Other Laboratory Studies

Other laboratory studies including blood chemistries, urinalysis, and kidney function tests were reviewed; no new safety signals were identified.

Vital Signs and Electrocardiograms (ECGs)

Irregularities in vital signs and ECGs were reviewed for both treatment groups, and no safety signal was identified.

Special Safety Concerns

Infections other than PML

Natalizumab's mechanism of action has the potential to increase the risk for certain types of infections. Because natalizumab blocks the interaction of α4-integrins (which are expressed on all leukocytes with the exception of neutrophils) with their receptors,

natalizumab could impair the recruitment of lymphocytes and monocytes to sites of infection. Natalizumab could also lead to weakened mucosal immunity, altered B cell function, and maturation defects in hematopoiesis, each of which could lead to an increased incidence of infections.

The sponsor conducted separate analyses for both infections overall and serious infections (infections that were also SAEs) in MS and CD studies.

MS Studies

In the placebo-controlled MS studies, the rate and incidence of infections overall were similar for placebo-treated subjects and natalizumab-treated subjects (73.7% of natalizumab-treated subjects vs. 73.9% of placebo-treated subjects).

The incidence of serious infections was also similar in natalizumab- and placebo-treated subjects. In controlled studies, 2.4% (39/1617) of natalizumab-treated subjects and 2.3% (26/1135) of placebo-treated subjects had serious infections.

The following table summarizes the infections that occurred in at least 1% of natalizumab-treated subjects and were reported more frequently in natalizumab-treated subjects than in placebo-treated subjects:

Table 22: Infection Adverse Events Occurring in ≥1% of Natalizumab-treated Subjects and More Frequently Than in Placebo-treated Subjects by Decreasing Frequency; Multiple Sclerosis Placebo-controlled Trials

Infection Adverse Event Preferred Term	**Natalizumab (n=1617); % (no.)**	**Placebo (n=1135); % (no.)**
All infections	73.7% (1192)	73.9% (839)
Upper respiratory tract infection (URI) NOS	15.3% (247)	14.9% (169)
Influenza	13.9% (225)	12.9% (146)
Sinusitis NOS	11.4% (184)	10.7% (122)
URI viral NOS	8.3% (134)	7.8% (88)
Pharyngitis	6.6% (125)	5.2% (59)
Herpes simplex	4.9% (80)	4.7% (53)
Vaginosis fungal NOS	4.0% (64)	3.5% (40)
Gastroenteritis NOS	3.5% (56)	1.9% (21)
Tonsillitis	3.2%(51)	2.0%(23)
Bladder infection NOS	2.4% (38)	1.4% (16)
Tooth infection	2.3% (37)	1.9% (22)
Herpes zoster	2.0% (33)	1.4% (16)
Lower respiratory tract infection NOS	2.0% (33)	1.6% (18)
Cystitis NOS	2.0% (32)	1.7% (19)
Respiratory tract Infection NOS	1.9% (30)	1.3% (15)
Vaginitis	1.5% (25)	1.1% (12)
Pharyngitis viral NOS	1.2% (19)	0.8% (9)
Gingival infection	1.1% (18)	0.5% (6)
Pneumonia NOS	1.1% (18)	0.9% (10)

When all terms suggesting upper respiratory tract infections were considered together, the incidence of upper respiratory tract infections was similar in natalizumab-treated subjects (59.6%; 964/1617) and placebo-treated subjects (59.8%; 679/1135).

When all terms suggesting lower respiratory tract infections were considered together, natalizumab-treated subjects had a higher incidence of lower respiratory tract infections

compared to placebo treated subjects (13.3% [215/1617] compared to 12.2% [138/1135]).

The absolute and relative risks for serious infections overall were similar in Studies 1801 and 1802. The absolute and relative risks for serious lower respiratory tract infections (all preferred terms combined) were higher in Study 1801 than in Study 1802. In Study 1801, serious lower respiratory tract infections occurred in 0.6% (4) of natalizumab-treated subjects and no placebo-treated subjects. In Study 1802, serious lower respiratory tract infections occurred in 0.2% (1) of natalizumab-treated subjects and 0.7% (4) of placebo-treated subjects.

When all terms denoting different types of gastroenteritis were considered together, natalizumab- and placebo-treated subjects had similar incidences of gastroenteritis (9.1% of natalizumab-treated subjects and 9.0% of placebo-treated subjects).

When all events suggestive of urinary tract infections were considered together, natalizumab-treated subjects and placebo-treated subjects had a similar urinary tract infection incidence (21.5% in the natalizumab group compared to 21.4% in the placebo group).

Herpes infections considered together occurred in 7.0% (113/1617) of natalizumab-treated subjects and 6.1% (69/1135) of placebo-treated subjects.

Serious infections

The following table lists all of the infections that were serious adverse events that occurred more frequently in natalizumab-treated subjects than in placebo-treated subjects:

Table 23: Infection Serious Adverse Events Occurring More Frequently in Natalizumab-treated Subjects vs. Placebo-treated Subjects by Decreasing Frequency; Multiple Sclerosis Placebo-controlled Trials

Infection Adverse Event Preferred Term	Natalizumab (n=1617); % (no.)	Placebo (n=1135); % (no.)
All serious infections	2.4% (39)	2.3% (26)
Appendicitis	0.4% (6)	0.3% (3)
Urinary tract Infection NOS	0.4% (6)	0.2% (2)
Pneumonia NOS	0.2% (3)	0.2% (2)
Viral infection NOS	0.2% (3)	0
Infection NOS	0.1% (2)	<0.1% (1)
Pyelonephritis NOS	0.1% (2)	<0.1% (1)
Sinusitis NOS	0.1% (2)	<0.1% (1)
Urosepsis	0.1% (2)	<0.1% (1)
Abdominal abscess NOS	<0.1% (1)	0
Bronchopneumonia NOS	<0.1% (1)	0
Cellulitis streptococcal	<0.1% (1)	0
Condyloma acuminatum	<0.1% (1)	0
Febrile infection	<0.1% (1)	0
Gastroenteritis cryptosporidial	<0.1% (1)	0
Hepatitis B	<0.1% (1)	0
Infectious mononucleosis	<0.1% (1)	0
Lobar pneumonia NOS	<0.1% (1)	0
Pilonidal sinus infected	<0.1% (1)	0
Pneumonia primary atypical	<0.1% (1)	0
Progressive multifocal leukoencephalopathy	<0.1% (1)	0
Sinusitis chronic NOS	<0.1% (1)	0
Tonsillitis acute NOS	<0.1% (1)	0

Appendicitis, urinary tract infections, and pneumonia were the most frequently occurring serious infections in natalizumab-treated subjects. When all UTI-related preferred terms were considered together, serious UTIs occurred in 0.6% (10) of natalizumab-treated

subjects compared to 0.5% (6) of placebo-treated subjects. All natalizumab-treated subjects with serious urinary tract infections responded to antibiotics and had resolution of symptoms in the expected interval.

When all preferred terms suggestive of pneumonia (pneumonia NOS, bronchopneumonia NOS, lobar pneumonia NOS, and pneumonia primary atypical) were considered together, natalizumab-treated subjects had an increased incidence of serious pneumonia compared to placebo-treated subjects. Pneumonia serious adverse events occurred in 0.4% (6) of natalizumab-treated subjects compared to 0.2% (2) of placebo-treated subjects.

Three of the subjects who developed pneumonia while being treated with natalizumab and required hospitalization had clinical courses typical for subjects with community-acquired pneumonia. These subjects had lobar consolidation on chest X-ray and responded to antibiotics while natalizumab was continued. Three subjects (two from 1801 and one from 1802) had courses more protracted than is typical for community-acquired pneumonia, although atypical causative organisms were not documented in any of the cases.

One subject in a placebo-controlled MS study had a serious atypical infection—a prolonged course of cryptosporidial gastroenteritis. The subject was a 31 year old man in Study 1801 with no significant medical history other than MS. After 16 natalizumab infusions, he developed diarrhea and was diagnosed with cryptosporidial gastroenteritis. His diarrhea resolved 70 days after onset, approximately 50 days after his 17th natalizumab infusion. In immunologically healthy subjects, cryptosporidial gastroenteritis usually resolves without therapy within approximately two weeks.

In summary, the overall incidence of infections was not increased in natalizumab-treated subjects compared to placebo-treated subjects in placebo-controlled MS studies. The incidence of all serious infections and of specific types of infections was increased slightly. Natalizumab-treated subjects may have had a very slightly increased risk for pneumonia and other lower respiratory tract infections, herpes infections, vaginal infections, tooth infections, and gingival infections.

The differences between natalizumab- and placebo-treated subjects in the incidences of urinary tract infections, upper respiratory tract infections, and appendicitis were marginal

and unlikely to be clinically significant.

The finding from the original BLA that natalizumab-treated subjects had an increased risk for gastroenteritis was not observed in the larger dataset with additional natalizumab exposure. The incidence of gastroenteritis, when all gastroenteritis cases were considered together, was approximately equal among natalizumab- and placebo-treated subjects.

CD Studies

In placebo-controlled trials in active CD, in which subjects received from one to three study drug infusions, natalizumab-treated subjects had an increased risk for infections overall (40.4% of natalizumab-treated subjects vs. 35.8% of placebo-treated subjects), upper respiratory tract infections (26.6% vs. 21.3%), unspecified viral infections (2.9% vs. 1.6%), herpes simplex (1.2% vs. 0.8%) and herpes zoster (0.3% vs. 0.2%) infections, perianal abscesses (1.1% vs. 0.6%), vaginal fungal infections (1.3% vs. 1.0%), and viral meningitis (0.2% vs. 0).

Appendix 12 includes a table summarizing the incidence of infections that were more frequently reported in natalizumab-treated patients compared to placebo-treated patients and occurred in at least 1% of natalizumab-treated patients.

Serious infections

In controlled studies, the incidence of serious infections was similar in natalizumab- and placebo-treated subjects (2.5% [29/1182] of natalizumab-treated subjects and 2.6% [13/506] of placebo-treated subjects).

Appendix 13 includes a table summarizing the incidences of all serious infections that occurred more frequently in natalizumab-treated patients than in placebo-treated patients.

Serious perianal abscesses were the most frequently reported serious infections in natalizumab-treated subjects, although they occurred with the same frequency in natalizumab- and placebo-treated subjects (0.6% [7/1182] compared to 0.6% [3/506]).

Serious viral meningitides, serious UTIs, and serious abdominal abscesses all occurred slightly more frequently in natalizumab- than in placebo-treated subjects.

The two cases of viral meningitis, both of which were serious, had fairly typical courses. Abnormal liver function tests and low CSF blood glucose were atypical features of one of the two cases. One of the subjects who developed viral meningitis was taking concomitant immunosuppressive/immunomodulatory agents (prednisone and 6-mercaptopurine), whereas the other subject was not.

The incidence of lower respiratory tract infections was not increased compared to placebo-treated subjects. There were no serious lower respiratory tract infections in natalizumab-treated subjects.

There was one serious atypical infection (cytomegalovirus [CMV] colitis) in a natalizumab-treated subject and no cases in placebo-treated subjects. The subject who was diagnosed with CMV colitis was also receiving azathioprine. CMV rarely causes colitis in immunocompetent subjects.

In all CD trials (both short- and long-term), there were three serious herpes infections: two cases of serious herpes zoster and one case of varicella pneumonia.

Six serious atypical lower respiratory tract infections occurred in long-term CD trials: pneumonia with lung abscess, pulmonary aspergillosis, pneumocystis carinii pneumonia, herpes pneumonia, mycobacterium avium intracellulare complex pneumonia, and burkholderia cepacia lower respiratory tract infection.

Two of the seven subjects (the patients with CMV and varicella pneumonia) who developed an infection usually considered opportunistic (CMV or an atypical pulmonary infection) were not on any concomitant immunosuppressive drugs or immunomodulators and did not have any illnesses that cause immunodeficiencies (the cases of pneumocystis carinii pneumonia and varicella pneumonia). The remaining subjects were taking concomitant medications that suppress immunity—either glucocorticoids, azathioprine, or both.

The atypical infections observed in the CD trials—CMV colitis, PML, and the pulmonary infections caused by pathogens that are generally considered to be opportunistic—suggest the possibility of a compromise in cell-mediated immunity in these subjects. The increased risk for viral meningitis, herpes infections, and vaginal candidiasis that was

observed in natalizumab-treated subjects in placebo-controlled trials is also supportive of a compromise in cell-mediated immunity in subjects receiving natalizumab.

Appendix 14 includes narratives for selected serious infection cases in natalizumab-treated patients in CD trials.

Studies not in Integrated Safety Database

In Study 1808, urinary tract infections were the most common infections reported. Serious urinary tract infections were reported in four subjects. These cases were unremarkable and responded to antibiotics. There were three serious pulmonary infections that responded to appropriate therapy. In addition, there were two cases of appendicitis, one case of viral enterocolitis, one case of dental abscess, and one case of cellulitis of the hand. These infections responded to appropriate treatment and did not involve atypical organisms.
One atypical infection, a case of acute CMV with transaminase elevations following two natalizumab infusions, was reported.

In UC201, two serious infections were reported—one case of campylobacter enteritis and one urinary tract infection. Both subjects required hospitalization and responded to antibiotic therapy.

In RA201 and RA251, there were two cases of pneumonia and one case of an unspecified respiratory tract infection. Causative organisms were not known. In RA 251, there was a case of a toe abscess (cultures of wound grew *S. aureus*, *E. coli*, and *S. faecalis*).

There were no serious infections in healthy subjects who received natalizumab in Studies 101, 1805, and 1806. The most commonly reported infections among subjects in studies 1805 and 1806 were upper respiratory tract infections.

Post-marketing Reports

During natalizumab's marketing interval (between November 23, 2004 and February 28, 2005) a total of 20 serious infections were reported for 16 patients. Two cases resulted in death.

The table below, which is from the sponsor's application, summarizes the types of

serious infections that have been reported in the post-marketing setting. The table presents the cases reported by consumers and the cases reported by healthcare professionals (HCP) separately.

Table 7-2 Frequency of serious infections by infection type in post-marketing

Type of infection	HCP Cases	Consumer Cases	Total Cases
Pneumonia	3	4	7
Herpes meningitis / Encephalitis	2	0	2
Viral gastroenteritis	1	1	2
Infectious mononucleosis	1	0	1
Sepsis	1	0	1
Sinus infection	1	0	1
Urinary tract infection	1	1	2
Cystitis	0	2	2
Gangrene	0	1	1
Infection	0	1	1
Total	**10**	**10**	**20**
Cases Mentioning PML	2	0	2

As the table above indicates, pneumonia was the most common serious infection reported for patients who received natalizumab-in the post-marketing setting. Pneumonias were reported for 0.1% (7/7000) of the patients who are estimated to have received natalizumab in the post-marketing setting. None of these patients was reported to have atypical organisms causing their infections, although a specific pathogen was not reported in any of the cases.

Urinary tract infections were the second most frequently reported serious infection; urinary tract infection was reported in two patients and cystitis in an additional two patients. Two of these urinary tract infections were particularly severe. Urinary tract infections resulted in death in one case and ICU admission in the second case. No organisms were reported for any of the cases of urinary tract infection.

There were two reported cases of herpes meningitis/encephalitis. The case of encephalitis caused by HSV-2 resulted in death. The narratives for these two cases follow:

Herpes encephalitis

A 54- year-old man subject with a 20- year history of MS was diagnosed with herpes encephalitis. Concomitant medications at the time of the event included gabapentin,

fampridine, and baclofen. After receiving one dose of natalizumab, he experienced viral symptoms that were diagnosed as cold or flu. He was hospitalized three months later with seizures. He continued to receive gabapentin; fampridine was decreased, and he was started on zonisamide. He became febrile and confused 2- 3 days after admission, and his next MRI showed new significant right temporal changes. CSF was positive for HSV Type 2, and he was started on IV acyclovir. The patient experienced more seizures, went into coma, and died after withdrawal of life support.

Herpes meningitis

A 52-year-old woman with a history of migraine headaches developed a severe headache in the evening following her first dose of natalizumab. Two days later, she was admitted to hospital with signs of meningismus. CT scan was normal but CSF showed elevated white and red cell counts and increased protein (white blood cell count: 28/mm^3 [normal range 0-5/mm^3]; red blood cell count: 10/mm^3 [normal range 0-5/mm^3]; protein: 51 mg/dL [normal range 15-45 mg/dL]; glucose: 56 mg/dL [normal range 49-105 mg/dL]). The CSF was positive for HSV by PCR. The patient was diagnosed with herpes simplex meningitis. Brain MRI scan at the time showed no evidence of encephalitis. The patient responded to treatment with IV acyclovir, after which oral famciclovir was prescribed. After discharge from the hospital, her symptoms recurred, requiring re-admission. An MRI scan at this time showed only non-specific non-enhancing white matter lesions consistent with MS. Intravenous acyclovir was restarted and continued after hospital discharge. The patient recovered with no clinical sequelae. The neurologist considered the event related to natalizumab.

Summary of Infections

The overall risk for infections in natalizumab-treated patients was similar to the risk in placebo-treated patients in the MS placebo-controlled trials and slightly increased in CD placebo-controlled trials. The risk for specific types of infections was increased in natalizumab-treated subjects in both MS and CD studies. In the MS trials, specific types of infections occurring more frequently in natalizumab-treated subjects than placebo-treated subjects included lower respiratory tract infections, herpes simplex and zoster infections, vaginal fungal infections, tooth infections, and gingival infections. In the CD trials, upper respiratory tract infections, herpes simplex and zoster infections, perianal abscesses, vaginal fungal infections, and viral meningitis all occurred more frequently in

natalizumab-treated subjects than in placebo-treated subjects. However, the absolute incidence differences were small , for all of these infections.

There were two cases of atypical infections in natalizumab-treated subjects in placebo-controlled trials (one case of prolonged cryptosporidial gastroenteritis in an MS trial and one case of CMV colitis in a CD trial) and none in placebo-treated subjects. In extension studies for CD, there were several pulmonary infections caused by organisms that are generally considered to be opportunistic—mycobacterium avium intracellulare, pneumocystis carinii, aspergillus, and burkholderia cepacia. In addition, there was a case of varicella pneumonia in a subject whose son had chicken pox and a case of pneumonia of unknown pathogenesis complicated by a lung abscess. These atypical infections were not limited to subjects on concomitant azathioprine or glucocorticoids, although the majority of the atypical infections did occur in these subjects. The atypical occurred after varying numbers (2—34) of natalizumab infusions.

The increased risk for gastroenteritis and urinary tract infections that were observed in the original BLA for Studies 1801 and 1802 were not borne out in the larger dataset.

Infections reported in the post-marketing setting, in which approximately 7000 patients have received natalizumab (most receiving one or two infusions), are notable for two cases of herpes central nervous system infections—a case of HSV-2 encephalitis leading to death and a case of HSV meningitis. In the encephalitis case, the patient developed clear encephalitis signs and symptoms approximately three months after receiving one natalizumab infusion (although viral symptoms had begun more immediately after the infusion). In the second case, the patient developed a headache the evening of the natalizumab infusion and developed clear signs and symptoms of meningitis two days later. Both of these cases are concerning, particularly given the increased incidence of herpes infections and viral meningitis observed in the MS and CD clinical trials.

Although concomitant immunosuppressive and immunomodulatory medications may have played a role in many of the atypical infections observed in CD clinical trials, the increased incidences of viral meningitis and herpes infections observed in the MS and CD placebo-controlled trials, along with the atypical pulmonary and gastrointestinal infections observed in both development programs and the two cases of herpes CNS infections observed in the post-marketing setting, suggest that natalizumab may have an

adverse effect on cell-mediated immunity.

Immunogenicity

Treatment with therapeutic proteins such as natalizumab can lead to the formation of antibodies against the product. Anti-natalizumab antibody formation has the potential to affect natalizumab clearance, cause adverse events such as hypersensitivity reactions, and decrease therapeutic efficacy (which might occur if the antibodies are of sufficient affinity and titer to compete effectively with the binding of natalizumab to its targets).

The sponsor monitored the formation of anti-natalizumab antibody formation in the Phase 3 MS studies and selected CD studies and assessed the impact of anti-natalizumab antibody formation on adverse events, focusing on infusion reactions and hypersensitivity reactions.

MS Studies

MS Studies 1801 and 1802 included anti-natalizumab antibody testing every 12 weeks. Antibody responses were characterized as negative, transiently positive, or persistently positive. Subjects who were transiently antibody positive had a positive response at only one time point, and subsequently had a negative result. Subjects who were persistently antibody positive had detectable antibodies at two or more time points separated by at least 42 days, or had positive antibodies at their last follow-up visit with no subsequent assessments.

10% (127/1210) of subjects in Studies 1801 and 1802 had a positive antibody titer at least once during the studies. 6% (75) of subjects were persistently positive, and 4% (52) were transiently positive. For this 10% of subjects who were anti-natalizumab antibody positive at anytime, median time to the first antibody detection was 12 weeks.

The incidence of anti-natalizumab antibody formation was slightly higher in Study 1802 (12%) than in Study 1801 (9%). This difference was the result of an increased incidence of transiently positive antibody formation in Study 1802 (5% vs. 3% in 1801); the incidences of persistently positive antibody formation were similar in the two studies.

Analyses related to anti-natalizumab antibody formation in the MS development program

were based on the combined data from Studies 1801 and 1802.

Anti-natalizumab antibody formation was strongly associated with infusion reactions (adverse events that occurred within two hours of starting natalizumab) and hypersensitivity reactions. Persistently positive antibodies appeared more strongly associated with these events than were transiently positive antibodies, although this may be a spurious finding since subjects who developed anaphylactoid reactions or urticaria were required to discontinue natalizumab per protocol (and would thus be classified as having persistently positive antibodies).

The following table summarizes the incidences of infusion reactions by antibody status for those infusion reactions that occurred more frequently in the persistently positive anti-natalizumab antibody group compared to the overall group of anti-natalizumab-treated subjects and occurred in at least 2% of persistently antibody-positive subjects:

Table 24: Incidence of infusion reactions that occurred more frequently in subjects with persistently positive anti-natalizumab antibodies and in at least 2% of persistently antibody-positive subjects; MS Studies 1801 and 1802

	Anti-natalizumab antibody status			
Preferred Term	**Persistently positive (n=75); no. (%)**	**Transiently positive (n=52); no. (%)**	**Negative (n=1083); no. (%)**	**All (n=1216); no. (%)**
All	58 (77.3%)	15 (28.8%)	211 (19.5%)	287 (23.6%)
Rigors	15 (20.0%)	0	2 (0.2%)	17 (1.4%)
Nausea	14 (18.7%)	1 (1.9%)	24 (2.2%)	39 (3.2%)
Headache	12 (16.0%)	1 (1.9%)	44 (4.1%)	57 (4.7%)
Urticaria NOS	10 (13.3%)	1 (1.9%)	6 (0.6%)	17 (1.4%)
Flushing	8 (10.7%)	0	6 (0.6%)	14 (1.2%)

Table 25 (continued): Incidence of infusion reactions that occurred more frequently in subjects with persistently positive anti-natalizumab antibodies and in at least 2% of persistently antibody-positive subjects; MS Studies 1801 and 1802

	Anti-natalizumab antibody status			
Preferred Term	**Persistently positive (n=75); no. (%)**	**Transiently positive (n=52); no. (%)**	**Negative (n=1083); no. (%)**	**All (n=1216); no. (%)**
Hypersensitivity NOS	6 (8.0%)	0	1 (<.1%)	7 (0.6%)
Vomiting NOS	5 (6.7%)	0	1 (<.1%)	6 (0.5%)
Dizziness	5 (6.7%)	0	30 (2.8%)	35 (2.9%)
Pruritus	5 (6.7%)	2 (3.8%)	6 (0.6%)	17 (1.4%)
Tremor	4 (5.3%)	0	0	4 (0.3%)
Tachycardia NOS	4 (5.3%)	0	1 (<0.1%)	5 (0.4%)
Feeling cold	4 (5.3%)	0	0	4 (0.3%
Dyspnea	4 (5.3%)	0	0	4 (0.3%)
Hypotension NOS	3 (4.0%)	0	4 (0.4%)	7 (0.6%)
Pyrexia	3 (4.0%)	0	6(0.6%)	9 (0.7%)
Back pain	3 (4.0%)	0	2 (0.2%)	5 (0.4%)
Chest pain	3 (4.0%)	0	2 (0.2%)	5 (0.4%)
Erythema	2 (2.7%)	0	4 (0.4%)	7 (0.6%)
Urticaria generalized	2 (2.7%)	1 (1.9%)	0	3 (0.2%)
Sinus congestion	2 (2.7%)	0	0	2 (0.2%)
Throat irritation	2 (2.7%)	0	0	2 (0.2%)
Abdominal pain NOS	2 (2.7%)	0	0	2 (0.2%)
Pain in extremity	2 (2.7%)	0	0	2 (0.2%)
Chest tightness	2 (2.7%)	0	4 (0.4%)	6 (0.5%)
Feeling hot	2 (2.7%)	0	1 (<0.1%)	3 (0.2%)
Influenza like illness	2 (2.7%)	0	0	2 (0.2%)
Anaphylactic reaction	2 (2.7%)	1 (1.9%)	0	3 (0.2%)
Anaphylactoid reaction	2 (2.7%)	0	0	2 (0.2%)

5.3% (4) of subjects with persistently positive anti-natalizumab antibodies had adverse events that were coded as anaphylactic or anaphylactoid reactions. All of these events were categorized as infusion reactions, and all four occurred in Study 1801.

The majority of infusion reactions overall occurred in antibody-negative subjects (211/287; 73.5%). Anaphylactic/anaphylactoid reactions, however, were limited to subjects with positive antibodies.

MS relapses were reported more frequently in subjects with positive anti-natalizumab antibodies, suggesting that antibody formation may decrease natalizumab efficacy. Approximately 50% of subjects with positive anti-natalizumab antibodies had an adverse event of MS relapse.

The incidence of infections, particularly certain types of respiratory tract infections, viral gastroenteritis, and herpes simplex and zoster, was decreased in subjects with anti-natalizumab antibodies. Infections were reported in 69.3% (52) of persistently positive antibody group subjects, 82.7% (43) of transiently positive antibody subjects, and 81.9% (887) of antibody negative subjects. Herpes infections (both simplex and zoster) were reported more frequently in antibody negative subjects (8.4% in antibody negative subjects compared to 2.7% in the persistently positive antibody group and 7.7% in the transiently positive antibody group). This finding supports an association between natalizumab and infections.

Localized injection/infusion site reactions were not reported more frequently in subjects with anti-natalizumab antibodies.

There were no cases of vasculitis reported in subjects with anti-natalizumab antibodies in MS Studies 1801 or 1802. There were no cases of hepatitis or hepatotoxicity. There were also no cases of anemia or neutropenia. There was one adverse event of thrombocytopenia in the persistently positive anti-natalizumab antibody group (1.3%; 1/75) compared to four cases (0.4%; 4/1083) in the antibody-negative group.

CD Studies

The sponsor assessed the incidence of anti-natalizumab antibodies in the Phase 3 CD studies (CD301, CD303, CD306, CD307, and CD351). In these studies, 10.3% of subjects assessed had anti-natalizumab antibodies at one or more time points. 8.6% (101/1175) of subjects were characterized as persistently positive for anti-natalizumab antibodies, and 1.7% (20/1175) had a transiently positive result. In placebo-controlled studies, only a single sample may have been collected, and all of the positive results would by definition have been characterized as persistently positive unless the subject entered an extension study and subsequently had only negative results.

The sponsor conducted analyses of the relationship of anti-natalizumab antibody status to all adverse events and to infusion reactions for Studies 301 and 307. In these two placebo-controlled studies of natalizumab for active CD, subjects received three natalizumab infusions. Antibodies were characterized as being either present or absent, with no distinction between persistent and transient positivity; .

Eight percent (80/983) of subjects in CD301 and CD307 tested positive for anti-natalizumab antibodies. Anti-natalizumab antibody formation was strongly associated with infusion reactions in CD Studies 301 and 307. Infusion reactions were reported in 36.3% (29/80) of subjects who tested positive for anti-natalizumab antibodies compared to 8.9% (72/811) of antibody-negative subjects. The most commonly reported infusion reactions, all of which occurred substantially more frequently in antibody-positive subjects compared to antibody-negative subjects, were urticaria not otherwise specified (NOS) (7.5% of anti-natalizumab antibody-positive subjects vs. 0.7% of antibody-negative subjects), pruritus (7.5% vs. 0.5%), nausea (6.3% vs. 1.1%), flushing (5.0% vs. 0.6%), and dyspnea (5.0% vs. 0.4%).

Hypersensitivity NOS was reported in two (2.5%) anti-natalizumab antibody-positive subjects, compared to 0.5% (4) of antibody-negative subjects. One anaphylactic reaction was reported in one subject (1.3%) who tested positive for anti-natalizumab antibodies. No anaphylactic reactions were reported in any subjects who were antibody negative.

Subjects who tested positive for anti-natalizumab antibodies had higher incidences of the following adverse events compared to antibody-negative subjects: Crohn's disease (reported as an adverse event in 17.5% of antibody positive subjects vs. 7.8% of

antibody-negative subjects), pruritus (7.5% vs. 2.6%), rash NOS (7.5//5 vs. 3.7%), urticaria (7.5% vs. 1.0%), rigors (6.3% vs. 1.7%), chest pain (6.3% vs. 2.0%), peripheral edema (6.3% vs. 2.5%), and flushing (5.0% vs. 1.0%).

Anti-natalizumab antibody assessments were conducted separately for CD251, in which subjects received chronic intermittent natalizumab dosing (after the first two infusions at Weeks 0 and 4, subjects received repeated infusions only if they had active disease). In this study, 20% (19/96) of subjects became positive for anti-natalizumab antibodies during the course of the study, a higher incidence than was observed in the studies in which natalizumab was administered at regular intervals.

Hypersensitivity Reactions

Natalizumab was associated with an increased risk for hypersensitivity reactions in both MS and CD trials. As described above, these events were highly associated with the development of anti-natalizumab antibodies. These reactions occurred most frequently during or immediately after the second infusion.

During the first seven infusions in MS placebo-controlled studies, 4.6% of natalizumab-treated subjects and 1.9% of placebo-treated subjects developed a skin or subcutaneous tissue disorder infusion reaction, the most frequently reported of which was urticaria (in 1.6% of natalizumab-treated subjects and 0.3% of placebo-treated subjects). During the same period, 0.9% (12) of natalizumab-treated subjects and 0 placebo-treated subjects had infusion reactions characterized as hypersensitivity or anaphylactic reactions.

Anaphylactic reactions occurred in 0.4% (6) of natalizumab-treated and 0.2% (2) of placebo-treated subjects in MS placebo-controlled studies. In all cases, symptoms resolved with appropriate therapy without clinical sequelae.

Although the incidence of positive anti-natalizumab antibody formation was higher in Study 1802 than Study 1801 (due to a greater percentage of subjects with transiently positive antibodies in Study 1802), the incidence of and relative risk for serious hypersensitivity reactions among natalizumab-treated subjects was higher in Study 1801 than in Study 1802. The one case of anaphylaxis that occurred in Study 1802 was described as an allergic reaction to ceftriaxone, not natalizumab. All five subjects who

developed anaphylactic reactions in Study 1801 had positive anti-natalizumab antibodies. Three of the five subjects developed the reaction during or immediately after the end of the second infusion. One subject had the event after the fourth infusion, and the fifth subject had the event after the 13th infusion.

The incidences of serious hypersensitivity adverse events in Study 1801 and Study1802 are summarized in the table below:

Table 26: Incidence of Hypersensitivity Adverse Events in Studies 1801 and 1802

Preferred Term	**Study 1801**		**Study 1802**	
	Natalizumab; no. (%) n=627	**Placebo; no. (%) n=312**	**Natalizumab (and Avonex); no. (%) n=589**	**Placebo (and Avonex); no. (%) n=582**
All immune system disorders	1.6% (10)	0	0.3% (2)	0.2% (1)
Anaphylactic reaction	0.5% (3)	0	0.2% (1)	0.2% (1)
Anaphylactoid reaction	0.3% (2)	0	0	0
Hypersensitivity NOS	0.5% (3)	0	0.2% (1)	0
Drug hypersensitivity	0.2% (1)	0	0	0

In the CD placebo-controlled trials, 0.9% (9) of natalizumab-treated subjects had an infusion reaction characterized as hypersensitivity or anaphylaxis compared to 0 placebo-treated subjects. Urticaria occurred as an infusion reaction in 1.2% of natalizumab-treated subjects and 0.2% of placebo-treated subjects. There were two cases of delayed hypersensitivity reactions in all CD trials: a biopsy-proven case of leukocytoclastic vasculitis (which occurred in a 50 year old woman in CD303 after the fifth infusion of natalizumab) and one case of a type IV hypersensitivity reaction (which occurred in a 46 year old woman in Study CD301 four days after the second natalizumab infusion).

Human carcinogenicity

Natalizumab interferes with lymphocyte trafficking and tumor immunosurveillance is mediated by T lymphocytes. Therefore, the potential for natalizumab to increase the risk for malignancies has been a concern. Also, immunosuppressant and immunomodulatory drugs such as azathioprine, cyclosporine, and infliximab have been shown to increase the risk for malignancy.

MS Studies

In placebo-controlled MS studies, 11 natalizumab-treated subjects (0.7%) and 15 placebo-treated subjects (1.3%) developed malignancies. The overall rate of malignancy in natalizumab-treated subjects was 0.38 per 100 person-years (11/2910.4 person-years) compared to 0.73 per 100 person-years (15/2060.4 person-years) in the placebo group. The incidences of the malignancies observed in MS placebo-controlled trials are listed in the table below:

Table 27: Incidence of Malignancies; MS Placebo-controlled Studies

Preferred Term	Placebo	Natalizumab
Number of Subjects Dosed	1135 (100)	1617 (100)
Number of Subjects with an Event	15 (1.3)	11 (0.7)
Basal cell carcinoma	4 (0.4)	4 (0.2)
Breast cancer NOS	3 (0.3)	3 (0.2)
Breast cancer in situ	1 (<0.1)	1 (<0.1)
Cervical carcinoma stage 0	0	1 (<0.1)
Colon cancer NOS	0	1 (<0.1)
Metastatic malignant melanoma	0	1 (<0.1)
Breast cancer metastatic	1 (<0.1)	0
Breast cancer stage III	1 (<0.1)	0
Malignant melanoma	2 (0.2)	0
Malignant pleural effusion	1 (<0.1)	0
Secretory adenoma of pituitary	1 (<0.1)	0
Squamous cell carcinoma of skin	1 (<0.1)	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column.
SOURCE: ANTEGREN\SU2_MS\TABFIG\MS_MALIGN.SAS DATE: 14JUN2005

The incidence of malignancies was similar in Studies 1801 and 1802. In Study 1801, 0.8% (5/627) of natalizumab-treated subjects had malignancies compared to 0.3% (1/312) of placebo-treated subjects (RR for natalizumab vs. placebo: 2.7). In Study 1802, 1.0 % (6/589) of natalizumab-treated subjects had malignancies compared to 2.2% (13/582) of placebo-treated subjects (RR for natalizumab vs. placebo: 0.45).

CD Studies

In placebo-controlled CD studies, seven natalizumab-treated subjects (0.6%) and one placebo-group subject (0.2%) developed malignancies. The overall rate of malignancies in natalizumab-treated subjects was 1.60 per 100 person-years (7/438.6 person-years) compared to 0.60 per 100 person-years (1/165.7 person-years) in the placebo group. The incidences of the malignancies observed in CD placebo-controlled trials are listed below:

Table 28: Incidence of Malignancies; Placebo-controlled CD studies

	Placebo	Natalizumab
Number of Subjects Dosed	506 (100)	1182 (100)
Number of Subjects with a Malignancy	1 (0.2)	7 (0.6)
Event		
Lung adenocarcinoma NOS	0	2 (0.2)
Bladder cancer NOS	0	1 (<0.1)
Breast cancer NOS	0	1 (<0.1)
Breast cancer invasive NOS	0	1 (<0.1)
Colon cancer NOS	0	1 (<0.1)
Malignant melanoma	0	1 (<0.1)
Uterine cancer NOS	1 (0.2)	0

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column.
SOURCE: ANTEGREN\SU2_CD\TABFIG\CP_MALIGN.SAS DATE: 29JUN2005

In addition to the malignancies in the table above, there was one case of rectal carcinoma reported after the close of CD301. Subject CD559003 was diagnosed with adenocarcinoma 10 months after discontinuing natalizumab in CD301. He had received

two infusions of natalizumab and was also taking azathioprine.

As the table above indicates, breast and lung cancers were the most frequently reported malignancies in CD placebo-controlled studies. Both cases of lung cancer occurred in subjects with a history of smoking. In the first case, a 59 year old woman was diagnosed with poorly differentiated pulmonary adenocarcinoma seven days after her first natalizumab infusion. In the second case, a 58 year old man with COPD was diagnosed with pulmonary adenocarcinoma 4 months after his third natalizumab infusion.

The overall incidence of breast cancer among natalizumab-treated subjects in CD placebo-controlled trials was 0.2% (2/1182); the rate was 0.45/100 person years (2/438.6 person-years). In the first case, infiltrating ductal carcinoma was diagnosed 3 months following the third natalizumab infusion. A mammogram done four months previously had reportedly been negative. The second case of breast cancer was diagnosed 270 days after the subject's only natalizumab infusion (she had discontinued the study drug after developing hives following the first infusion).

An additional nine malignancies were diagnosed in subjects who received natalizumab in CD extension studies—3 cases of basal cell carcinoma of the skin (after 3, 6, and 16 natalizumab infusions), 2 cases of squamous cell carcinoma of the skin (after 13 and 18 infusions), two cases of uterine carcinoma (after 4 infusions in each case), one case of breast ductal carcinoma in situ (after 27 infusions), 1 case of clear cell renal cell carcinoma (after 6 infusions), and 1 case of metastatic rectal carcinoma (diagnosed 3 years after two infusions).

MS and CD Placebo-controlled Studies Pooled

In placebo-controlled MS and CD studies pooled, 18 natalizumab-treated subjects (0.6%) and 16 placebo-treated subjects (1.0%) developed malignancies. The overall rate of malignancy in natalizumab-treated subjects was 0.54 per 100 person-years (18/3349.0 person-years) compared to 0.72 per 100 person-years (16/2226.0 person-years) in the placebo group.

Studies not included in Integrated Safety Database

Three malignancies occurred in Study 1808 subjects who had previously participated in

studies 1801 or 1802—one case of basal cell carcinoma, one case of breast carcinoma, and one case of papillary thyroid carcinoma.

The case of basal cell carcinoma was diagnosed two days after the subject's first natalizumab infusion (she had previously received 30 placebo infusions in Study 1802). The case of breast carcinoma was diagnosed two months after the subject's 35th natalizumab infusion (30 in Study 1802 and five in Study 1808).

The case of papillary thyroid carcinoma occurred in a 40 year old man who had received 36 infusions of natalizumab (30 in Study 1801 and 6 in Study 1808). Approximately four months after his last natalizumab infusion, he was diagnosed with papillary thyroid carcinoma

In addition, one subject in a rheumatoid arthritis trial, a 58 year old woman (from RA201), was diagnosed with invasive ductal breast carcinoma 20 days after her third natalizumab infusion.

There were no other cases of malignancies in any other studies not included in the integrated safety database.

Post-marketing Reports

There have been two post-marketing spontaneous reports of malignancies in patients with MS treated with natalizumab—one case of ovarian cancer and one case of malignant melanoma. Both patients were also receiving Avonex. The patient with ovarian cancer was a 68 year old woman who had been taking Avonex for four years; she was diagnosed with ovarian cancer one month after her first dose of natalizumab and died two weeks later of the ovarian malignancy. The patient with malignant melanoma was a 30 year old woman. The sponsor did not report the number of infusions she received prior to her diagnosis.

Summary of Malignancies

The overall risk and rate of malignancies was not increased in natalizumab-treated subjects compared to placebo-treated subjects in MS placebo-controlled studies. There was no evident increase in the risk for any specific type of malignancy in the MS

placebo-controlled trials. There was a slight increase in both the overall risk and rate of malignancies in natalizumab-treated CD placebo-controlled studies. However, given that these subjects received only one to three natalizumab infusions, the biological plausibility of an association between natalizumab and malignancies in the CD placebo-controlled trials is low. Moreover, the two subjects who developed lung cancer (one of the two most common cancers reported in the CD placebo-controlled trials) had a smoking history, a strong risk factor for pulmonary malignancy.

Given the limited number of person-years accrued in CD placebo-controlled trials compared to the MS placebo-controlled trials, the increased incidence and rate of malignancies observed in natalizumab-treated subjects in the CD trial should not be given undue weight.

In the MS and CD placebo-controlled studies combined, natalizumab-treated subjects did not have an increased incidence or rate of malignancies compared to placebo-treated subjects. There were higher rates of three individual malignancies—colon, lung, and bladder—in natalizumab-treated subjects compared to placebo-treated subjects. These rates are based on a small number of cases and caution should be used in interpreting these differences.

No signal for malignancy is apparent in the post-marketing setting, although patients received a limited number of infusions. No leukemias or lymphomas were observed in the development program or reported in patients who received natalizumab after its approval. No unusual type or pattern of malignancies was observed in any natalizumab-treated patients.

Overall, the data currently available do not provide compelling evidence that natalizumab increases the risk for malignancies. It must be kept in mind that the effects of exposure to natalizumab beyond two years are unknown. Moreover, the data currently available do not provide adequate information regarding any effects of natalizumab that may require time to become manifest. Both of these issues are particularly relevant when considering the potential risk for malignancies.

Depression, self-injury, and suicide-related events

Depression was reported slightly more frequently in natalizumab-treated subjects in MS but not CD placebo-controlled studies.

In all MS placebo-controlled studies, adverse events related to depression, self-injury, or suicide-related events (suicide attempt or suicidal ideation) were reported in 18.3% (296) of natalizumab-treated subjects and 16.7% (189) of placebo-treated subjects.

In the Phase 3 MS studies, adverse events coded to preferred terms indicating depression were reported in 18.8% of natalizumab- and 16% of placebo-treated subjects in Study 1801 and 22.4% of natalizumab- and 19.8% of placebo-treated subjects in Study 1802. Although depression was more frequently reported in Study 1802, the natalizumab-associated relative risk for depression was similar in Studies 1801 and 1802.

Self-injurious behavior (intentional self-injury or self-injurious behavior) was reported in two natalizumab-treated and no placebo-treated subjects in Study 1802 and 0 subjects in Study 1801.

Four natalizumab-treated subjects and one placebo-group subject had suicidal ideation, suicide attempt, or suicidal depression in Study 1801 (0.6% of natalizumab group vs. 0.3% of placebo group; RR 2.0). Seven natalizumab-treated subjects and six placebo-group subjects had one of these events in Study 1802 (1.2% vs. 1.0%; RR 1.2).

Menstrual Irregularities

Review of one-year safety data from MS placebo-controlled trials in the original BLA indicated that natalizumab was associated with an increased incidence of menstrual disorders. Specific menstrual disorders associated with the use of natalizumab included dysmenorrhea, menstrual irregularities, and amenorrhea. In the current application, the sponsor presents analyses of the risk for menstrual disorders among all pre-menopausal women in MS placebo-controlled trials. Menstrual disorders overall were marginally more frequent among natalizumab-treated subjects than among placebo-treated subjects (12.9% vs. 11.7%). Specific menstrual disorders that were more frequent in natalizumab-treated subjects in MS placebo-controlled trials were menstruation with increased bleeding events (menorrhagia, metrorrhagia, polymenorrhea, and menometrorrhagia; 5.9% in natalizumab group vs. 5.0% in placebo group) and irregular menstruation (3.1%

vs. 1.5%). The incidence of dysmenorrhea was not increased compared to placebo.

In CD placebo-controlled trials, the incidence of dysmenorrhea was slightly increased in natalizumab-treated subjects (2.1% of natalizumab-treated subjects vs. 0.8% of placebo-treated subjects). The incidence of menstrual disorders overall and menstruation adverse events characterized by increased bleeding was not increased compared to placebo in the CD placebo-controlled studies.

Proposed Risk Minimization Action Plan (RiskMAP)

The sponsor proposes returning natalizumab to the market with a RiskMAP, the Tysabri Outreach Unified Commitment to Health (TOUCH) program and other registries. The TOUCH program is voluntary for physicians and patients, and includes a "prescribing and enrollment process" and a "dispensing process," each designed to educate physicians and patients about the potential risks and benefits of natalizumab. In addition to the TOUCH program, the sponsor plans to develop a natalizumab registry of 5000 patients with MS who will be followed for up to five years. A pregnancy registry is planned, as well as an epidemiological study of PML in an insurance claims database.

FDA has concerns about the proposed RiskMAP, particularly the voluntary nature of the program. The Office of Drug Safety (ODS) was consulted on the proposed natalizumab RiskMAP, and the reader is referred to the ODS consult located in the AC briefing package. ODS has provided a comprehensive review of the RiskMAP, including the TOUCH program. The FDA review team and ODS consultants recently contacted the sponsor to discuss concerns about the proposed RiskMAP. While the FDA generally believes that participation in a natalizumab RiskMAP should be mandatory, the specific components that would be required in such a RiskMAP have not been determined.

After discussions with the FDA, the sponsor has proposed a registry with mandatory participation for all patients prescribed natalizumab and their prescribing physicians.

Summary

Multiple Sclerosis (MS) is a serious, often disabling disorder that afflicts approximately 300,000 patients in the United States. Currently available MS treatments provide only modest benefit and are not tolerated by many patients. Therefore, there remains a substantial and urgent need for new treatments that are more effective in controlling the clinical manifestations of MS.

The marketing approval of natalizumab in November, 2004, was met with general enthusiasm by the MS community. This optimism was replaced with disappointment when the discovery of an association of natalizumab with progressive multifocal leukoencephalopathy (PML) resulted in the withdrawal of natalizumab from the marketplace. FDA asks this Advisory Committee to reassess the risks and benefits of natalizumab and advise FDA on the possible return of natalizumab (trade name: Tysabri) to the marketplace.

Natalizumab – Effectiveness

i. Relapse Rate: Natalizumab was originally granted accelerated approval based on one-year data that provided evidence of effectiveness in decreasing the MS relapse rate. The current submission provides the follow-up two-year data from the two large, double-blind, placebo-controlled, Phase 3 clinical trials. In a monotherapy study (Study 1801), natalizumab administration was associated with a relative decrease in the relapse rate of approximately 67% (annualized relapse rate of 0.761 in the placebo group and 0.248 in the natalizumab group). In an add-on study in subjects receiving concomitant Avonex (Study 1802), natalizumab administration was associated with a relative decrease in the relapse rate of approximately 58% (annualized relapse rate of 0.785 in the placebo group and 0.326 in the natalizumab group). In both studies, the evidence of effectiveness on the relapse rate was statistically compelling ($p<0.001$), and this result was supported by similar statistically compelling results on other pre-specified primary and secondary endpoints. These studies provide substantial evidence of the effectiveness of natalizumab in decreasing the MS relapse rate, confirming the clinical benefit seen at one year. Comparisons across clinical trials are problematic; however, the magnitude of natalizumab's benefit on the relapse rate, pending further investigation, appears to be approximately twice the benefit of

currently available first line treatments for MS.

ii. Add-on Therapy: As noted above, Study 1802 provides evidence of the effectiveness of natalizumab in decreasing the relapse rate when natalizumab is added to Avonex. Natalizumab is the first MS treatment to provide evidence of effectiveness as an add-on therapy in subjects with active disease while on an approved, first line MS treatment. Therefore, natalizumab has the ability to address an unmet medical need.

iii. Disability Progression: In the monotherapy study (Study 1801), natalizumab administration was associated with a 12% absolute decrease in the percentage of subjects with disability progression at two years (29% in the placebo group and 17% in the natalizumab group; hazard ratio = 0.58; $p < 0.001$). In the add-on study in subjects receiving concomitant Avonex (Study 1802), natalizumab administration was associated with a 6% absolute decrease in the percentage of subjects with disability progression at two years (29% in the placebo group and 23% in the natalizumab group; hazard ratio = 0.76; $p = 0.024$). In each study, alpha of 0.025 was allocated to the disability primary endpoint at two years. Therefore, the disability progression results are statistically compelling in Study 1801 and marginal in Study 1802. Considering also the statistically strong evidence of a positive effect on all of the pre-specified secondary endpoints in each study, the submission provides substantial evidence that natalizumab conveys a modest benefit in preventing disability progression. Although this benefit is clear with natalizumab monotherapy, there is likely also some benefit, although smaller in magnitude, when natalizumab is administered as add-on therapy to a beta interferon.

Natalizumab – Safety

iv. Progressive Multifocal Leukoencephalopathy (PML): PML is rapidly progressive and almost always either fatal or severely disabling. Natalizumab administration has been associated with three cases of PML. The available data are insufficient to permit a definitive assessment of the risk of PML associated with natalizumab administration. Although the three confirmed PML cases occurred in subjects who received a concomitant immune-modulating agent, the data is also insufficient to determine whether natalizumab monotherapy conveys some risk of PML. Many MS patients have a relatively benign disorder; for these patients, natalizumab administration with

an accompanying risk of developing PML may be unacceptable. Primarily because of the risk of PML, which is not well-quantified, it is unclear for which patients the risk-benefit profile would be acceptable.

v. Other serious infections: Natalizumab administration was associated with an increased incidence of atypical and serious infections, including viral meningitis, herpes infections, and atypical pulmonary and gastrointestinal infections. Also, two patients who received natalizumab during the few months of marketing developed herpes central nervous system infections. The available data suggests that natalizumab may have an effect on cell-mediated immunity.

vi. Other safety issues: The available data suggests that natalizumab administration does not increase the risk of malignancy. However, long-term follow-up data will be necessary to reliably assess the risk of carcinogenicity. The risks of infection and hypersensitivity/allergic reactions associated with natalizumab administration may be substantial.

Natalizumab – Immunogenicity

vii. Natalizumab administration was associated with anti-natalizumab antibody formation in approximately 10% of subjects in Studies 1801 and 1802. Antibody formation, particularly persistent antibody positivity (as occurred in approximately 6% of subjects), was associated with decreased efficacy (i.e., a relatively increased incidence of MS relapses) and an increased risk of hypersensitivity and anaphylactic reactions. Therefore, anti-natalizumab antibody formation is likely to be clinically important in some patients if natalizumab returns to the marketplace. However, the clinical utility of routine monitoring for antibody formation is unclear.

Risk Minimization Plan (RMP)

viii. The primary concern at this time is the risk of PML, and perhaps other opportunistic infections, associated with natalizumab administration. If Natalizumab returns to the marketplace, a risk minimization plan is essential to monitor, and hopefully decrease, the risks associated with natalizumab administration. Unfortunately, the utility of

various risk minimization procedures, such as regular neurological examinations, MRI scans, cerebrospinal fluid studies, and serum studies for the JC virus, is unclear. FDA believes that a RMP should be mandatory, and the sponsor has proposed that all patients prescribed natalizumab be required to enroll in a registry. The specific elements of the RMP require further discussion.

Appendix 1: References

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Appendix 2: Kurtzke Expanded Disability Status Scale (EDSS)

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 I excluding Cerebral grade 1).

1.5 No disability, minimal signs in more than one FS (more than one grade I 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.

* see Kurtzke JR. 1983

Appendix 3: Study 1801 Protocol Summary

Title

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab in Subjects with Relapsing-Remitting Multiple Sclerosis

Objective

The study was designed to have one-year and two-year objectives. The one-year objectives were discussed in the initial clinical review, available on the FDA internet web site.

The primary objective at 2 years was to determine whether natalizumab, when compared with placebo, was effective in slowing the progression of disability at 2 years.

The secondary objectives at two years included assessments of whether natalizumab, when compared to placebo, was effective in reducing the rate of clinical relapses.

Design

The study was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial to assess safety and efficacy of natalizumab infusions versus matching placebo in subjects with RRMS. Subjects were randomized 2:1 to natalizumab or placebo. The randomization was block stratified by site

Location

The study was a multicenter, multi-national trial. Infusions were administered in a supervised infusion clinic setting

Duration

The total duration of the trial was 128 weeks. Subjects went through a screening process and later then were randomized and received their first infusion at Week 0. Study agent infusions were administered every 4 weeks for a total of 116 weeks, for a total of 30 infusions. After completion of the infusions, the subjects were then followed until Week 128. The two-year treatment duration of these pivotal trials is similar to what FDA has accepted for approval of other MS treatments.

Sample Size

Approximately 900 subjects were planned; 942 were enrolled**.**

Inclusion Criteria

Men and women between the ages of 18 and 50 years (inclusive) were eligible to participate if they met the following criteria:

- Had a diagnosis of MS as defined by the McDonald Committee (McDonald 2001)
- Had a baseline EDSS score (Appendix 2: Kurtzke Expanded Disability Status Scale (EDSS) between 0.0 and 5.0, inclusive
- Had a brain MRI scan demonstrating lesion(s) consistent with MS
- Had at least one medically documented clinical relapse with onset within the 12 months prior to randomization

Exclusion Criteria:

Subjects were excluded from the trial if they met any of the following criteria at the time of randomization:

- 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 three 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
- Prior to randomization and in the opinion of the investigator, an MS relapse occurred within 50 days prior to randomization and/or the subject had not stabilized from a previous relapse
- A clinically significant infectious illness within 30 days prior to randomization
- History of, or abnormal lab 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
- History of severe allergic or anaphylactic reactions or known drug hypersensitivity

- Unable to perform the Timed 25-Foot Walk, 9-Hole Peg Test (9HPT) with both upper extremities, and Paced Auditory Serial Addition Test (PASAT 3)
- Abnormal blood test, 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 (3XULN)
    - Total WBC count <2,300/mm^3
    - Platelet count < 100,000/mm^3
    - Creatinine >2XULN
    - Prothrombin time (PT) > ULN
- History of treatment with either interferon-beta (IFN-β) or glatiramer acetate for a total of 6 or more months. For example, a subject who was treated with IFN-β for 4 months and glatiramer acetate for 4 months was eligible for the study. A subject who was treated with IFN-β for a total of 6 months and glatiramer acetate for 4 months was not eligible for the study
- Any prior treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, natalizumab, or other therapeutic monoclonal antibody
- Treatment with mitoxantrone or cyclophosphamide within one year prior to randomization
- Treatment with any of the following medications or procedures within 6 months prior to randomization: cyclosporine, azathioprine, methotrexate, subcutaneous glatiramer acetate, IFNβ-1b or IFNβ-1a, intravenous immunoglobulin (IVIG), plasmapheresis, or cytopheresis.
- Treatment with oral glatiramer acetate within 3 months prior to screening.
- Treatment with IV or oral corticosteroid, 4-aminopyridine, or products related to 4-aminopyridine, within 50 days prior to randomization.
- History of alcohol or drug abuse within 2 years prior to randomization.
- Female subjects who were not postmenopausal for at least 1 year, not surgically sterile, and 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
- Nursing mothers, pregnant women, and women who planned to become pregnant while on study
- Participation in previous natalizumab studies (unless subject was on placebo)

- Participation in any other investigational study within 6 months prior to randomization
- Unwillingness or inability to comply with the requirements of the protocol including the presence of any condition (physical, mental, or social) that was likely to affect the subject's ability to comply with the study protocol
- Any other reasons that, in the opinion of the investigator and/or the sponsor, the subject was determined to be unsuitable for enrollment into the study

Concomitant Medications

The protocol for Study 1801 did not allow for treatment with any of the following agents, unless the subject received approval from the Biogen Idec Medical Director or the Study Advisory Committee, or its use was otherwise specified in the protocol:

- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications
- Any alternative drug treatments directed towards the treatment of MS, such as chronic immunosuppressant therapy or other immunomodulatory treatments. Subjects who experienced disability progression were given the option to add treatment with either IFN-β or glatiramer acetate, if those treatments were available to them
- Any systemic steroid therapy including, but not limited to, oral corticosteroids or periodic (e.g. monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined treatment of relapses. Steroids that were administered by non-systemic routes were allowed in the study

Subjects who received any of the restricted drugs without approval may have been required to permanently discontinue the study agent, but were to remain in the trial for follow-up visits. Other symptomatic therapies, such as treatments for spasticity, depression, or fatigue, were not restricted, but investigators attempted to optimize the drugs as early as possible to maintain consistent treatment during the trial.

Dosage

Subjects were randomized to one of two groups: 300 mg natalizumab IV infusion or matching placebo infusion every four weeks.

The infusions of 300 mg natalizumab or placebo were to be administered intravenously every 4 weeks. The study agent was provided in 5mL vials and refrigerated until ready to use. Then, the study agent from three vials was injected into a 100 mL bag of 0.9% saline. The solution was allowed to warm to room temperature before administering it, but the infusion had to begin within 5 hours of mixing the solution. The solution was administered IV over approximately 60 minutes in a clinical setting under the supervision of a physician. Subjects were monitored for at least one hour after the infusion was complete.

Use of Placebo in Control Group

Study 1801 was a monotherapy trial of natalizumab compared to placebo. The use of placebo in patients with MS is somewhat controversial given the disabling nature of the disease and the availability of approved MS therapies. In 2001, Lublin and colleagues in conjunction with the National MS Society addressed the ethical issues of using placebo in patients with MS in the article, "Placebo-Controlled Clinical Trials in Multiple Sclerosis: Ethical Considerations." The authors concluded that it is ethically permissible to use placebo controls in subjects with MS when there are approved MS therapies available, so long as a number of concerns are addressed. Of utmost importance, the subject must be fully informed of the availability of approved MS therapies. This is discussed in great detail in the article, and the sponsor used the recommendations as a model for developing the placebo control group in this trial.

Schedule

Subjects entering Study 1801 were to complete screening studies at least 35 days prior to randomization. These studies included baseline laboratory studies (urinalysis, hematology, blood chemistry, and prothrombin time), serum pregnancy test for women of childbearing potential, physical examination, EDSS examination, brain MRI with and without gadolinium, MSFC, and optional genetic testing. Then, the scheduling of all visits was calculated based on the baseline (Week 0) visit, when the subject received the first dose of study drug.

The study drug was administered at baseline and then every 4 weeks (+/- 3 days) through Week 116. These visits were also identified as Study Drug Administration Visits (SDAVs). In addition to receiving the study drug, monitoring and recording of adverse events and concomitant medications occurred at the SDAVs. Also, women of

childbearing potential received a urine pregnancy test prior to the infusion at these visits.

Clinical evaluations of subjects were performed during scheduled and unscheduled Clinical Evaluation Visits (CEVs). The scheduled CEVs took place at baseline and every 12 weeks (+/- 1 week) through Week 120. Every scheduled CEV included a physical examination, laboratory studies (urinalysis, hematology, chemistries, prothrombin time, anti-natalizumab antibodies, and limited PK sampling), MSFC, and EDSS examinations.

Unscheduled CEVs were the result of subjects calling the treating neurologist within 48 hours of the onset of new neurological symptoms suggestive of a clinical relapse. The treating neurologist was to schedule an appointment within 72 hours of the onset of the suspected relapse, and determine whether a relapse may have occurred. If the treating neurologist believed that the subject did have a relapse, then the subject was referred to the examining neurologist who conducted an EDSS examination within 5 days of the suspected relapse.

Also, subjects underwent an MRI evaluation of the brain at baseline, Weeks 52 and 104 (+/- 4 weeks). Brain MRIs were not performed during the 5 days following study drug administration or within 30 days of receiving a course of steroids. These visits for radiological testing were referred to as MRI Evaluation Visits (MEVs).

An End-of-study Visit was scheduled for Week 120. At this visit the subject was not dosed, but instead underwent a battery of tests. The tests included physical examination, urine pregnancy test for women of childbearing potential, laboratory studies (urinalysis, hematology, chemistries, limited PK sampling, and anti-natalizumab antibodies), MSFC examination, EDSS examination, and monitoring and recording of any adverse event or concomitant medications. This visit was also considered the first visit of the open-label extension and subjects entering the open-label extension, received their first dose of study drug at this visit.

At Week 128 (+/- 5 days), the subjects were tested for anti-natalizumab antibodies and monitored for adverse events and concomitant medications. If subjects discontinued the study drugs, they were monitored by telephone visits every 4 weeks (+/- 3 days) in place of the SDAVs. Any subject who withdrew from the trial underwent a Premature Study Withdrawal Visit. This visit included a battery of tests, including physical examination,

urine pregnancy test for women of childbearing potential, laboratory studies (urinalysis, hematology, chemistries, and anti-natalizumab antibodies), MSFC examination, EDSS examination, and monitoring and recording of any adverse event or concomitant medications.

A cohort of 50 subjects from the US and Canadian sites had intensive PK monitoring. The testing included PK measurements taken at time points around the infusions at Week 0 and Week 20. These subjects had PK sampling pre-infusion, immediately post-infusion, and then 2 hours, 24 hours, 1 week, 2 weeks, 3 weeks, and 4 weeks post-infusion start time.

A separate group of 40 subjects from U.S. and Canadian sites were selected for additional monitoring. The α4-integrin saturation of mononuclear cells was measured at Week 0 (prior to infusion), Week 24, Week 48, Week 72, and Week 96. These samples were collected pre-infusion, and at 2 hours, 1 week, 2 weeks, 3 weeks, and 4 weeks post-infusion start time.

Outcome Measure:

One-Year Efficacy Endpoints

The results of the one-year analysis are available in the initial clinical review, which is located on the FDA internet web site. That review contains a comprehensive discussion of the one-year endpoints.

Two-Year Efficacy Endpoints

The endpoints from the second year of data are the focus of this review. These are described in the following subsections.

Primary Efficacy Endpoint for Two-Year Analysis

The primary endpoint for the two-year analysis is time to onset of the progression of disability, defined as at least a 1.0 point increase in baseline EDSS (if baseline was 1.0 or more) or at least a 1.5 point increase from baseline EDSS (if baseline EDSS was 0), sustained for 12 weeks.

The analysis of the primary endpoint at 2 years was performed using a Cox proportional hazards model. The model included terms for treatment and baseline EDSS. The three

baseline factors included in the model were selected using a backwards selection procedure. This resulted in the inclusion of baseline Gd-enhancing lesions, baseline T2 lesions, and age at baseline into the model. Kaplan-Meier methodology was also used to estimate the percentage of subjects progressing by 2 years.

Determination of Disability Progression

According to the protocol, confirmation of disability progression could not occur within 30 days after onset of a relapse. EDSS was measured at unscheduled visits during suspected relapses, as well as scheduled visits every 12 weeks. Yet, progression could not be confirmed at an unscheduled visit. Instead, the subject was required to return for confirmation at a later scheduled visit.

Two consecutive visits that were at least 12 weeks (84 days) apart qualified for defining sustained progression, but the actual visits may have been +/- 5 days from the scheduled visit, resulting in EDSS examinations that were less than 84 days apart. The minimum number of days apart for visits to confirm progression of EDSS was 74 days by protocol. Death due to MS was counted as progression. If a subject was in a tentative progression at the time of death, then the progression date was the start of the progression. Otherwise, the progression date was the date of death.

If a subject returned for confirmation of a tentative EDSS progression, but the EDSS value measured at the confirmatory visit was not at least as high as the minimum change required for progression, then the EDSS progression could not be confirmed. For example, if a subject with a baseline EDSS score of 0.0 was observed to have an EDSS score of 1.5 at the Week 36 visit, but an EDSS score of 1.0 at Week 48, then progression could not be confirmed at Week 48.

If a subject had an increase in EDSS score that met the criteria for progression, but then missed one or more visits to confirm the increase in EDSS, but later was tested and found to have the persistent increase in EDSS score, then the subject was considered to have progressed. Disability progression could also be confirmed at an early study withdrawal visit, as long as the subject was not also having a relapse.

In both trials, a statistically significant effect was seen on time to progression of sustained disability. However, a substantial issue in interpreting the results of these studies is the

high rate of censoring.

Censoring Rules
Subjects were censored if they prematurely ended treatment. They were to remain in the study for follow-up, and follow-up was only terminated if they completely withdrew from the trial. Otherwise, follow-up ended on the last visit when subjects withdrew from the study.

Subjects without confirmed disease progression who took alternate MS medications, were censored at the time that they took the alternate MS medications. Confirmation of disease progression may have led some subjects to begin taking alternate MS medications.

Secondary Efficacy Endpoints for Two-Year Analysis
The secondary endpoints for the two-year analysis, in order of decreasing importance, include the following:

- the rate of MS relapses
- the mean volume of T2-hyperintense lesions
- the mean number of T1-hypointense lesions
- the progression of disability as determined by changes in the MSFC

Analyses of the secondary endpoints were prioritized in order of importance. A closed testing procedure was used. If an endpoint did not achieve statistical significance, then all endpoints of a lower rank were considered to be not statistically significant.

Tertiary Efficacy Endpoints
Natalizumab was compared to placebo on multiple tertiary endpoints. There was no statistical adjustment made for the multiple comparisons among the tertiary endpoints. The analyses of tertiary endpoints are not reviewed in this document. These endpoints include the following measurements.

- A VAS assessing the subject's global impression of well-being
- Brain atrophy as measured by BPF
- The MSQLI
- The number and volume of gadolinium-enhancing lesions on brain MRI scans at 2 years

- The proportion of relapse-free subjects at 2 years
- The number of relapses requiring IV steroid use
- The volume of gadolinium-enhancing lesions on brain MRI scans at 1 year
- The volume of T2 lesions on brain MRI scans at 1 year
- The volume of T1-hypointense lesions on brain MRI scans at 2 years
- The number of T1-hypointense lesions on brain MRI scans at 1 years
- The number of new or newly emerging T2 lesions on brain MRI scans at 2 years
- The extent of confirmed change in EDSS from baseline to 2 years
- Time-to-sustained progression to an EDSS ≥4.0 from a baseline EDSS ≤3.0
- Time-to-sustained progression to an EDSS ≥6.0 from a baseline EDSS ≤5.0
- Cognitive change, as assessed by the change in the PASAT 3 component of the MSFC from baseline to 2 years
- Time-to-onset of a 0.5 SD worsening in the PASAT 3 that was sustained for 12 weeks
- The change in visual function from baseline to 2 years, as assessed by the low-contrast Sloan letter chart
- The number of hospitalizations at 1 year and 2 years
- Multiple safety outcome measurements, such as vital signs and laboratory findings
- The incidence and titer of serum antibodies to natalizumab
- The PK of natalizumab, as measured by an ELISA
- The degree of natalizumab saturation of the α4-integrin on peripheral mononuclear cells during treatment with natalizumab

Analysis Plan

Co-primary Endpoints

As mentioned above, Study 1801 had two co-primary endpoints. Thus, the sponsor attempted to control for Type I error at 0.05 for the two co-primary endpoints by use of the Hochberg procedure (Hochberg 1988). This statistical procedure preserves the overall Type I error at 0.05, but is not based on specific assumptions about the distribution of the multiple endpoints. The following rule was used as a result of the procedure: if the maximum of the two p-values ≤ 0.05, then both endpoints are considered statistically significant. If not, then the minimum p-value must be ≤ 0.025 to be considered statistically significant. So, the statistical significance level of the first endpoint, relapse rate, was set at 0.025 to ensure no false interpretation of the

significance.

Study 1801 had a primary endpoint for the one-year analyses and a primary endpoint for the two-year analyses. FDA analyzed the primary endpoint for the one-year analyses at the time of the original application, and those reviews are available on the FDA internet web site.

The primary outcome for the two-year analyses is progression of disability at two years, as measured by at least a 1.0 point increase in baseline EDSS (if baseline was 1.0 or more) or at least a 1.5 point increase from baseline EDSS (if baseline EDSS was 0), sustained for 12 weeks. The analysis of the primary endpoint at 2 years was performed using a Cox proportional hazards model. The model included terms for treatment group and baseline EDSS. The three baseline factors included in the model were selected using a backwards selection procedure. This resulted in the inclusion of baseline Gd-enhancing lesions, baseline T2 lesions, and age at baseline into the Cox proportional hazards model. Kaplan-Meier estimates were then obtained.

Secondary and Tertiary Endpoints

Secondary endpoints at 2 years in order of decreasing importance, include the following:

- the rate of MS relapses
- the mean volume of T2-hyperintense lesions
- the mean number of T1-hypointense lesions
- the progression of disability as determined by changes in the MSFC

Analyses of the secondary endpoints are prioritized in order of importance. A closed testing procedure was used for each set so that if an endpoint did not achieve statistical significance, then all endpoints of a lower rank were considered to be not statistically significant.

Baseline Values

Baselines values were defined as the assessment taken closest to, but prior to, the date and time of the first study drug infusion, unless otherwise specified.

Safety Population

The safety population was defined as all subjects who received at least one dose of study

drug and had at least one post-baseline assessment of the safety parameter being analyzed.

Intent-to-Treat (ITT) Population

If subjects stopped taking the study medication, the sponsor tried to keep them in the study and complete all assessments. All primary and secondary outcome analyses were conducted using the ITT population. The ITT population was defined as all subjects who were randomized. Subjects were analyzed in the group to which they were randomly assigned.

Efficacy Evaluable Population

The efficacy evaluable population was defined as a subset of the ITT population that excluded subjects who did not receive at least 26 (85%) infusions of study drug. This population was used in exploratory analyses of the primary and secondary outcomes.

Techniques for Minimization of Bias

Investigational Site Personnel

To reduce bias and preserve the blind, the protocol included several features. First, all study personnel were blinded to treatment assignment. Each site designated two neurologists: a treating neurologist to oversee clinical management of the subject, including the assessment and treatment of new neurological events and any adverse events, and an examining neurologist who conducted EDSS evaluations at the scheduled visits. Both of these neurologists were blinded to treatment. The examining neurologist was also available to conduct EDSS evaluations at unscheduled visits if needed. Both the examining and the treating neurologists had a back-up neurologist so there would be no delays in assessment or treatment of subjects.

Other than performing the EDSS evaluations, the examining neurologist had no role in the care or treatment of the subjects. In fact, the roles of "treating" and "examining" neurologists were not interchangeable, even for different subjects. In addition to the examining neurologist, an examining technician administered the MSFC. Both the examining neurologist and the examining technician remained blinded to the subject's adverse events, concomitant medications, laboratory data, MRI data, and any other information that was thought to have the potential to bias the examinations. This technique of using both a treating and an examining neurologist has been used in other

MS trials.

Central Laboratories

One of the known pharmacodynamic effects of natalizumab is an elevation of circulating lymphocytes. Thus, knowledge of a subject's laboratory results could compromise the blind. To prevent this from happening and protect the blind, all WBC and associated differential counts were reviewed centrally by an independent physician monitor. After the screening visit, the investigational site personnel were not allowed to see any of the laboratory WBC data, including differential counts, except absolute neutrophil count. Likewise, analysis of all MRIs was performed by a central reading laboratory whose staff members were blinded to the treatment assignments. In addition to the central analysis, the MRIs were also assessed at the site by blinded physicians and technicians who reviewed the scans for non-MS pathology.

Statistical Analyses

Another challenge in protecting the blind late in the study was due to the dual one-year and two-year objectives and outcomes. The study was designed such that if a robust effect and adequate safety was shown in the one-year analysis, then a BLA would be submitted at that time for accelerated approval using the one year primary outcome of relapse rate as a surrogate marker for two-year relapse rate. To protect the blind the database was frozen when the last randomized subject completed the pre-specified required visit for the one-year analysis and all clarifications of the one-year data were resolved. The one-year data analysis was then completed by a group at the sponsor's headquarters, and as soon as they had access to the treatment assignments then they no longer had any operational role in the conduct of Study 1801 or 1802, or in any review of the two-year data prior to the unblinding at two years.

Study Drug

To protect the blind natalizumab and placebo were provided in matching vials and were identical in color and appearance.

Randomization Codes

The study was randomized to prevent bias. The telecommunications center generated the randomization scheme, and this was implemented by an interactive voice response system. This system was used to assign treatments and the study drug kits to the subjects.

Study Committees

The members of the Advisory Committee were blinded to subject treatment. This committee was formed to provide scientific and medical direction for the study. They met approximately once a month to monitor subject accrual and non-compliance with the protocol at individual sites. They also determined whether the study should be stopped or amended for non-safety reasons. Members of the Safety Monitoring Committee were independent from the sponsor and its affiliates. They held closed meetings in which unblinded safety data could be discussed. This information, including the reports from the statistician, was withheld from the sponsor until after the final database was locked and unblinded at the end of the study.

Safety Monitoring:

A variety of safety monitoring techniques was used during the trial, including many laboratory studies, urinalysis, pregnancy testing, ECGs, and physical examinations. The sponsor provided a comprehensive study schedule. All subjects were closely monitored during the study drug infusion and for at least one hour after the infusion was complete, to watch for signs of hypersensitivity reactions.

Appendix 4: Study 1802 Protocol Summary

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

- Target enrollment was approximately 1200 subjects
- 1:1 randomization to either natalizumab or placebo
- Inclusion criteria – subjects between 18 and 55 years of age, inclusive
- Inclusion criteria that all subjects must have received Avonex for at least 12 months prior to randomization. (Subjects were excluded from Study 1801 if they had ≥ 6 months exposure to Avonex.)
- Subjects were to receive 30 µg Avonex by IM injection once a week throughout the study. Avonex was not to be administered within 24 hours of the study drug infusion.
- Subjects had to have had at least one relapse in the prior 12 months while on Avonex
- Exclusion criteria based on prior treatment – mycophenolate mofetil was not allowed within 6 months of randomization in 1802 (no restriction in 1801)
- The way that T1-hypointense lesions were counted in Study 1802 varied slightly from the method used in Study 1801, as per their respective protocols. In Study 1801, all T1-hypointense lesions were counted; however, in Study 1802, only the non-enhancing T1-hypointensities, or T1-black holes, were counted. Also, in Study 1802, individual lesion counts per slice were assessed rather than total number of lesions. Thus, a single lesion that traversed three MRI slices was counted three times in Study 1802 and once in Study 1801.

Appendix 5: Natalizumab Drug Exposure in Subjects Included in the DSMSSA (from Studies 1801, 1802, or 1803)

	Number of Natalizumab Infusions																																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	Overall
Previous natalizumab	2	18	6	5	5	11	8	4	2	6	2	3	6	12	3	4	5	15	6	13	3	2	5	1	3	8	2	9	33	99	122	100	108	87	202	145	79	23	18	13	1	1199
Natalizumab	1	12	4	1	1	1	0	0	2	0	1	0	3	6	2	2	2	1	1	1	1	1	1	0	2	3	1	1	3	24	9	40	54	47	156	116	60	17	16	10	0	603
Natalizumab + Avonex	1	6	2	4	3	5	5	4	0	4	0	3	3	4	0	1	2	1	0	2	1	1	4	1	1	5	1	8	30	75	113	60	54	40	46	29	19	6	2	3	1	550
Natalizumab + GA	0	0	0	0	1	5	3	0	0	2	1	0	0	2	1	1	1	13	5	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	46
Placebo/Avonex/GA then Natalizumab	118	95	83	54	118	78	57	17	13	8	8	10	3	7	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	670
Placebo then Natalizumab	5	23	28	20	74	53	33	10	10	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	261
Avonex then Natalizumab	113	71	55	32	44	25	22	6	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	375
GA then Natalizumab	0	1	0	2	0	0	2	1	0	1	6	10	3	7	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	34

NOTE: Analysis includes dosing data in the database as of August 1, 2005.
ABBREVIATIONS: GA=Glatiramer Acetate.

SOURCE: ANTEGREN\ADHOC\SAFETY\ADHOC\FDA QUESTIONS\C-1808\EXPOSUREINCLUDEDSV.SAS

DATE: 02JAN2006

Appendix 6: Natalizumab Drug Exposure in Subjects Excluded in the DSMSSA (from Studies 1801, 1802, or 1803)

	Number of Natalizumab Infusions																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	24	25	26	28	29	30	31	37	Overall
Previous natalizumab	5	7	1	13	2	10	6	1	3	2	1	1	2	1	2	1	2	1	3	2	1	3	2	1	1	1	1	5	2	1	84
Natalizumab	1	3	1	0	1	3	2	1	2	1	0	0	0	1	0	1	0	1	0	0	0	2	0	1	0	0	0	1	2	0	24
Natalizumab + Avonex	2	3	0	13	1	1	4	0	1	1	1	1	2	0	2	0	2	0	3	2	1	1	2	0	1	1	1	4	0	1	51
Natalizumab + GA	2	1	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9
Placebo/Avonex/GA then Natalizumab	1	0	1	1	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6
Placebo then Natalizumab	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Avonex then Natalizumab	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
GA then Natalizumab	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2

Appendix 7: Natalizumab Drug Exposure in Subjects Included in the DSCDRASA

	Number of Natalizumab Infusions																																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	Overall
Number of subjects included in the DSV Analysis who were dosed	93	95	121	97	96	57	63	52	20	13	14	9	8	10	15	14	16	18	17	21	23	27	36	25	36	46	53	16	27	15	11	11	16	4	7	7	7	2	2	1220
Natalizumab only	14	7	35	36	19	8	13	5	4	2	4	0	3	2	6	5	8	5	3	3	7	4	10	2	2	17	10	6	7	3	3	4	3	0	1	3	1	1	0	266
Natalizumab and concurrent immunosuppresants/steroids	79	88	86	61	77	49	50	47	16	11	10	9	5	8	9	9	8	13	14	18	16	23	26	23	34	29	43	10	20	12	8	7	13	4	6	4	6	1	2	954
STEROIDS (a)	56	56	59	44	54	31	34	30	11	11	9	8	5	7	8	7	8	9	12	12	11	18	17	17	26	24	28	7	16	9	5	5	11	4	4	3	4	1	1	682
AZATHIOPRINE	19	13	30	17	13	16	8	4	7	3	3	3	3	1	2	4	3	5	6	5	7	5	13	12	13	15	12	4	11	4	5	3	7	3	1	2	2	1	2	287
METHOTREXATE	39	51	20	19	36	17	25	31	4	3	0	2	0	0	0	1	2	0	1	5	2	1	2	2	1	3	8	0	1	1	1	0	1	1	1	1	0	0	0	282
MERCAPTOPURINE	7	5	6	7	6	5	3	2	2	1	1	0	0	0	0	1	2	1	1	3	3	5	5	1	6	5	9	1	1	0	0	1	3	0	2	0	2	0	0	97
INFLIXIMAB	1	3	3	1	1	4	1	1	0	2	2	2	1	1	0	1	0	1	0	5	1	1	6	5	4	1	2	1	0	0	0	0	0	0	0	0	0	0	0	51
LEFLUNOMIDE	3	1	1	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8
CELESTAMINE	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3
CICLOSPORIN	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
ETANERCEPT	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
TACROLIMUS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
TIOGUANINE	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

NOTE 1: Analysis includes dosing data as of June 22, 2005 for CD studies and September 15, 2005 for RA studies. Subjects who were dosed with natalizumab and did not have natalizumab dosing data in the database at the time of the analysis were excluded.

2: Immunosuppresants/steroids are sorted by decreasing frequency in the overall column.

(a) Steroids include concurrent medications coded to a WHO description of Prednisone, Hydrocortisone, Methylprednisolone, Budesonide, Prednisolone, Dexamethasone, Triamcinolone, Betamethasone, Meprednisone, Corticosteriod NOS, Deflazacort, Beclometasone, Cortisone, and Depo-medrol med lidokain.

SOURCE: ANTEGREN\ADHOC\SAFETY\ADHOC\FDA QUESTIONS\CDRA\EXPOSUREINCONMED.SAS DATE: 02JAN2006

Appendix 8: Natalizumab Drug Exposure in Subjects Excluded from the DSCDRASA

	Number of Natalizumab Infusions																																
	1	2	3	4	5	6	7	8	9	10	11	12	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	32	33	38	Overall
Number of subjects excluded from the DSV Analysis who were dosed	12	16	18	11	14	12	11	6	9	7	3	2	3	7	2	6	7	2	7	2	2	1	6	4	10	8	2	1	3	1	1	1	197
Natalizumab only	1	3	5	3	5	2	2	2	2	3	1	0	2	2	0	0	2	0	2	0	2	0	0	0	1	4	1	1	0	1	1	0	48
Natalizumab and concurrent immunosuppresants/steroids	11	13	13	8	9	10	9	4	7	4	2	2	1	5	2	6	5	2	5	2	0	1	6	4	9	4	1	0	3	0	0	1	149
STEROIDS (a)	9	9	8	6	7	8	8	2	4	4	1	0	1	4	1	5	4	1	4	1	0	0	5	3	8	4	1	0	2	0	0	0	110
AZATHIOPRINE	2	3	4	2	1	3	1	0	1	1	0	2	0	2	1	4	2	1	4	0	0	0	1	3	4	2	1	0	1	0	0	1	47
METHOTREXATE	4	5	3	2	2	2	3	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	25
MERCAPTOPURINE	0	0	1	2	0	0	0	0	1	0	0	0	0	1	0	1	1	0	2	1	0	1	2	0	1	0	0	0	0	0	0	0	14
INFLIXIMAB	0	0	0	1	0	0	2	1	0	1	0	0	0	0	0	0	0	0	3	0	0	0	0	1	0	0	0	0	0	0	0	0	9
FOLINIC ACID	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

NOTE 1: Analysis includes dosing data as of June 22, 2005 for CD studies and September 15, 2005 for RA studies. Subjects who were dosed with natalizumab and did not have natalizumab dosing data in the database at the time of the analysis were excluded.

2: Immunosuppresants/steroids are sorted by decreasing frequency in the overall column.

(a) Steroids include concurrent medications coded to a WHO description of Prednisone, Hydrocortisone, Methylprednisolone, Budesonide, Prednisolone, Dexamethasone, Triamcinolone, Betamethasone, Meprednisone, Corticosteriod NOS, Deflazacort, Beclometasone, Cortisone, and Depr-medrol med lidokain.

SOURCE: ANTEGREN\ADHOC\SAFETY\ADHOC\FDA QUESTIONS\CDRA\EXPOSUREEXCCONMED.SAS DATE: 02JAN2006

Appendix 9: DSMSSA Evaluations Conducted in Subjects with Previous Natalizumab Exposure

Number of Natalizumab Infusions

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Previous natalizumab	2	18	6	5	5	11	8	4	2	6	2	3	6	12	3	4	5	15	6	13
Natalizumab	1	12	4	1	1	1	0	0	2	0	1	0	3	6	2	2	2	1	1	1
Neurological exam	0	10	4	0	1	1	0	0	2	0	1	0	3	6	1	2	1	1	1	1
MRI exam	0	11	4	1	1	1	0	0	2	0	1	0	3	6	2	2	1	1	1	1
JCV plasma testing	0	4	2	0	1	0	0	0	0	0	0	0	1	4	2	2	0	0	0	0
CSF testing	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Natalizumab + Avonex	1	6	2	4	3	5	5	4	0	4	0	3	3	4	0	1	2	1	0	2
Neurological exam	1	5	2	3	3	3	4	4	0	3	0	3	1	4	0	1	2	0	0	1
MRI exam	1	5	2	4	3	5	5	4	0	4	0	3	3	4	0	1	2	1	0	2
JCV plasma testing	0	1	2	2	1	2	1	3	0	2	0	2	1	4	0	0	2	0	0	1
CSF testing	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0	0	0
Natalizumab + GA	0	0	0	0	1	5	3	0	0	2	1	0	0	2	1	1	1	13	5	10
Neurological exam	0	0	0	0	1	5	2	0	0	2	1	0	0	2	1	1	1	13	2	8
MRI exam	0	0	0	0	1	4	3	0	0	2	1	0	0	0	0	0	1	13	5	10
JCV plasma testing	0	0	0	0	0	2	1	0	0	2	1	0	0	0	1	1	0	12	5	6
CSF testing	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	9	1	3

	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	Overall
Previous natalizumab	3	2	5	1	3	8	2	9	33	99	122	100	108	87	202	145	79	23	18	13	1	1199
Natalizumab	1	1	1	0	2	3	1	1	3	24	9	40	54	47	156	116	60	17	16	10	0	603
Neurological exam	1	1	1	0	2	2	1	1	3	22	8	40	52	43	143	102	52	14	16	10	0	549
MRI exam	1	1	1	0	2	3	1	0	2	21	7	39	53	45	150	110	58	17	16	9	0	574
JCV plasma testing	0	1	1	0	2	2	1	1	1	15	3	13	33	21	94	54	44	9	12	8	0	331
CSF testing	0	0	0	0	0	1	0	0	0	3	1	4	9	6	17	18	17	1	4	1	0	84
Natalizumab + Avonex	1	1	4	1	1	5	1	8	30	75	113	60	54	40	46	29	19	6	2	3	1	550
Neurological exam	1	1	2	1	1	5	1	7	27	64	102	53	52	36	41	27	18	4	2	3	1	489
MRI exam	1	1	3	1	1	5	1	8	29	72	102	51	52	36	46	28	16	6	2	3	1	514
JCV plasma testing	0	0	3	0	0	2	1	3	14	37	73	27	33	23	35	22	11	5	1	2	1	317
CSF testing	0	0	1	0	0	2	1	1	3	16	34	8	10	6	17	12	5	2	0	1	1	123
Natalizumab + GA	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	46
Neurological exam	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40
MRI exam	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	41
JCV plasma testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	31
CSF testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14

NOTE: Analysis includes dosing data in the database as of August 1st 2005.
ABBREVIATIONS: GA=Glatiramer Acetate.

SOURCE: ANTEGREN\ADHOC\SAFETY\ADHOC\FDA QUESTIONS\C-1808\DSEVALEXPOSUREPREVIOUS.SAS DATE: 03JAN2006

Appendix 10: DSMSSA Evaluations Conducted in Subjects with Placebo/Avonex/G.A. then Natalizumab Exposure

	Number of Natalizumab Infusions															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	Overall
Placebo/Avonex/GA then Natalizumab	118	95	83	54	118	78	57	17	13	8	8	10	3	7	1	670
Placebo then Natalizumab	5	23	28	20	74	53	33	10	10	5	0	0	0	0	0	261
Neurological exam	5	22	25	18	71	49	28	9	9	3	0	0	0	0	0	239
MRI exam	4	21	26	20	72	53	29	8	10	5	0	0	0	0	0	248
JCV plasma testing	2	15	16	7	46	26	22	8	4	4	0	0	0	0	0	150
CSF testing	0	2	7	2	5	7	6	2	2	1	0	0	0	0	0	34
Avonex then Natalizumab	113	71	55	32	44	25	22	6	3	2	2	0	0	0	0	375
Neurological exam	102	61	51	30	43	23	21	4	3	2	2	0	0	0	0	342
MRI exam	100	62	52	29	43	23	22	6	3	2	2	0	0	0	0	344
JCV plasma testing	66	33	24	22	32	15	17	4	2	1	2	0	0	0	0	218
CSF testing	13	5	7	9	8	3	4	1	0	0	2	0	0	0	0	52
GA then Natalizumab	0	1	0	2	0	0	2	1	0	1	6	10	3	7	1	34
Neurological exam	0	0	0	2	0	0	2	1	0	1	6	10	2	6	1	31
MRI exam	0	1	0	2	0	0	1	0	0	1	5	10	3	7	1	31
JCV plasma testing	0	0	0	1	0	0	1	0	0	0	3	10	3	5	1	24
CSF testing	0	0	0	0	0	0	0	0	0	0	2	7	1	3	1	14

NOTE: Analysis includes dosing data in the database as of August 1st 2005.
ABBREVIATIONS: GA=Glatiramer Acetate.

SOURCE: ANTEGREN\ADHOC\SAFETY\ADHOC\FDA QUESTIONS\C-1808\DSVEVALEXPOSURETHENNAT.SAS DATE: 02JAN2006
ABBREVIATIONS: GA=Glatiramer Acetate.

Appendix 11: DSCDRASA Evaluations in Subjects with Natalizumab Exposure and +/- Immunosuppressant Agents

	Number of Natalizumab Infusions																																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	Overall
Number of subjects included in the DSV Analysis who were dosed	93	95	121	97	96	57	63	52	20	13	14	9	8	10	15	14	16	18	17	21	23	27	36	25	36	46	53	16	27	15	11	11	16	4	7	7	7	2	2	1220
Neurological exam	84	84	104	83	84	48	53	49	17	8	11	7	7	6	13	9	13	17	14	18	17	25	30	21	30	40	46	11	25	13	8	9	13	4	7	5	7	2	2	1044
MRI exam	74	63	93	72	71	39	46	39	16	9	11	5	6	5	13	10	11	18	14	13	18	21	30	23	25	34	38	12	23	9	8	10	11	3	5	6	7	2	2	915
JCV plasma testing	88	89	111	87	93	53	62	47	18	9	12	8	7	7	12	10	14	16	16	17	19	26	31	19	33	44	47	14	27	15	10	11	15	2	6	6	7	2	1	1111
CSF testing	6	0	4	5	8	2	3	1	0	0	0	0	0	0	0	0	2	1	2	1	2	2	4	4	2	3	2	1	3	2	1	0	0	0	0	0	1	0	0	62
Natalizumab only	14	7	35	36	19	8	13	5	4	2	4	0	3	2	6	5	8	5	3	3	7	4	10	2	2	17	10	6	7	3	3	4	3	0	1	3	1	1	0	266
Neurological exam	12	7	28	29	16	6	10	5	4	1	3	0	3	2	6	3	6	5	2	2	6	3	8	1	1	16	9	5	7	3	3	2	3	0	1	2	1	1	0	222
MRI exam	12	4	28	25	11	7	10	4	3	1	3	0	3	1	5	3	6	5	2	2	5	3	9	1	1	13	5	4	6	1	3	3	3	0	1	3	1	1	0	198
JCV plasma testing	13	7	32	32	17	8	13	4	4	2	4	0	3	0	6	3	6	4	2	2	5	3	8	1	2	17	10	5	7	3	3	4	2	0	1	2	1	1	0	237
CSF testing	1	0	1	0	3	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	12
Natalizumab and concurrent immunosuppresants/steroids	79	88	86	61	77	49	50	47	16	11	10	9	5	8	9	9	8	13	14	18	16	23	26	23	34	29	43	10	20	12	8	7	13	4	6	4	6	1	2	954
STEROIDS (a)	56	56	59	44	54	31	34	30	11	11	9	8	5	7	8	7	8	9	12	12	11	18	17	17	26	24	28	7	16	9	5	5	11	4	4	3	4	1	1	682
Neurological exam	52	49	52	41	49	26	28	28	8	7	8	6	4	3	6	5	7	8	10	10	7	17	15	15	23	20	23	3	15	8	3	5	8	4	4	2	4	1	1	585
MRI exam	48	42	42	35	41	21	23	22	9	8	7	4	3	4	7	6	5	9	10	6	8	14	14	17	18	17	21	6	14	6	3	5	7	3	3	2	4	1	1	516
JCV plasma testing	54	53	52	41	54	29	33	27	9	7	8	7	4	6	5	6	8	8	12	9	9	18	15	13	24	22	24	6	16	9	5	5	11	2	4	3	4	1	1	624
CSF testing	2	0	1	4	3	2	0	0	0	0	0	0	0	0	0	0	2	0	1	0	2	0	3	2	2	1	1	1	1	0	0	0	0	0	0	0	1	0	0	29
AZATHIOPRINE	19	13	30	17	13	16	8	4	7	3	3	3	3	1	2	4	3	5	6	5	7	5	13	12	13	15	12	4	11	4	5	3	7	3	1	2	2	1	2	287
Neurological exam	15	10	27	15	10	13	5	4	6	1	2	3	3	0	2	2	3	5	5	5	4	5	12	9	9	12	11	4	9	4	4	3	6	3	1	2	2	1	2	239
MRI exam	13	9	25	12	8	10	5	3	6	3	3	2	3	1	2	3	2	5	4	4	5	4	12	11	10	11	10	3	9	2	4	3	3	3	0	1	2	1	2	219
JCV plasma testing	18	12	29	16	12	15	8	3	6	1	2	3	3	1	2	3	3	5	6	4	7	5	10	9	12	13	12	4	11	4	4	3	7	2	0	2	2	1	1	261
CSF testing	2	0	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	2	2	1	1	0	0	3	1	1	0	0	0	0	0	0	0	0	20
METHOTREXATE	39	51	20	19	36	17	25	31	4	3	0	2	0	0	0	1	2	0	1	5	2	1	2	2	1	3	8	0	1	1	1	0	1	1	1	1	0	0	0	282
Neurological exam	37	46	17	18	34	16	24	29	4	1	0	2	0	0	0	0	2	0	1	5	1	1	2	2	1	3	7	0	1	1	0	0	1	1	1	1	0	0	0	259
MRI exam	31	32	13	17	31	10	21	24	3	2	0	1	0	0	0	0	2	0	1	1	2	0	1	2	0	2	6	0	1	1	0	0	1	0	0	1	0	0	0	206
JCV plasma testing	37	47	16	16	36	15	25	29	4	2	0	2	0	0	0	1	2	0	1	4	0	1	2	2	1	2	7	0	1	1	1	0	1	0	1	1	0	0	0	258
CSF testing	2	0	0	4	3	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12
MERCAPTOPURINE	7	5	6	7	6	5	3	2	2	1	1	0	0	0	0	1	2	1	1	3	3	5	5	1	6	5	9	1	1	0	0	1	3	0	2	0	2	0	0	97
Neurological exam	6	4	6	5	4	5	2	2	1	1	1	0	0	0	0	1	2	1	0	3	3	5	4	1	6	5	8	1	1	0	0	1	2	0	2	0	2	0	0	85
MRI exam	4	3	6	5	5	5	2	2	1	0	1	0	0	0	0	1	1	1	1	3	3	3	4	1	4	5	6	1	1	0	0	1	2	0	2	0	2	0	0	76
JCV plasma testing	6	4	6	6	6	4	3	2	2	1	1	0	0	0	0	0	2	0	1	3	3	5	5	1	6	4	7	1	1	0	0	1	3	0	2	0	2	0	0	88

NOTE 1: Analysis includes dosing data as of June 22, 2005 for CD studies and September 15, 2005 for RA studies. Subjects who were dosed with natalizumab and did not have natalizumab dosing data in the database at the time of the analysis were excluded.

2: Immunosuppresants/steroids are sorted by decreasing frequency in the overall column.

(a) Steroids include concurrent medications coded to a WHO description of Prednisone, Hydrocortisone, Methylprednisolone, Budesonide, Prednisolone, Dexamethasone, Triamcinolone, Betamethasone, Meprednisone, Corticosteriod NOS, Deflazacort, Beclometasone, Cortisone, and Depr-medrol med lidokain.

SOURCE: ANTEGREN\ADHOC\SAFETY\ADHOC\FDA QUESTIONS\CDRA\DSVEXPOSUREINCONMED.SAS DATE: 02JAN2006

CD/RA Subjects - Total Number of Natalizumab Infusions for Subjects Included in the DSV Analysis by Concurrent Immunosuppresant Use and Type of DSV Evaluation
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	Number of Natalizumab Infusions																																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	Overall
CSF testing	0	0	0	0	2	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	7
INFLIXIMAB	1	3	3	1	1	4	1	1	0	2	2	2	1	1	0	1	0	1	0	5	1	1	6	5	4	1	2	1	0	0	0	0	0	0	0	0	0	0	0	51
Neurological exam	0	2	2	1	1	4	1	1	0	2	2	2	1	1	0	1	0	1	0	5	1	1	3	3	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0	41
MRI exam	0	1	0	1	1	3	1	0	0	2	1	1	1	0	0	1	0	1	0	2	1	1	3	4	4	1	0	1	0	0	0	0	0	0	0	0	0	0	0	31
JCV plasma testing	0	2	3	1	1	4	1	0	0	1	2	2	1	1	0	0	0	1	0	4	1	1	6	4	4	1	2	1	0	0	0	0	0	0	0	0	0	0	0	44
CSF testing	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6
LEFLUNOMIDE	3	1	1	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8
Neurological exam	2	1	1	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7
MRI exam	2	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
JCV plasma testing	3	1	1	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8
CSF testing	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
OLESTYRAMINE	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3
Neurological exam	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
MRI exam	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3
JCV plasma testing	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3
CSF testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
CICLOSPORIN	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Neurological exam	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
MRI exam	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
JCV plasma testing	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
CSF testing	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
ETANERCEPT	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Neurological exam	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
MRI exam	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
JCV plasma testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CSF testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TACROLIMUS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Neurological exam	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
MRI exam	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
JCV plasma testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
CSF testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TIOGUANINE	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Neurological exam	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
MRI exam	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
JCV plasma testing	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
CSF testing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NOTE 1: Analysis includes dosing data as of June 22, 2005 for CD studies and September 15, 2005 for RA studies. Subjects who were dosed with natalizumab and did not have natalizumab dosing data in the database at the time of the analysis were excluded.

2: Immunosuppresants/steroids are sorted by decreasing frequency in the overall column.

(a) Steroids include concurrent medications coded to a WHO description of Prednisone, Hydrocortisone, Methylprednisolone, Budesonide, Prednisolone, Dexamethasone, Triamcinolone, Betamethasone, Meprednisone, Corticosteroid NOS, Deflazacort, Beclometasone, Cortisone, and Depr-medrol med liddokain.

SOURCE: ANTEGREN\ADHOC\SAFETY\ADHOC\FDA QUESTIONS\CDRA\DSVEXPOSUREINCCONMED.SAS DATE: 02JAN2006

Appendix 12: Infection Adverse Events Occurring in ≥1% of Natalizumab-treated Patients and More Frequently Than in Placebo-treated Patients by Decreasing Frequency, CD Placebo-controlled Trials

Infection Adverse Event Preferred Term	Natalizumab (n=1182); % (no.)	Placebo (n=506); % (no.)
Nasopharyngitis	13.2% (156)	9.7% (49)
URI NOS	4.1% (49)	3.8% (19)
Sinusitis NOS	3.1% (37)	2.4% (12)
Viral infection NOS	2.9% (34)	1.6% (8)
Urinary tract infection NOS	2.6% (31)	1.4% (7)
Gastroenteritis NOS	2.2% (26)	2.0% (10)
Pharyngitis viral NOS	1.9% (23)	0.8% (4)
Herpes simplex	1.2% (14)	0.8% (4)
Perianal abscess	1.1% (13)	0.6% (3)
Upper respiratory tract infection viral NOS	1.1% (13)	0.6% (3)

Appendix 13: Infection Serious Adverse Events Occurring More Frequently in Natalizumab-treated Patients vs. Placebo-treated Patients by Decreasing Frequency; CD Placebo-controlled Trials

Infection Adverse Event Preferred Term	Natalizumab (n=1182); % (no.)	Placebo (n=506); % (no.)
All serious infections	2.5% (29)	2.6% (13)
Abdominal abscess NOS	0.3% (3)	0.2% (1)
Meningitis viral NOS	0.2% (2)	0
Urinary tract infection NOS	0.2% (2)	0
Abscess NOS	<0.1% (1)	0
Abscess intestinal	<0.1% (1)	0
Appendiceal abscess	<0.1% (1)	0
Appendicitis	<0.1% (1)	0
Bacteraemia	<0.1% (1)	0
Bronchopneumonia NOS	<0.1% (1)	0
Cytomegalovirus infection	<0.1% (1)	0
Prostatitis	<0.1% (1)	0
Psoas abscess	<0.1% (1)	0
Salpingitis NOS	<0.1% (1)	0
Septic shock	<0.1% (1)	0
Staphylococcal infection	<0.1% (1)	0
Vaginal abscess	<0.1% (1)	0

Vulval abscess	<0.1% (1)	0

Appendix 14: Selected CD Infection Narratives

Viral meningitis cases

1. A 52 year-old female (from CD301) was hospitalized for viral meningitis 20 days after her first infusion of natalizumab. Concomitant CD medication at the time of the event was Budesonide 6 mg qd. She awoke with a severe headache, muscle aches, neck pain, dizziness, nausea, generalized pain, and a temperature of 103 ° F. She was instructed to present to the emergency department that same morning and was admitted to the hospital for the symptoms. Upon admission to the hospital, a head CT scan was normal. An ultrasound-guided lumbar puncture was negative for organisms by stain, culture and antigen testing. An infectious disease consultation diagnosed the subject as having viral meningitis. She was treated with intravenous ceftriaxone for two days. She was discharged from the hospital in stable condition on oral cefuroxime and hydrocodone for headache. The event resolved and the subject received her 2nd infusion of study drug two days later.

2. A 31 year-old male (from CD301) was hospitalized for viral meningitis 30 days after his second infusion of natalizumab. Concomitant medications at the time of the event included Colazal (balsalazide disodium), Prednisone 10 mg qd, and 6-mercaptopurine 75 mg qd. The subject complained of headaches, body aches, back pain, a temperature of 101.5 °F, and two episodes of vomiting. The subject presented to the emergency department and was noted to have neck stiffness. A computed tomography scan of the head was negative. A cerebrospinal fluid study including cultures was performed. CSF WBC count was 255/uL, RBC count was 110/ uL, protein was 378 mg/ dL, and glucose was 19 mg/dL. Gram stain revealed no microorganisms and few white cells. CSF cultures were negative, as were blood cultures. A Directigen test was negative for bacterial meningitis. The subject was treated with oral vancomycin, intravenous ceftriaxone, and intramuscular ampicillin for six days. The patient was found to have transaminase and alkaline phosphatase elevations on the day of presentation to the ER: AST 134 IU/L (normal range 15—37 IU/L), ALT 197 (normal range 30—65 IU/L), and alkaline phosphatase 300 IU/L (normal range 50—136 IU/L). The investigator reported that the subject's increased LFTs could have been due to either a viral syndrome with aseptic meningitis or to 6-mercaptopurine therapy. ALT had decreased to 68 IU/L four days after onset of the adverse event. The event resolved and the subject was discharged. The patient continued in the study.

Cytomegalovirus colitis

A 33- year-old female (from CD202) with a history of an eating disorder, intestinal malabsorption, migraines, joint pain, and dry skin, was hospitalized with cytomegalovirus (CMV) colitis after her 2nd dose of natalizumab. Concomitant medications included mesalazine, azathioprine, evening primrose oil, codeine, desogestrel/ ethinylestradiol, and potassium carbonate. The subject reported a 10-day history of fever and night sweats and was admitted for evaluation. The subject continued to experience fevers for 10 days. The diagnosis of CMV was made based on positive serum CMV IgM and IgG. In addition, PCR (from sigmoid colon) biopsy was positive for CMV DNA. Malarial blood film and blood, urine, stool, and fungal culture results were negative. An abdominal CT scan revealed normal liver, spleen, and kidneys, but thickening of the small bowel loops and the left side of the colon, consistent with active Crohn's disease. Endoscopic biopsy revealed an increase in chronic inflammatory cells, consistent with Crohn's disease. Flexible sigmoidoscopy revealed inflammation and linear ulceration consistent with mildly active Crohn's disease. Approximately 2 weeks later, the CMV infection resolved and the subject was discharged from the hospital.

Pulmonary aspergillosis

A 73 year-old male (from CD351) developed pulmonary aspergillosis and subsequently died after a complicated hospital course following perforation of a duodenal ulcer and a severe gastric bleed. This event occurred approximately 1 month after his tenth infusion of natalizumab; he had received three infusions in CD301 and seven in CD351. He received two placebo infusions in CD303. The subject was taking concomitant NSAIDs and high dose prednisolone (50 mg daily) without a cytoprotective agent at the time of the event. He underwent laparotomy. His hospitalization was further complicated by peritonitis and he required intensive care support. After several weeks in the hospital, the subject began to deteriorate with bilateral infiltrates on chest X- ray. Sputum cultures grew aspergillus. He subsequently developed multi-organ system failure and died.

Pneumocystis carinii pneumonia

A 69 year-old male (from CD351) developed a pneumocystis carinii infection and subsequently died after being treated for hepatic encephalopathy, acute renal failure, and anemia. He had received 34 infusions of natalizumab. He was not on any steroids or immunosuppressive agents at the time of the event.

The subject had a history of cirrhosis secondary to nonalcoholic steatohepatitis (NASH), esophageal varices, probable portal hypertension, splenomegaly, and

ascites. The subject previously participated in Studies CD301 and CD303 and received his 34th infusion of natalizumab one month prior to developing hepatic encephalopathy. He was hospitalized for treatment of this hepatic encephalopathy in addition to acute renal failure and anemia. Natalizumab was discontinued. He returned to baseline and was discharged from the hospital.

Two months after the last dose of natalizumab, the subject was readmitted to the hospital with recurrent hepatic encephalopathy. He developed acute renal failure and was transferred to the intensive care unit and intubated. The subject received blood transfusions secondary to anemia, and a sputum culture was positive for pneumocystis carinii. The subject had no known risk factors for human immunodeficiency virus (HIV). An HIV test had not been obtained. The subject died, and the autopsy revealed that the subject died of multi-organ failure including respiratory, hepatic, and renal failure.

Pneumonia herpes viral

A 30 year old female (from CD303) developed varicella pneumonia after receiving a total of seven natalizumab infusions—three in Study CD301 and four in CD303. She was not taking concomitant immunosuppressive/immunomodulatory agents.

The subject has a history of Crohn's disease involving the ileum. No other current medical history was reported. The subject's concomitant medications at enrollment included mesalazine for Crohn's disease.

The patient was exposed to varicella zoster virus when her son developed a varicella infection; she had not previously been exposed to this virus. On 18 April XXXX, the subject developed cutaneous lesions on her face and trunk; varicella serology was IgG and IgM positive. On 20 April XXXX, the subject presented to the emergency room with respiratory difficulty and high fever (not specified), and was admitted to the hospital with a diagnosis of severe pneumonia varicella associated with shortness of breath. Treatment with acyclovir 50 mg, paracetamol, and salbutamol was initiated. On 06 May XXXX, the subject's pneumonia resolved, and she was discharged from the hospital. No action was taken with study drug due to this event. The subject continued in the study received further infusions of study drug on 15 May XXXX, 10 June XXXX, 10 July XXXX, and 07 August XXXX.

Cavitating pneumonia and lung abscess (unknown pathogen)

A 37 year old male (from CD351) with a 10 year history of Crohn's disease developed a right lung abscess and right upper lobe pneumonia leading to hospitalization and natalizumab discontinuation during participation in Study CD351. He had received 11 natalizumab infusions: three in CD301; seven in CD303; and one in CD351. Other Crohn's disease medications included mesalazine and azathioprine (which he had been taking for three years).

He had discontinued participation in CD303 due to ongoing soreness in both thighs. Three months later, he enrolled in CD351 and received his first natalizumab infusion on September 1, XXXX. On September 12,XXXX , he developed a cough and pleuritic chest pain. He developed hemoptysis on 16 September XXXX . Chest x- ray revealed severe right upper lobe pneumonia with cavitation and severe right lung abscess. The subject was admitted to the hospital and IV antibiotic treatment was initiated. The subject received IV benzyl penicillin 1.2 g, IV metronidazole 500 mg, naproxen 250 mg TID, and pethidine 50- 100 mg QID. Sputum cultures revealed moderate gram-negative cocci-bacilli, numerous mixed bacteria, and no acid-fast bacilli or fungal elements. Blood cultures revealed no growth. On 17 September XXXX , penicillin was discontinued and Cefotaxime IV 1 gram TID was started. On 19 September XXXX , the cefotaxime and metronidazole were discontinued and Timentin IV 3.1 grams QID commenced.

On September 22 XXXX, he was transferred from the hospital to HITH (hospital in the home). On 23 September XXXX, the subject had a chest x- ray that revealed continued infiltrate with cavitation at the right hilum. He continued to cough bloody sputum and to have persistent pleuritic pain. Additional information received on 30 September 2000 revealed that the subject had a chest x- ray performed on 29 July with normal results, prior to enrollment in Study CD301. The Investigator reported that the subject had not traveled recently, had not received a PPD test, and had a tuberculosis vaccination at age 14. Bronchoscopy was not performed as part of the evaluation of this SAE. As of 30 September XXXX, the subject continued to receive Timentin IV 3.1 g QD, and was not isolated. According to the Investigator, the lung abscess was estimated by a radiologist as a "thick wall cavity with outside diameter of approximately 4 cm."

On 03 October XXXX, the subject was seen for an early termination visit, and treatment with natalizumab was discontinued due to the subject's right lung abscess. Follow- up information received on 16 October XXXX, revealed that the patient had responded to treatment and no longer produced sputum. The only organism that grew from the cultured sputum was Candida albicans, which was assumed to be from mouth contamination. According to the Investigator,

"Mycobacterial and fungal infection were ruled out." Results of a CT scan of the chest performed on 07 October XXXX showed residual cavitation. Needle aspiration to determine the microbiological diagnosis was not performed due to potential risk of seeding the pleural space. There was no evidence of lymphadenopathy and no endobronchial lesion identified. Elsewhere the lungs were normal per CT. As of 23 October XXXX , an infectious disease specialist managing the subject anticipated that the subject would receive 1-2 more weeks of IV antibiotics and then one month of oral antibiotics.

A chest x- ray performed on 17 October XXXX showed resolution of the right upper lobe lung abscess, with some residual scarring. According to the Investigator, the subject continued to experience moderate pain in the right side of his chest at the time of discharge from HITH on 30 October XXXX. After discharge, the subject received 2 weeks of oral antibiotics (not specified). As of 04 December XXXX, the subject's right upper lobe pneumonia was reported as ongoing.

Mycobacterium avium intracellulare complex pneumonia

A 65 year-old white female (from CD351), was diagnosed with Mycobacterium avium complex pneumonia after receiving five natalizumab infusions in Study 351. She had previously received three natalizumab infusions in Study CD301 (September—November, 2002) and placebo infusions in CD303. Concomitant Crohn's disease medications included prednisone; she had been taking 60 mg daily at the time of enrollment in CD351 (in 6/03) and had undergone a slow taper, decreasing by 10 mg approximately every two weeks. She was taking 5 mg every other day at the time of the adverse event. Two years prior to enrollment, she had been treated with azathioprine.

In addition to Crohn's disease, her medical history included arthritis, sinusitis, Bell's palsy, migraine headaches, gastroesophageal reflux disease, hypothyroidism, hypertension, aphthous ulcers, and a hysterectomy. Results of an immunodeficiency panel revealed no abnormalities and an HIV antibody test was non-reactive.

After receiving four natalizumab infusions in CD351 (on June 3, July 2, July 29, and August 26 XXXX), she developed moderate sinusitis and a non-productive cough. Treatment for sinusitis, including azithromycin, was begun. Her symptoms persisted over the next month and she developed dyspnea on exertion. She received her fifth natalizumab infusion on 23 September XXXX. On the same day, she had a chest x- ray, which revealed right lung abnormalities including a

discoid band of increased density, parahilar abnormalities, and right upper and lower lobe infiltrative changes. CT scan on October 2 XXXX revealed subcarinal and bilateral hilar lymph nodes suggestive of prior granulomatous disease. Scattered bilateral lower lobe calcified granulomas were also noted. Peribronchial airspace opacities were identified in a segmental distribution in the right upper lobe, right middle lobe, and superior segment of the right lower lobe. Scattered focal calcifications were also identified throughout the liver and spleen, suggestive of prior granulomatous disease. On 09 October XXXX, she was admitted to the hospital and had a bronchoscopy. Washings were done and cytology revealed Mycobacterium avium intracellular complex infection. She was treated with azithromycin, ciprofloxacin, ethambutol, and rifabutin. On 14 October XXXX, the subject was discharged from the hospital in good condition. On 30 October XXXX, the subject's pneumonia resolved. X-ray performed on 05 November XXXX revealed findings consistent with resolution of Mycobacterium avium pneumonia. On that same date, the subject was seen for an early termination visit and treatment with natalizumab was discontinued due to this event.

Burkholderia cepacia lower respiratory tract infection

A 62- year- old female (from CD351), with a history of tobacco use, Type II diabetes mellitus and hypertension, was diagnosed with a Burkholderia cepacia lower respiratory tract infection after receiving three infusions of natalizumab in CD351 (previously, she had participated in Study CD307, receiving three placebo infusions). Concomitant Crohn's disease medication included prednisone (20 mg) and Pentasa.

She was hospitalized for a nonproductive cough, dyspnea, and symptoms of congestive heart failure one month after her third infusion of natalizumab. Chest X-ray revealed cardiomegaly, hydrothorax, and congestion in the pulmonary vessels. Ultrasound confirmed congestive failure. A spiral CT revealed an effusion on the right side and fluid in the pleural cavity. A repeat CT scan 12 days later noted a wide band of residual atelectactic condensation in the right middle lobe and the central part of the basal segment of the lower lobe. The subject was started empirically on oral amoxicillin/ clavulanate and ciprofloxacin for possible pneumonia. Bronchoscopy and lavage were undertaken and the microbe Burkholderia cepacia was identified. Antibiotic therapy was continued until June 2005. The bronchial infection was considered to be secondary to cardiac failure and hospital admission.