**Food and Drug Administration**
**Center for Drug Evaluation and Research**

# BACKGROUND MATERIALS

**Joint Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC)**
**and the Drug Safety and Risk Management Advisory Committee (DSaRMAC)**

**JULY 31, 2007**

**TYSABRI (natalizumab) for Crohn's Disease**
**Applicant: Biogen Idec, Inc.**
**Biologics Marketing Application: STN 125104/33**

# Table of Contents

Section

# Section 1

# FDA Clinical Review

DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
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Division of Gastroenterology Products
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# Joint Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee

# Briefing Document

Applicant: Biogen Idec

Biologics Marketing Application: STN 125104 / 33

Natalizumab (Tysabri) for Crohn's Disease

# Table of Contents

# 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 Crohn's disease (CD). Issues for discussion include, but are not limited to, the possible approval of Tysabri for the Crohn's disease indication, the risk of progressive multifocal leukoencephalopathy, and the proposed risk management plan for Tysabri for Crohn's disease.

Sponsor(s): Biogen Idec and Elan Pharmaceuticals have been partners in the development of Natalizumab as a treatment for CD. However, Biogen Idec is the specified applicant for the current submission.

## Executive Summary

The marketing approval of natalizumab for Multiple Sclerosis (MS) in November 2004 was largely based on the magnitude of natalizumab's treatment effect which appeared to be considerably greater than that of existing MS therapies; natalizumab's adverse event profile indicated no greater risk than that of existing MS therapies. The finding of two cases of progressive multifocal leukoencephalopathy (PML) in MS trials of natalizumab resulted in the withdrawal of natalizumab from market in February 2005; a third case was retrospectively identified in a CD patient.

PML is a rare disorder associated with progressive demyelination of the CNS, caused by the JC virus infection, and typically only seen in patients that are immunocompromised. It generally causes a progressive neurological decline, and is usually fatal within six months of diagnosis. There is no accepted method for early detection, and currently no adequate treatment.

The two PML cases in MS patients both occurred on concomitant interferon; one patient had been exposed to natalizumab for approximately two and one-half years and the other for approximately three years before PML symptoms began. The CD patient had a history of deficient hematopoiesis with lymphopenia and anemia predominating (intermittent signs for six years), prior use of azathioprine (more than four years, discontinued eight months before PML symptoms developed), remote prior use of infliximab (discontinued 20 months before PML symptoms developed), and was exposed to natalizumab for a total of eight months (three months, followed by nine months of placebo, followed by five months).

Largely to assess the benefit to risk ratio in MS, an Advisory Committee (AC) was convened in March 2006. The AC members stated that they did not believe that the risk of PML is entirely limited to patients concomitantly or recently exposed to a second immunosuppressive agent, but the AC recommended that natalizumab should not be taken with concomitant immunosuppressants used in MS, and that a washout period would be needed if switching from one of those medications to natalizumab.

FDA review was completed in June 2006 with the following key decisions on approval: (1) Natalizumab should be returned to the market at least in some limited form largely because of

the magnitude of the treatment effect; (2) The indicated population should be those unable to tolerate or with inadequate response to other available MS therapies; (3) Natalizumab should be administered as monotherapy (i.e., no concomitant immunosuppressants, and a washout period for prior immunosuppressants) because the risk of PML may increase with increasing immunosuppression; (4) Access must be tightly controlled and risk must be monitored via implementation of a risk minimization and action plan (TOUCH; Tysabri Outreach: Unified Commitment to Health).

Clinical trials for CD had already been designed and were ongoing prior to the concern of PML risk; these trials were stopped at the same time that natalizumab was withdrawn from the market. Thus, the study designs did not include considerations to minimize the PML risk (e.g., baseline MRI, neurological exams, algorithm to rule out PML if suspected, or criteria to minimize exposure to prior or concomitant immunosuppressants or steroids).

Key to the risk-benefit analysis is the issue of prior or concomitant immunosuppressive therapy, which is considerably more difficult to address in the CD population compared to the MS population because of differences in the clinical management of each of these diseases. CD patients are more likely to have been treated chronically with immunosuppressive therapies. Also, CD patients are more likely to be treated with high dose and/or chronic steroids, whereas MS patients are more likely to be treated with pulse steroids.

Proportions of concomitant medication use for natalizumab-treated subjects (n=1182) in short-term placebo-controlled studies of active CD were: (a) monotherapy, 32%; (b) steroids only, 29%; (c) immunosuppressants only, 17%; (d) steroids and immunosuppressants, 22%. Similar proportions of concomitant medication use were found in longer-term studies. The proportion of natalizumab-treated subjects (n=168) in the maintenance study (Study CD303) receiving steroids and receiving immunosuppressants was 37% and 38%, respectively.

Proportions of previous medication use for natalizumab-treated subjects (n=724) in the first induction study (Study CD301) were: (a) steroids, 89%; (b) immunosuppressants, 67%; (c) anti-TNF agents, 40%. The second induction study (Study CD307) had similar proportions of prior medication use in natalizumab-treated subjects (n=259): (a) steroids, 92%; (b) immunosuppressants, 75%; (c) anti-TNF agents, 51%.

The sponsor also categorized subjects by proportion with inadequate response to prior medications. However, the sponsor may not have adequately identified "true failures" of prior medications (particularly anti-TNF agents) as these were not based on pre-specified criteria, but were captured based on information marked by the investigator in case report forms. An information request to clarify criteria to define inadequate response to prior medications is pending.

With regard to demonstration of efficacy in CD, two Phase 3 induction studies and one Phase 3 maintenance study were conducted. The first induction study (CD301) failed to demonstrate a statistically significant difference in clinical response rates (defined as CDAI reduction of 70 or more from baseline) at Week 10 between the natalizumab group (n=724) and placebo group (n=181) with rates of 56% and 49%, respectively (p=0.051). In a post-hoc analysis of a subset

of patients from that study with elevated CRP, however, the natalizumab group (n=526) had a higher clinical response rate than the placebo group (n=134) with rates of 58% and 45%, respectively (nominal p=0.007). The second induction study (CD307) enrolled patients with elevated CRP, and demonstrated a higher clinical response rate in the natalizumab group (n=259) than the placebo group (n=250) with rates of 48% and 32%, respectively ($p<0.001$). The maintenance study (CD303) enrolled patients that were responders from CD301, and demonstrated a higher response in the natalizumab group (n=168) than in the placebo group (n=170) through six additional months of therapy with rates of 61% and 28%, respectively ($p<0.001$). In a subset of patients taking steroids at baseline, a higher proportion of patients were able to be withdrawn from steroids and maintain remission in the natalizumab group (n=67) than the placebo group (n=76) after six months with proportions of 45% and 22%, respectively (p=0.014).

With regard to safety in CD studies, the submission contains data from the same studies as that in the previous submission (for MS, results presented in AC March 7-8, 2006) with additional data on long-term CD patients; conclusions regarding safety concerns have not changed. The safety concerns remain the following: (1) PML; (2) Infections other than PML that include Herpes infections, lower respiratory tract infections (especially atypical pathogens), and viral meningitides; (3) Hypersensitivity reactions (are associated with immunogenicity); (4) Carcinogenicity (there was no clear increase in risk; however, in placebo-controlled studies, overall malignancies were balanced in MS, but higher in CD)

The sponsor included efficacy analyses in subgroups defined by concomitant medication use and prior medication use (where medications included steroids, immunosuppressants, anti-TNF agents, and combinations thereof) to try to help identify a population that might have a more favorable benefit to risk ratio. The results suggested that clinical response rates in the subgroups were similar to the overall clinical response rates. However, the set of subgroup analyses is not complete; an information request is pending.

With regard to safety in subgroups defined by concomitant medication use or prior medication use, subgroup analyses may help to determine if the risk of infections including serious infections is increased based on concurrent immunosuppressant use, and help identify a population which may have a more favorable benefit to risk ratio. No clear pattern has emerged. However, the sponsor has not performed all analyses desired. First, safety analyses by prior medication use were limited. Second, many of the safety analyses by concomitant medications were for short-term studies, and not longer term studies in CD. Additional analyses were requested to address each of these points.

FDA asks this Advisory Committee to assess the risks and benefits of natalizumab in the CD population and to advise FDA on: the possible marketing approval of natalizumab for CD; the possible CD population in which to be indicated based on severity of disease and response to prior medications; requirements for concomitant or prior medications; requirements of and modifications to the proposed TOUCH program for the CD population.

# Background and Regulatory History

## Crohn's Disease

Inflammatory bowel disease (IBD) includes two autoimmune diseases, CD and ulcerative colitis (UC). Whereas UC is a chronic inflammatory disease of the superficial epithelial layer of the gut mucosa and predominantly affects the colon and rectum, CD involves chronic inflammation of all layers of the bowel and may affect any segment of the GI tract. For CD, the most common patterns of GI involvement are in descending order, (1) the distal small intestine and colon, (2) the small intestine alone, and (3) the colon alone. Common symptoms of CD are diarrhea, abdominal pain, weight loss, fever, and rectal bleeding.

The inflammation can extend beyond the mucosa and involve the wall of the bowel, leading to the development of strictures (narrowing), fistulae between diseased parts of the bowel and adjacent structures (i.e., bladder, other bowel segments and skin) and abscesses. Perianal manifestations are common. Extraintestinal tissues (skin, eyes and joints) may also be inflamed. In addition, there may be sequelae due to malabsorption (anemia, vitamin deficiency, cholelithiasis, nephrolithiasis or metabolic bone disease).

CD typically has a chronic relapsing course with acute clinical episodes. Some patients, however, have chronic poor health due to active bowel inflammation, fistulae, or other disease-related events. Morbidity may be considerable, particularly for patients whose disease is not controlled by currently available agents. An increased risk of mortality has been reported. (Canavan et al., 2007; Canavan et al., 2007; Wolters et al., 2006)

The annual incidence in North America (United States and Canada) is estimated to be between 3.1 and 14.6 cases per 100,000 person-years, with between 10,000 and 47,000 new cases of CD diagnosed annually. It is estimated that over 630,000 people in North America have CD based on a prevalence of 199 cases per 100,000 persons (Loftus 2004).

Formal treatment guidelines have been developed (Hanauer and Sandborn, 2001) that suggest a step-wise approach as follows. Initially, a patient may be treated with an aminosalicylate (5-ASA) before receiving treatment with oral steroids. A patient that fails treatment with oral steroids, either by lack of response, steroid intolerance, or by repeated disease flares while attempting to reduce the dose of the drug, may then be given an immunosuppressant. Biological therapies such as infliximab or adalimumab (both are anti-TNFα antibodies) are used in patients with continued disease activity despite an adequate trial of an oral steroid and an immunosuppressant. Surgery is used to treat complications such as bowel obstructions or abscesses or to control the patient's symptoms when medical therapy fails. Thus, infliximab and adalimumab are currently the medical options available for CD patients that have an inadequate response to the conventional CD therapies (steroids and immunosuppressants). In addition to those treatment guidelines, there are advocates of the "top-down" approach that suggests that biological therapies (e.g., infliximab or adalimumab) be used earlier than in present treatment paradigms.

**Product**

Natalizumab is a recombinant humanized anti-α4 integrin monoclonal antibody that binds to α4β1 integrin (also known as very late antigen 4 [VLA-4]), which is expressed at high levels on the surface of all circulating leukocytes, except neutrophils, and blocks the interaction with its counter-receptor on endothelial cells, vascular cell adhesion molecule-l (VCAM-1). Similarly, natalizumab blocks the interaction of α4β7 integrin (which is also expressed on leukocytes) with mucosal addressin cell adhesion molecule-l (MAdCAM-1), another counter-receptor expressed prominently on endothelial cells in the gut.

The specific mechanisms by which natalizumab may exert its effects in multiple sclerosis (MS) and in CD have not been fully defined. In MS, natalizumab may produce its clinical effect by interfering with the movement of inflammatory white blood cells from the blood vessels into the brain and spinal cord (by blocking the interaction of α4β7 integrin with VCAM-1). In CD, natalizumab may produce its clinical effect by interfering with the movement of inflammatory white blood cells from the blood vessels into the parenchymal gut tissue (by blocking the interaction of α4β1 integrin with MAdCAM-1, and by blocking the interaction of α4β1 integrin with VCAM-1 which is not normally expressed on gut endothelial cells but is upregulated in response to inflammatory cytokines in the setting of CD).

Natalizumab is supplied as a sterile, colorless, and clear to slightly opalescent concentrate for intravenous (IV) infusion. From the currently approved labeling, the recommended dose of natalizumab for MS 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.

**Regulatory History**

The table below summarizes the regulatory history of natalizumab for CD and MS.

**Table 1. Regulatory History of Natalizumab**

| | |
|---|---|
| 11/23/04 | Original Approval for MS |
| 2/28/05 | Withdrawal because two PML cases |
| 3/05 - 9/05 | Dose Suspension Safety Assessment (MS and CD/RA): additional PML case identified |
| 2/15/06 | MS IND Hold Removed |
| 3/7/06 - 3/8/06 | Peripheral and Central Nervous System Drugs Advisory Committee |
| 6/5/06 | Return to Market for MS (Monotherapy, RiskMAP) |
| 12/15/06 | Current Submission for CD |

***Original Approval for MS***

FDA review of the marketing application led to the approval of Natalizumab for the treatment of patients with relapsing forms of MS, to reduce the frequency of clinical exacerbations.

Two multicenter, randomized, double-blind, placebo-controlled studies, Study 1801 (enrolling patients who had never received interferon beta or glatiramer acetate) and Study 1802

(enrolling patients that had experienced relapses on interferon beta-1a), provided the primary evidence of safety and efficacy of natalizumab in relapsing-remitting MS (RRMS). Although both studies were two years in duration, the end of one year results were favorable leading Biogen Idec to submit a marketing application.

In Study 1801, the "monotherapy" study, the natalizumab group (n=627) and the placebo group (n=315) had annualized relapse rates of 0.25 and 0.74 relapses/patient-year, respectively ($p<0.001$), representing a relative reduction of 66% with treatment; this is nearly twice the magnitude of effect observed with registration trials for other MS therapies (Avonex®, Betaseron®, Copaxone®, and Rebif®). In Study 1802, the "add-on" study, the natalizumab group (n=589) and the placebo group (n=582) had annualized relapse rates of 0.36 and 0.78 relapses/patient-year, respectively ($p<0.001$), representing a relative reduction of 54% with treatment.

A total of 1617 MS patients, 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 available first-line MS therapies (Avonex®, Betaseron®, Copaxone®, and Rebif®).

The magnitude of the treatment effect at one year was quite robust, and was deemed reasonably likely to predict a clinical benefit at two years. FDA approved natalizumab for marketing based on the Accelerated Approval regulations, Subpart E of the BLA regulations (21 CFR 601 Subpart E); completion of the ongoing studies as post-marketing commitments was necessary to verify that the efficacy observed at one year was sustained. Each of the other currently approved MS agents have demonstrated evidence of benefit at two years in order to gain marketing approval.

***Withdrawal from Market***

In February 2005, Biogen Idec informed FDA of the occurrence of two cases of progressive multifocal leukoencephalopathy (PML) 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. INDs for CD, for MS, and for other indications were placed on clinical hold. Each of the two PML cases is described briefly below.

PML Case #1: This was a 46 year old woman with RRMS that was being treated with concurrent Avonex (Interferon-beta1a) for approximately three years. This patient was treated with natalizumab for approximately three years before PML symptoms developed. The patient died.

PML Case #2: This was a 46 year old man with RRMS that was being treated with concurrent Avonex (Interferon-beta1a) for approximately two and one-half years. This patient was treated with natalizumab for approximately two and one-half years before PML symptoms developed. The patient became disabled.

During marketing of natalizumab between 11/23/04 and 2/28/05, approximately 7000 patients received up to 3 doses of Natalizumab.

***Dose Suspension Safety Assessment***

Starting in March 2005, a detailed review of subjects (a total of 3116 patients that included 1869 MS patients and 1247 CD or rheumatoid arthritis [RA] patients) who received natalizumab during drug development was conducted and is described in the literature (see Yousry 2006). The review included physical examination findings, neurological examination findings, brain magnetic resonance imaging (MRI) scans, JC viral DNA analyses (plasma and CSF), and results of cases reviewed by the Independent Adjudication Committee. The objective was to identify any additional cases of PML in order to better characterize the risk associated with natalizumab administration.

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.

PML Case #3: This was a 60 year old man with CD who was treated with eight months of natalizumab total but with a duration of placebo treatment in between natalizumab treatment (natalizumab three months, placebo nine months, followed by natalizumab five months). The patient died, and was diagnosed with astrocytoma; PML was determined on a retrospective pathology review. Analysis of banked samples showed that serum JC virus samples were positive two months before the event. The patient had intermittent signs of deficient hematopoiesis for approximately six years with lymphopenia and anemia predominating. The patient was on azathioprine at doses of approximately 75 to 150 mg daily for more than four years, but had been discontinued eight months before the event because of lymphopenia, refractory anemia, and low platelet count. The patient had received infliximab in the past, the last dose 20 months before the event, and had received intermittent corticosteroids in the past.

Therefore, natalizumab administration has been associated with PML in a total of three subjects, two with MS and one with CD. The detailed review of possible cases of PML in patients exposed to natalizumab in clinical trials (3116 patients exposed for a mean of 17.9 monthly doses) described by Yousry TA et al., 2006, suggests a risk of PML of roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9 months, and that the risk associated with longer treatment is not known.

***Peripheral and Central Nervous System Advisory Committee***

On March 7 to March 8, 2006, a Peripheral and Central Nervous System Advisory Committee was convened. Issues for discussion included, but were 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. Key recommendations of the Advisory Committee are summarized below.

With regard to demonstration of efficacy in MS on reducing the frequency of relapses through two years, the committee consensus was that Biogen has demonstrated natalizumab's efficacy on reducing the frequency of relapses through two years. The committee further agreed that Biogen had fulfilled their commitment made under the Accelerated Approval regulations.

About important safety-related issues other than PML, the committee consensus was that hypersensitivity reactions and development of antibodies were important considerations in making a risk-benefit assessment. When asked about non-PML disease risks, the committee consensus was that there is some concern of serious viral infections.

When asked if the natalizumab-associated risk of PML is entirely limited to patients concomitantly or recently exposed to a second immunosuppressive agent, the committee consensus was that the risk of PML is not limited to such patients.

Concerning whether they recommend additional data or studies should be obtained by FDA prior to determining whether natalizumab may return to the marketplace, the committee consensus was that additional data was not needed to determine whether natalizumab may return to the marketplace.

There was a consensus that natalizumab should only be used in MS patients. Regarding whether natalizumab should be permitted as first line therapy, the committee was split with seven saying "Yes" and five saying "No."

When asked whether natalizumab should be taken as "add-on" therapy with MS patients who were receiving Avonex, Betaseron, Copaxone, Rebif, or Novantrone, the committee came to a consensus that natalizumab should not be taken with these other therapies. In addition, the committee came to the consensus that a washout period would be needed if switching from one of those medications to natalizumab.

About when to evaluate concurrent use of natalizumab and an interferon-beta, committee members chose the option of evaluating concurrent use in clinical trials only after the risk of PML or other infections in monotherapy is better quantified.

***Return to Market for MS***

On June 5, 2006, the determination was made by the FDA that natalizumab should be returned to the market. Based on the clinical review, the key reason for the return to the market was the magnitude of the treatment effect. It was determined that natalizumab should return to the market at least in some limited form until the risks are better understood. With regard to the

population to receive natalizumab, that was to be patients that were unable to tolerate or with an inadequate response to other available MS therapies. [From BLA Review of 125104/15 by Susan S. McDermott, M.D. and Alice Hughes, M.D. (5/18/06)]

Approval as monotherapy was based on the concern that PML risk increases with increasing immunosuppression. However, there is limited data and it is not entirely clear that PML risk increases with a concomitant immunomodulator or immunosuppressant. Short courses of steroids to treat relapses was deemed reasonable. [From Team Leader Memo for BLA 125104/15 by Wilson W. Bryan, M.D. (6/5/06)]

### *TOUCH Program*

A Risk Minimization and Action Plan (RiskMAP) called the Tysabri Outreach: Unified Commitment to Health (TOUCH) program was to be used for the distribution and monitoring of natalizumab. This is the only access, and a tightly controlled system for monotherapy. Immunomodulators, immunosuppressants, and steroids (in the past month or concomitant) are discouraged. Intermittent steroid courses for relapses are allowed. The population enrolled in the TOUCH program is relapsing MS only. At initiation, no serum JCV is required, and no baseline MRI is required; however, in the MS population, patients would likely have had MRIs recently for their condition.

### *Current Submission for CD*

The current submission for CD was received on December 15, 2006. This is an efficacy supplement for treatment of CD.

In the current submission for CD, there is a proposed TOUCH program modified for CD, CD-TOUCH. It is essentially the same as the original TOUCH program for MS, with one new proposal as follows. For patients on steroids at initiation, these patients are to taper steroids after response to Tysabri. It appears that they must be tapered off of steroids by six months; otherwise, they must discontinue Tysabri.

# Review of Efficacy

## Proposed Indication for Crohn's Disease

The proposed indication (wording as proposed) is as follows:

> "TYSABRI® is indicated for inducing and maintaining sustained response and remission, and eliminating corticosteroid use in patients with moderately to severely active Crohn's disease with inflammation, as evidenced by elevated CRP level or another objective marker.
>
> "Because TYSABRI® increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies *[see Boxed Warning, Warnings and Precautions (5.1)]*."

## Methods

The clinical data from the three randomized, double-blind, placebo-controlled studies (Studies CD301, CD303, and CD307) were analyzed to determine whether a clinical benefit was seen for subjects with active CD who received natalizumab therapy versus placebo.

## General Discussion of Endpoints

In the induction studies, ENACT-1 (Study CD301) and ENCORE (Study CD307), the primary endpoint was clinical response at Week 10 and clinical response at Weeks 8 and 12, respectively, based upon the use of the Crohn's Disease Activity Index (CDAI). The CDAI score is a widely used and validated measure of disease activity in CD patients (see Appendix 1). In current literature and current CD submissions to the Agency, a common definition of clinical "response" is considered a reduction in the CDAI score of $\geq$ 70 points. The Sponsor also evaluated the proportions of subjects who were able to achieve clinical "remission" (defined as an absolute CDAI score of < 150) as a secondary endpoint.

In the maintenance study, ENACT-2 (Study CD303), the primary endpoint was maintenance of clinical response (i.e., clinical response not lost) at each month for an additional six months in subjects that demonstrated a clinical response at Week 12 of ENACT-1 (Study CD301); the contingent primary endpoint was maintenance of clinical remission (i.e., clinical remission not lost) at each month for an additional six months in subjects that demonstrated clinical remission at Week 12 of ENACT-1 (Study CD301). The contingent primary endpoint was to be tested only if the primary endpoint was significant. The Sponsor also evaluated the proportions of subjects that were on baseline steroids in ENACT-1 (Study CD301) who were able to achieve withdrawal of oral steroids after an additional six months, and who were able to achieve withdrawal of oral steroids and clinical remission after an additional six months, as secondary endpoints.

## Study Design

### *ENACT-1 (Study CD301)*

ENACT-1 (Study CD301) was a randomized, international, multicenter, double-blind, placebo-controlled, and parallel-group study in subjects with moderately to severely active Crohn's disease (based on clinical evaluation and CDAI score ≥220 and ≤450). This study was conducted in 142 investigational sites in North America, Europe, and selected countries from the rest of the world.

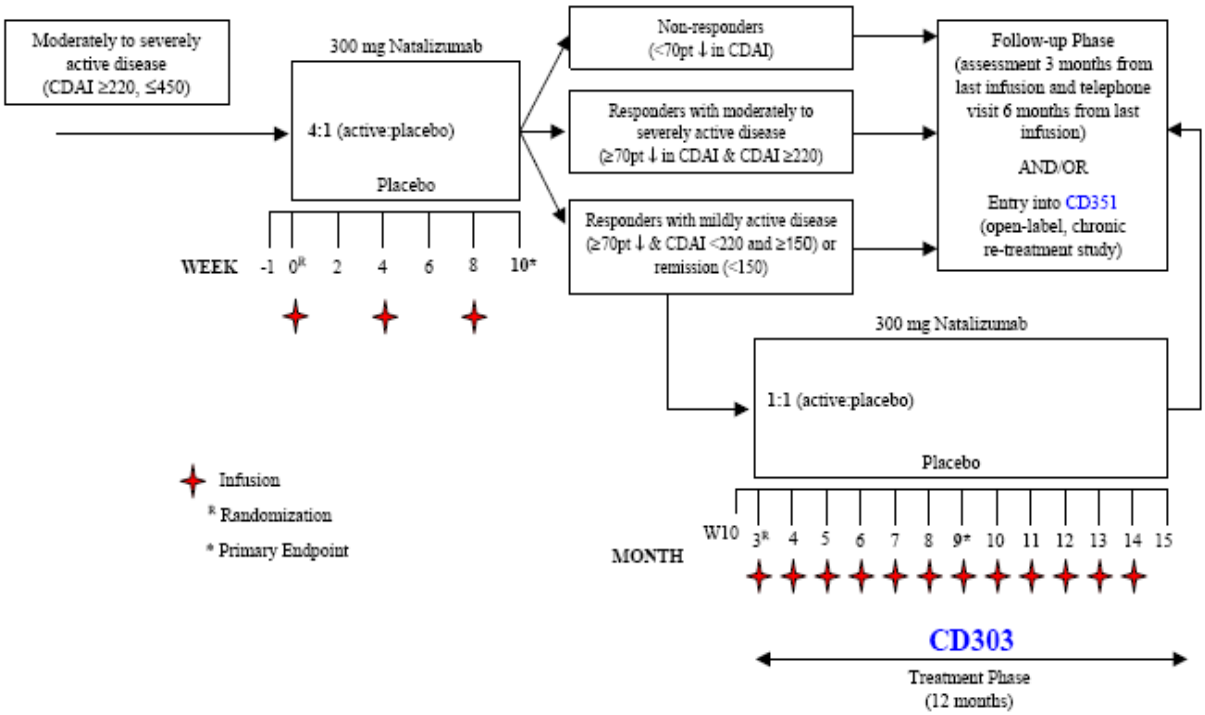
Subjects were screened for eligibility and randomized 7-14 days later at the baseline (Week 0) Visit to one of two treatment groups: natalizumab 300 mg or placebo at Weeks 0, 4, and 8 (4:1 in favor of treatment with natalizumab). Randomization was stratified based on baseline CDAI score and concomitant use of oral steroids.

Approximately 845 subjects with moderately to severely active Crohn's disease were planned to be randomized in this study in a 4:1 ratio of natalizumab to placebo: 676 subjects randomized to natalizumab and 169 to placebo. The date the first subject was enrolled was December 4, 2001, and the date the last visit was completed was September 3, 2003.

Following the Week 0 Visit, subjects returned to the clinic for safety and efficacy assessments every 2 weeks until the Week 12 Visit, including monthly (defined as a 4-week period) infusions with study drug at Weeks 0, 4, and 8.

Following completion of the Week 12 Visit, subjects had the potential, if eligible, to enter maintenance of response and remission Study CD303. If subjects did not enter Study CD303, they could either enter a safety follow-up period in Study CD301 up to Week 32 or enroll in an open-label extension Study CD351.

**Figure 1. Overall Design of Study CD301 (and Study CD303)**




(Above figure taken from Page 62 of the Clinical Study Report for Study CD301)

### *ENACT-2 (Study CD303)*

This was a Phase III, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with CD who had responded to treatment with three monthly infusions of natalizumab 300 mg in Study CD301. Placebo responders from Study CD301 were also enrolled in Study CD303 as it was impossible to unblind the subjects' treatment assignments while the CD301 study was ongoing and maintain the integrity of that study. The population defined in the protocol for analysis of efficacy in Study CD303, the CD303 Efficacy Population, was natalizumab responders from Study CD301. The study was conducted in 123 sites in North America, Europe, and selected countries from the rest of the world. (See Figure 1 above.)

Subjects were required to meet the criteria of clinical response at both Weeks 10 and 12 in CD301, and have a CDAI score <220, to be considered eligible for entry into Study CD303. Informed consent for CD303 was obtained at Week 10 of Study CD301, at which point subjects receiving concomitant oral steroids began a steroid taper according to a fixed algorithm. (See steroid taper algorithm in Appendix 3.) Subjects who continued to meet eligibility criteria at Week 12 (i.e., Month 3 in Study CD301) were re-randomized (1:1 ratio) to receive monthly intravenous (IV) infusions of natalizumab 300 mg or placebo for up to 12 consecutive months in Study CD303 (Figure 1).

Approximately 285 subjects who completed Study CD301 and responded to treatment with

either placebo or natalizumab were planned to be randomized in Study CD303. A total of 428 subjects (214 natalizumab and 214 placebo) were randomized to treatment. The date the first subject enrolled was March 23, 2002; the date the last subject completed the Month 15 visit was March 25, 2004.

Randomization was central and stratified according to three factors: disease status at Week 12 in Study CD301 (remission versus no remission [i.e., a CDAI score <150 or ≥150]), use of oral steroids at entry in Study CD301, and use of immunosuppressants at entry in Study CD301. Subjects were to return for their final treatment assessment approximately one month after their last study drug infusion (Month 15, i.e., 12 months of treatment in CD303). Efficacy assessments and safety evaluations were scheduled to occur every 4 weeks during monthly clinic visits (Months 3 through 15).

Subjects who either completed the treatment phase (i.e., up to Month 15), or who were identified as treatment failures after receiving at least two study drug infusions in CD303 were assessed for their eligibility to enter an open-label, chronic treatment study (CD351). All subjects enrolled in CD351 received monthly infusions of natalizumab 300 mg. Subjects who completed the CD303 treatment phase, but did not enroll in Study CD351 were followed for an additional 6 months (after the last infusion at Month 14) and were evaluated for safety during a clinic visit at Month 17 and a telephone contact at Month 20.

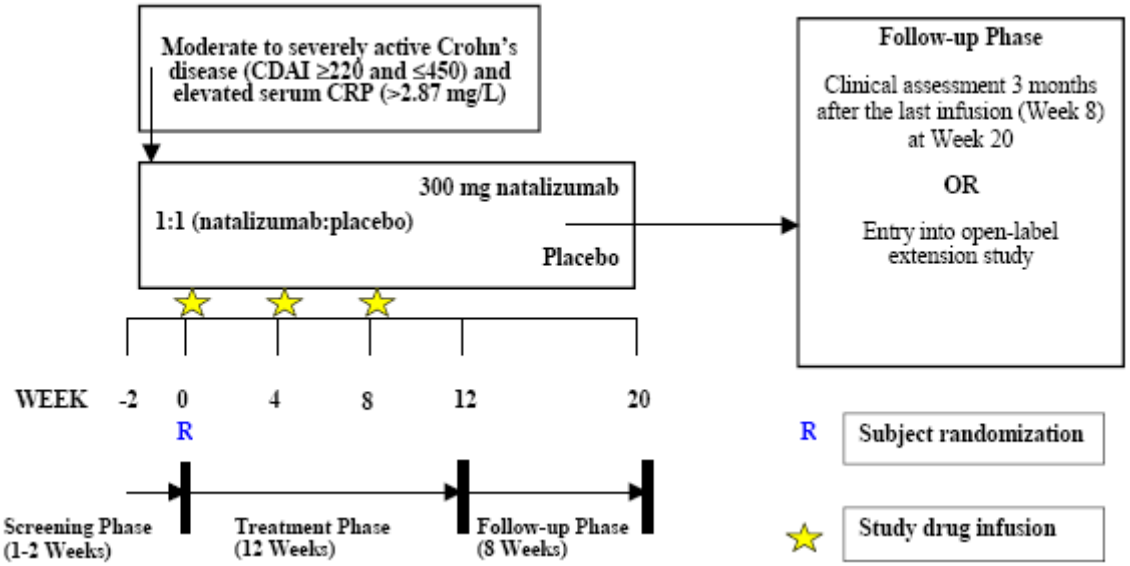
### *ENCORE (Study CD307)*

ENCORE (Study CD307) was a Phase III, multinational (11 countries), multicenter (114 sites), double-blind, placebo-controlled, randomized, parallel-group study in subjects (n=510) with moderately to severely active CD (as defined by a baseline CDAI score between 220 and 450 inclusive), and elevated C-reactive Protein (CRP) levels at baseline (defined as >2.87 mg/L, the upper limit of normal [ULN] as assessed by the study central laboratory at the screening visit).

Approximately 462 subjects were planned to be randomized in the study in a 1:1 ratio of natalizumab to placebo. The date the first subject enrolled was March 29, 2004. The date the last efficacy (Week 12) visit for any subject was completed was March 14, 2005.

Subjects were screened for eligibility and randomized 7 to 14 days later at the baseline (Week 0) visit to receive monthly (defined as a 4-week period) intravenous (IV) infusions of natalizumab 300 mg or placebo (1:1 ratio) at Weeks 0, 4, and 8. Study visits were scheduled in relationship to the Week 0 visit. The overall design of the study is described in the figure below.

**Figure 2. Overall Design of Study CD307**




(Above figure taken from Page 56 of the Clinical Study Report for Study CD307)

## *Design Features Across Studies*

| | CD301 | CD303 | CD307 |
|---|---|---|---|
| Randomized, double-blind, parallel-group, placebo-controlled, multicenter study | Yes | Yes | Yes |
| Number of infusions of study drug (at 4-week intervals) | 3 (300 mg) | 12 (300 mg) | 3 (300 mg) |
| Follow-up clinic visits | To Week 20 | To Month 17* | To Week 20 |
| Primary Assessment of Response and Remission | CDAI[#] | CDAI[†] | CDAI[‡] |
| Evaluation of Primary Endpoint | Week 10 | Month 9* | Weeks 8 & 12 |

* Including the first three months of treatment during Study CD301

# CD301: Proportion of subjects with a clinical response (≥70-point decrease in baseline CDAI score) at Week 10

† CD303: Proportion of those subjects demonstrating a clinical response to natalizumab at Week 10 and Week 12 of Study CD301 and who did not lose that response for an additional 6 months with natalizumab compared to placebo treatment through Month 9 in Study CD303, with loss of response, defined as 1) a CDAI score ≥ 220 AND a ≥ 70-point increase from the baseline (Week 12 visit) OR 2) use of rescue intervention.

‡ CD307: Proportion (%) of subjects with a ≥70-point decrease in baseline (Week 0) CDAI score at both Weeks 8 and 12 of their study course.

(Table above adapted from Page 26 of Summary of Clinical Efficacy)

### *Eligibility Criteria Across Studies*

Main Inclusion Criteria:

| | CD301 | CD303 | CD307 |
|---|---|---|---|
| (1) Age ≥ 18 years | Yes | Yes | Yes |
| (2) ≥ 6-month history of CD | Yes | Yes* | Yes |
| (3) History of CD confirmed by radiological or endoscopic findings | Yes | Yes* | Yes |
| (4) CDAI score of ≥ 220 and ≤ 450 | Yes | No | Yes |
| (5) Response† in Study CD301 at Weeks 10 and 12 | N/A | Yes | N/A |
| (6) CRP > 2.87 mg/L | N/A | N/A# | Yes |

* Criteria for CD history met at enrollment in Study CD301.
† Response defined as ≥ 70-point reduction in CDAI score, CDAI score <220, and no use of rescue intervention.
# Post-hoc analysis in subgroup with CRP > 2.87 mg/L was conducted, but was not part of eligibility criteria.

Main Exclusion Criteria:

| | CD301 | CD303 | CD307 |
|---|---|---|---|
| (1) Anti-TNF therapy prohibited | Yes | Yes* | Yes |
| (2) Concomitant 5-ASA, oral steroids*, or immunosuppressants# allowed if on a stable dose for a period of time before enrollment | Yes | Yes* | Yes |
| (3) Exclude if active or draining fistulae, or short bowel syndrome | Yes | Yes | Yes |
| (4) Exclude if concomitant CD medication was changed during CD301 (except scheduled steroid taper, or clinically indicated dose reduction of immunosuppressant) | N/A | Yes | N/A |

* Maximum dose of 25 mg prednisolone or equivalent in Study CD301; 20 mg in Study CD307.
# Azathioprine, 6-MP, or MTX; other immunosuppressants (e.g., tacrolimus, cyclosporine, mycophenolate mofetil) prohibited and must have been discontinued ≥ 4 weeks prior to Week 0.

### *Prior and Concomitant CD Therapies Across Studies*

| | CD301 | CD303 | CD307 |
|---|---|---|---|
| 5-ASA, antibiotics (if used) | Stable dose ≥4 wks | Stable dose thru CD301 | Stable dose ≥4 wks |
| Oral steroids (if used) at ≤20 mg/day prednisolone (or equivalent)* | Prior use ≥4 wks<br>Stable dose ≥2 wks | Steroid Taper Algorithm# | Prior use ≥6 wks<br>Stable dose ≥4 wks |
| Azathioprine, 6-MP (if used) | Prior use ≥4 mo<br>Stable dose ≥2 mo | No criteria | Prior use ≥4 mo<br>Stable dose ≥2 mo |
| Methotrexate (if used) | Prior use ≥4 mo<br>Stable dose ≥2 mo | No criteria | Prior use ≥4 mo<br>Stable dose ≥2 mo |

5-ASA = 5-aminosalicylic acid, 6-MP = 6-mercaptopurine, N/A = Not Applicable
* 25 mg in Study CD301. Budesonide use capped at 6 mg/day for Study CD307.
# See Appendix 3 for Steroid Taper Algorithm
(Table above is adapted from Page 27 of Summary of Clinical Efficacy.)

## Efficacy Findings

### *Demographics and Baseline Disease Characteristics*

The baseline demographics across all three studies were comparable and typical of Crohn's disease trials studying patients with moderately to severely active disease. The demographic characteristics of each of the three studies are discussed by study below.

ENACT-1 (Study CD301)

All the demographic characteristics of the ITT Population were comparable between the natalizumab and placebo treatment groups. The mean ages of the subjects were 38.0 and 39.4 years in the natalizumab and placebo treatment groups, respectively, and with more female subjects in both treatment groups. Most of the subjects were classified as white by racial category; the rest were black, Asian, Hispanic, and other. Variables such as weight, height, body mass index (BMI), and smoking status, were comparable between groups. (See table below.)

**Table 2. Demographic Characteristics - Intent-to-Treat Population (Study CD301)**

| Variable<br>Statistic or Category | Placebo<br>(n=181) | Natalizumab<br>(n=724) | Overall<br>(n=905) |
|---|---|---|---|
| Age (yr) | | | |
| Mean | 39.4 | 38.0 | 38.3 |
| S.D. | 13.64 | 12.43 | 12.69 |
| Median | 37.0 | 36.0 | 37.0 |
| Min., Max. | 18,83 | 18,82 | 18,83 |
| Age Group (yr) N (%) | | | |
| <= 65 | 175 (97%) | 706 (98%) | 881 (97%) |
| > 65 | 6 (3%) | 18 (2%) | 24 (3%) |
| Gender N (%) | | | |
| Female | 108 (60%) | 413 (57%) | 521 (58%) |
| Male | 73 (40%) | 311 (43%) | 384 (42%) |
| Race N (%) | | | |
| Black | 4 (2%) | 25 (3%) | 29 (3%) |
| White | 171 (94%) | 679 (94%) | 850 (94%) |
| Asian | 0 (0%) | 1 (0%) | 1 (0%) |
| Hispanic | 0 (0%) | 6 (1%) | 6 (1%) |
| Other | 6 (3%) | 13 (2%) | 19 (2%) |
| Weight (kg) | | | |
| Mean | 71.1 | 71.6 | 71.5 |
| S.D. | 17.61 | 17.83 | 17.78 |
| Median | 68.0 | 69.0 | 69.0 |
| Min., Max. | 36,151 | 38,168 | 36,168 |
| Height (cm) | | | |
| Mean | 170.7 | 170.0 | 170.2 |
| S.D. | 9.50 | 9.40 | 9.42 |
| Median | 170.2 | 170.0 | 170.0 |
| Min., Max. | 150,197 | 145,193 | 145,197 |
| Body Mass Index (kg/m^2) | | | |
| Mean | 24.3 | 24.7 | 24.6 |
| S.D. | 5.31 | 5.71 | 5.63 |
| Median | 23.3 | 23.8 | 23.8 |
| Min., Max. | 15,42 | 15,60 | 15,60 |
| Smoking Status of More Than 10 Cigarettes per Day N (%) | | | |
| Yes | 44 (24%) | 164 (23%) | 208 (23%) |
| No | 137 (76%) | 560 (77%) | 697 (77%) |

(Table above is taken from Pages 123 of the Clinical Study Report for Study CD301)

Baseline CDAI score, CRP levels, and serum albumin were comparable between subjects in the natalizumab and placebo groups. Mean duration of CD was comparable between subjects in the natalizumab and placebo groups (10 vs. 9 years, respectively). The site of the disease was mainly ileocolonic in both the natalizumab and placebo groups (373 [52%] vs. 84 [46%], respectively). (See table below.)

**Table 3. Baseline Characteristics – Intent-to-Treat Population (Study CD301)**

| Variable<br>Statistic or Category | Placebo<br>(n=181) | Natalizumab<br>(n=724) | Overall<br>(n=905) |
|---|---|---|---|
| Baseline CDAI Score | | | |
| N | 181 | 721 | 902 |
| Mean | 303.4 | 301.8 | 302.1 |
| S.D. | 65.23 | 60.25 | 61.25 |
| Median | 287.0 | 292.0 | 292.0 |
| Min., Max. | 165, 518 | 171, 496 | 165, 518 |
| Baseline Disease Status N (%) | | | |
| CDAI < 330 | 122 (67%) | 510 (70%) | 632 (70%) |
| CDAI >= 330 | 59 (33%) | 211 (29%) | 270 (30%) |
| Not Available | 0 (0%) | 3 (0%) | 3 (0%) |
| Baseline C-Reactive Protein (mg/L) | | | |
| N | 173 | 695 | 868 |
| Mean | 22.9 | 20.2 | 20.8 |
| S.D. | 26.24 | 30.97 | 30.09 |
| Median | 12.2 | 8.7 | 9.0 |
| Min., Max. | 0,127 | 0,370 | 0,370 |
| Subjects with Elevated (> 2.87 mg/L) CRP at Baseline N(%) | | | |
| Yes | 134 (74%) | 526 (73%) | 660 (73%) |
| No | 39 (22%) | 169 (23%) | 208 (23%) |
| Not Available | 8 (4%) | 29 (4%) | 37 (4%) |
| Baseline Serum Albumin (g/L) | | | |
| N | 179 | 719 | 898 |
| Mean | 36.7 | 37.3 | 37.2 |
| S.D. | 5.31 | 5.57 | 5.52 |
| Median | 37.0 | 38.0 | 37.5 |
| Min., Max. | 19,51 | 9,53 | 9,53 |
| Duration of Disease[a] (months) | | | |
| N | 181 | 723 | 904 |
| Mean | 109.6 | 121.1 | 118.8 |
| s.d. | 93.21 | 98.36 | 97.41 |
| Median | 76.5 | 97.7 | 93.6 |
| Min., Max. | 0, 396 | 0, 673 | 0, 673 |
| Site of Disease N (%) | | | |
| (missing) | 1 (1%) | 0 (0%) | 1 (0%) |
| Colonic | 49 (27%) | 157 (22%) | 206 (23%) |
| Ileocolonic | 84 (46%) | 373 (52%) | 457 (50%) |
| Ileum | 47 (26%) | 194 (27%) | 241 (27%) |

a. Duration of Crohn's Disease is calculated from CD diagnosis date to date of first infusion. For subjects not treated date of randomization is used in the calculation. For partial date, 15 is used in the calculation if the day part is missing and June 30 is used if the month/day part is missing.

(Values in the table above are taken from pages 271-273 of the Study Report for Study CD307.)

Demographic and baseline characteristics in the subset of subjects with elevated CRP at baseline were comparable between subjects in the natalizumab and placebo groups.

ENACT-2 (Study CD303)

The table below provides a summary of demographic characteristics by treatment group. Demographic characteristics generally were comparable between the two treatment groups. The majority of subjects were white, and the mean age of subjects was similar in the natalizumab and placebo treatment groups (37.4 and 38.4 years, respectively). Disease status at study entry were well balanced. There was a greater proportion of females and heavy smokers (more than 10 cigarettes per day) in the placebo group; however, adjustment for these covariates did not change the conclusions drawn from the efficacy analyses.

**Table 4. Demographic Characteristics (Study CD303)**

| Variable<br>Statistic | Placebo<br>(n=214 ) | Natalizumab<br>(n=214) | Overall<br>(n=428) |
|---|---|---|---|
| Age (yr) | | | |
| Mean | 38.4 | 37.4 | 37.9 |
| s.d. | 13.3 | 12.51 | 12.91 |
| Median | 36 | 36 | 36 |
| Min., Max. | 18,78 | 18,74 | 18,78 |
| Age Group (yr) N (%) | | | |
| <=65 | 208 (97%) | 208 (97%) | 416 (97%) |
| >65 | 6 (3%) | 6 (3%) | 12 (3%) |
| Gender N (%) | | | |
| Female | 135 (63%) | 123 (57%) | 258 (60%) |
| Male | 79 (37%) | 91 (43%) | 170 (40%) |
| Race N (%) | | | |
| Black | 6 (3%) | 8 (4%) | 14 (3%) |
| White | 201 (94%) | 201 (94%) | 402 (94%) |
| Asian | 0 (0%) | 1 (0%) | 1 (0%) |
| Hispanic | 1 (0%) | 3 (1%) | 4 (1%) |
| Other | 6 (3%) | 1 (0%) | 7 (2%) |
| Smoking Status* N (%) | | | |
| Yes | 57 (27%) | 36 (17%) | 93 (22%) |
| No | 157 (73%) | 178 (83%) | 335 (78%) |
| Weight (kg) | | | |
| Mean | 72 | 72.4 | 72.2 |
| s.d. | 16.44 | 17.47 | 16.95 |
| Median | 69 | 69.5 | 69.2 |
| Min., Max. | 38,123 | 40,166 | 38,166 |
| Weight Group (kg) N (%) | | | |
| <50 | 11 (5%) | 11 (5%) | 22 (5%) |
| 50-75 | 122 (57%) | 123 (57%) | 245 (57%) |

* Smoking status is from CD301 baseline.
(Table above is taken from Pages 118, and 321-327 of the CD303 Study Report.)

The CD301 Natalizumab Responders Population and the CD301 Placebo Responders Population each had similar demographic characteristics to the overall CD303 population.

The mean duration of disease was comparable between subjects in the natalizumab and placebo treatment groups (10 vs. 9 years). The most frequent site of disease was ileocolonic (109 [51%] natalizumab vs. 103 [48%] placebo), followed by colonic (55 [26%] natalizumab vs. 57 [27%]

placebo) and ileal (50 [23%] natalizumab vs. 54 [25%] placebo). Subject CDAI scores were well balanced upon entry into Study CD303, with the majority of subjects in both treatment groups (71% natalizumab, 70% placebo) having a CDAI score < 150. (See table below.)

**Table 5. Baseline Disease Characteristics* (Study CD303)**

| Variable<br>Statistic | Placebo<br>(n=214 ) | Natalizumab<br>(n=214) | Overall<br>(n=428) |
|---|---|---|---|
| CD303 Baseline Disease Status | | | |
| CDAI >= 150 | 65 (30%) | 62 (29%) | 127 (30%) |
| CDAI < 150 | 149 (70%) | 152 (71%) | 301 (70%) |
| CD301 Baseline CDAI Score N (%) | | | |
| <330 | 160 (75%) | 160 (75%) | 320 (75%) |
| >=330 | 53 (25%) | 54 (25%) | 107 (25%) |
| Not Available | 1 (0%) | 0 (0%) | 1 (0%) |
| CD301 Baseline CDAI Score | | | |
| Mean | 298.3 | 296.1 | 297.2 |
| s.d. | 56.53 | 59.68 | 58.07 |
| Median | 288 | 283 | 286 |
| Min., Max. | 198,468 | 185,518 | 185,518 |
| CD303 Baseline C-Reactive Protein (mg/l) | | | |
| Mean | 9.6 | 11.2 | 10.4 |
| s.d. | 15.64 | 15.65 | 15.64 |
| Median | 4.6 | 5.4 | 4.9 |
| Min., Max. | 0,120 | 0,97 | 0,120 |
| CD301 Baseline C-Reactive Protein (mg/l) | | | |
| Mean | 22.3 | 20.4 | 21.4 |
| s.d. | 31.84 | 26.68 | 29.34 |
| Median | 10.8 | 9.1 | 9.3 |
| Min., Max. | 0,236 | 0,145 | 0,236 |
| Subjects with Elevated CD303 Baseline C-Reactive Protein N (%) | | | |
| Yes | 133 (62%) | 136 (64%) | 269 (63%) |
| No | 81 (38%) | 78 (36%) | 159 (37%) |
| Subjects with Elevated CD301 Baseline C-Reactive Protein N (%) | | | |
| Yes | 162 (76%) | 160 (75%) | 322 (75%) |
| No | 41 (19%) | 46 (21%) | 87 (20%) |
| Not Available | 11 (5%) | 8 (4%) | 19 (4%) |
| Duration of Disease (months) # | | | |
| Mean | 113.5 | 116.3 | 114.9 |
| s.d. | 89.33 | 92.85 | 91 |
| Median | 89.2 | 92.6 | 90.5 |
| Min., Max. | 7, 375 | 3, 446 | 3, 446 |
| Site of Disease N (%) | | | |
| Colonic | 57 (27%) | 55 (26%) | 112 (26%) |
| Ileocolonic | 103 (48%) | 109 (51%) | 212 (50%) |
| Ileum | 54 (25%) | 50 (23%) | 104 (24%) |

* Baseline disease characteristics of patients randomized to Study CD303 including their baseline disease characteristics at entry to Study CD301 are shown in the table.

# Duration of Crohn's Disease is calculated from CD diagnosis date to Month 3 date.

(Table above is taken from Pages 321-327, and 359 of the CD303 Study Report.)

The CD301 Natalizumab Responders Population and CD301 Placebo Responders Population each had similar demographic and baseline characteristics to the overall CD303 population.

ENCORE (Study CD307)

All the demographic characteristics of the ITT Population were comparable between the natalizumab and placebo treatment groups. The mean ages of the subjects were 38.1 and 37.7 years in the natalizumab and placebo treatment groups, respectively, and with more female subjects in both treatment groups. Most of the subjects were classified as white by racial category; the rest were black, Asian, Hispanic, and other. Variables such as weight, height, body mass index (BMI), and smoking status, as well as baseline CDAI score, CRP levels, serum albumin, and platelet counts were comparable between groups. (See table below.)

**Table 6. Demography Characteristics - Intent-to-Treat Population (Study CD307)**

| Variable<br>Statistic or Category | Placebo<br>(n=250) | Natalizumab<br>(n=259) | Overall<br>(n=509) |
|---|---|---|---|
| Age (yr) | | | |
| N | 250 | 259 | 509 |
| Mean | 37.7 | 38.1 | 37.9 |
| S.D. | 12.81 | 12.74 | 12.76 |
| Median | 35.0 | 36.0 | 36.0 |
| Min., Max. | 18,78 | 18,84 | 18,84 |
| Age Group (yr) N (%) | | | |
| <= 65 | 245 (98%) | 253 (98%) | 498 (98%) |
| > 65 | 5 (2%) | 6 (2%) | 11 (2%) |
| Gender N (%) | | | |
| Female | 148 (59%) | 154 (59%) | 302 (59%) |
| Male | 102 (41%) | 105 (41%) | 207 (41%) |
| Race N (%) | | | |
| Black | 6(2%) | 3(1%) | 9(2%) |
| White | 236(94%) | 247(95%) | 483(95%) |
| Asian | 1(0%) | 1(0%) | 2(0%) |
| Hispanic | 1(0%) | 1(0%) | 2(0%) |
| Other | 6(2%) | 7(3%) | 13(3%) |
| Weight (kg) | | | |
| Mean | 74.4 | 71.9 | 73.1 |
| S.D. | 19.30 | 19.03 | 19.19 |
| Median | 71.1 | 68.0 | 69.5 |
| Min., Max. | 37,145 | 40,180 | 37,180 |
| Weight Group (kg) N (%) | | | |
| < 50 | 14 (6%) | 18 (7%) | 32 (6%) |
| 50-75 | 128 (51%) | 151 (58%) | 279 (55%) |
| 76-100 | 83 (33%) | 67 (26%) | 150 (29%) |
| > 100 | 25 (10%) | 23 (9%) | 48 (9%) |
| Height (cm) | | | |
| Mean | 170.4 | 170.1 | 170.2 |
| S.D. | 9.20 | 9.59 | 9.39 |
| Median | 171.5 | 170.0 | 170.2 |
| Min., Max. | 150,199 | 149,195 | 149,199 |
| Body Mass Index (kg/m^2) | | | |
| Mean | 25.7 | 24.8 | 25.2 |
| S.D. | 6.74 | 5.80 | 6.29 |
| Median | 24.1 | 23.5 | 23.9 |
| Min., Max. | 16,63 | 15,54 | 15,63 |
| Body Mass Index Group (kg/m^2) N (%) | | | |
| <= 27 | 168 (67%) | 179 (69%) | 347 (68%) |
| > 27 | 82 (33%) | 80 (31%) | 162 (32%) |
| Smoking Status of More Than 10 Cigarettes per Day N (%) | | | |
| Yes | 48 (19%) | 57 (22%) | 105 (21%) |
| No | 201 (80%) | 201 (78%) | 402 (79%) |
| Missing | 1 (0%) | 1 (0%) | 2 (0%) |

(Table above is taken from Pages 112-114 of the Clinical Study Report for Study CD307)

The baseline disease characteristics of the ITT Population were comparable between the natalizumab and placebo treatment groups. Variables such as baseline CDAI score, CRP levels, serum albumin, and platelet counts were comparable between groups. The mean duration of CD was comparable between subjects in the natalizumab and placebo groups (121.4 vs. 120.3 months, respectively). The site of the disease was mainly ileocolonic in both treatment groups (134 [52%] natalizumab vs. 120 [48%] placebo). (See table below.)

**Table 7. Baseline Disease Characteristics – Intent-to-Treat Population (Study CD307)**

| Variable<br>Statistic or Category | Placebo<br>(n=250) | Natalizumab<br>(n=259) | Overall<br>(n=509) |
|---|---|---|---|
| Baseline CDAI Score | | | |
| Mean | 299.5 | 303.9 | 301.7 |
| S.D. | 63.19 | 64.80 | 63.99 |
| Median | 287.0 | 286.0 | 286.0 |
| Min., Max. | 149,483 | 147,472 | 147,483 |
| Baseline Disease Status N (%) | | | |
| CDAI < 330 | 178 (71%) | 174 (67%) | 352 (69%) |
| CDAI >= 330 | 71 (28%) | 84 (32%) | 155 (30%) |
| Missing | 1 (0%) | 1 (0%) | 2 (0%) |
| Baseline C-Reactive Protein(mg/L) | | | |
| Mean | 23.4 | 23.0 | 23.2 |
| S.D. | 27.93 | 27.82 | 27.85 |
| Median | 14.2 | 12.7 | 13.7 |
| Min., Max. | 1,165 | 0,208 | 0,208 |
| Baseline CRP (mg/L) N(%) | | | |
| <= 2.87 | 18 (7%) | 14 (5%) | 32 (6%) |
| > 2.87 | 232 (93%) | 245 (95%) | 477 (94%) |
| Baseline Serum Albumin (g/L) | | | |
| Mean | 36.8 | 36.7 | 36.7 |
| S.D. | 4.94 | 4.92 | 4.92 |
| Median | 38.0 | 37.0 | 37.0 |
| Min., Max. | 18,48 | 12,49 | 12,49 |
| Baseline Serum Albumin N (%) | | | |
| < LLN | 39 (16%) | 52 (20%) | 91 (18%) |
| >= LLN | 210 (84%) | 206 (80%) | 416 (82%) |
| Missing | 1 (0%) | 1 (0%) | 2 (0%) |
| Baseline Platelet Count(x10^9/L) | | | |
| Mean | 368.3 | 380.7 | 374.6 |
| S.D. | 122.03 | 115.41 | 118.75 |
| Median | 342.0 | 365.0 | 353.0 |
| Min., Max. | 164,953 | 140,978 | 140,978 |
| Baseline Platelet Count N (%) | | | |
| <= ULN | 168 (67%) | 160 (62%) | 328 (64%) |
| > ULN | 81 (32%) | 97 (37%) | 178 (35%) |
| Missing | 1 (0%) | 2 (1%) | 3 (1%) |

(Table above is taken from Pages 112-114 of the Clinical Study Report for Study CD307)

### *Prior and/or Concomitant Medications*

ENACT-1 (Study CD301)

Nearly all subjects (99%) in the ITT Population had received previous medication for CD. The majority of subjects (89%) had been previously treated with oral steroids and approximately two-thirds had previously received immunosuppressant treatment for CD. Approximately 40% of subjects had received treatment with an anti-TNF compound. See table below.

**Table 8. Previous Medications Taken for Crohn's Disease: Intent-to-Treat Population (Study CD301)**

| Medication | Placebo (N=181) n (%) | Natalizumab (N=724) n (%) | Overall (N=905) n (%) |
|---|---|---|---|
| None (Treatment Naïve) | 5 (3%) | 5 (<1%) | 10 (1%) |
| 5-ASA Compounds | 148 (82%) | 634 (88%) | 782 (86%) |
| Steroids | 158 (87%) | 643 (89%) | 801 (89%) |
| Immunosuppressants | 121 (67%) | 484 (67%) | 605 (67%) |
| Anti-TNF | 69 (38%) | 291 (40%) | 360 (40%) |
| Antibiotics | 83 (46%) | 301 (42%) | 384 (42%) |

(Values in natalizumab and placebo columns in table above taken from Page 126 of the Clinical Study Report for Study CD301)

In addition, approximately 47% of subjects had undergone at least one previous surgery for the treatment of Crohn's disease prior to entry into Study CD301.

Subjects were considered to have an "inadequate response" to a previous medication if they were unresponsive or intolerant to that previous medication; in particular, they did not respond to initial treatment, lost response and/or discontinued due to an adverse event (including infusion reactions, if applicable). For steroids, the definition of "inadequate response" included being dependent in addition to being unresponsive or intolerant. (See table below.)

**Table 9. Investigator-Reported Proportion of Subjects who had an Inadequate Response to Previous CD Medications (Study CD301)**

| Variable Category | Placebo n/N (%) | Natalizumab n/N (%) | Overall n/N (%) |
|---|---|---|---|
| Previous ASA Compounds Use<br>Unresponsive or Intolerant to Previous Medication Use | 96/148 (65%) | 437/634 (69%) | 533/782 (68%) |
| Previous Immunosuppressants Use<br>Unresponsive or Intolerant to Previous Medication Use | 83/121 (69%) | 335/484 (69%) | 418/605 (69%) |
| Previous Steroids Use<br>Unresponsive or Intolerant to or Dependent on Previous Medication Use | 102/158 (65%) | 455/643 (71%) | 557/801 (70%) |
| Previous Anti-TNF Use<br>Unresponsive or Intolerant to Previous Medication Use | 46/69 (67%) | 196/291 (67%) | 242/360 (67%) |
| Previous Antibiotics Use<br>Unresponsive or Intolerant to Previous Medication Use | 40/83 (48%) | 166/301 (55%) | 206/384 (54%) |

(Values in table above are taken from Page 128 of the Study Report for Study CD301.)

Detailed information about reasons for discontinuation by previous CD medication is provided in Appendix 2.

Approximately 87% of subjects were receiving treatment for Crohn's disease at the baseline visit. About half of the natalizumab-treated and placebo-treated subjects were on 5-ASA compounds (345 [48%] vs. 80 [44%], respectively), 39% were on oral steroids (283 [39%] vs. 71 [39%], respectively), and one-third were on immunosuppressants (247 [34%] vs. 53 [29%], respectively). Proportions in the elevated CRP subpopulation were similar by concomitant medication category.

**Table 10. Concomitant Medications Taken at Baseline: Intent-to-Treat Population (Study CD301)**

| Category | Placebo (n=181) N (%) | Natalizumab (n=724) N (%) | Overall (n=906) N (%) |
|---|---|---|---|
| 5-ASA compounds | 80 (44%) | 345 (48%) | 425 (47%) |
| Steroids | 71 (39%) | 283 (39%) | 354 (39%) |
| Immunosuppressants | 53 (29%) | 247 (34%) | 300 (33%) |
| Antibiotics | 12 (7%) | 43 (6%) | 55 (6%) |

(Values in table above taken from Page 301 of the CD301 Study Report)

ENACT-2 (Study CD303)

The table below provides a summary of previous medications taken for CD since diagnosis by subjects in the Total Safety Population. In each treatment group, most subjects had received prior treatment with steroids and ASA compounds. A majority of subjects also had been treated with immunosuppressants. Proportions of previous medication category in the natalizumab responders population, and the placebo responders population, were similar to that of the overall population.

**Table 11. Previous Medications Taken for Crohn's Disease - Total Safety Population (Study CD303)**

| Medication | Placebo (N=214) | Natalizumab (N=214) | Total (N=428) |
|---|---|---|---|
| Steroids | 191 (89%) | 190 (89%) | 381 (89%) |
| ASA Compounds | 185 (86%) | 183 (86%) | 368 (86%) |
| Immunosuppressants | 139 (65%) | 149 (70%) | 288 (67%) |
| Antibiotics | 85 (40%) | 84 (39%) | 169 (39%) |
| Anti-TNF Therapy | 78 (36%) | 74 (35%) | 152 (36%) |

(Table above taken from Page 120 of CD303 Study Report)

The table below summarizes the proportion of subjects intolerant to, unresponsive to, or dependent on CD-related medications (collected during screening of Study CD301) for the Total Safety Population. The proportion of subjects intolerant to or unresponsive to prior ASA compounds, immunosuppressants, and anti-TNF agents was similar between treatment groups, as was the proportion of subjects intolerant to, unresponsive to, or dependent on prior steroids. Proportions of subject's response to previous medications category in the natalizumab responders population, and placebo responders population, were similar to that of the overall population.

**Table 12. Summary of Subjects' Response to Previous Medications Taken for Crohn's Disease - Total Safety Population (Study CD303)**

| Subgroup Category | Placebo n/N (%) | Natalizumab n/N (%) |
|---|---|---|
| Previous ASA Compounds Use<br>Unresponsive or Intolerant to Previous Medication Use | 125/185 (68%) | 123/183 (67%) |
| Previous Immunosuppressants Use<br>Unresponsive or Intolerant to Previous Medication Use | 97/139 (70%) | 95/149 (64%) |
| Previous Steroids Use<br>Unresponsive or Intolerant to or Dependent on Previous Medication Use | 134/191 (70%) | 124/190 (65%) |
| Previous Anti-TNF Use<br>Unresponsive or Intolerant to Previous Medication Use | 46/ 78 (59%) | 46/ 74 (62%) |
| Previous Antibiotics Use<br>Unresponsive or Intolerant to Previous Medication Use | 38/ 85 (45%) | 46/ 84 (55%) |

(Table above is taken from Page 121 of the CD303 Study Report)

In the Total Safety Population, about half of the subjects in each treatment group (47% natalizumab, 55% placebo) received concomitant treatment with 5-ASA compounds, 40% were receiving oral steroids (37% natalizumab vs. 43% placebo), and 38% were receiving immunosuppressants: (38% natalizumab, 39% placebo). Anti-TNF therapy, which was not permitted by the study protocol, was used by 1% of subjects in the placebo group and by no subjects in the natalizumab group. (See table below.) Proportions of subject's receiving categories of concomitant medications in the natalizumab responders population, and placebo responders population, were similar to that of the overall population.

**Table 13. Concomitant CD-Related Medications Taken During the Treatment Phase: Total Safety Population (Study CD303)**

| Category | Placebo (n=214) N (%) | Natalizumab (n=214) N (%) | Overall (n=428) N (%) |
|---|---|---|---|
| Subjects with Concomitant Medications | 203 (95%) | 197 (92%) | 400 (93%) |
| 5-ASA compounds | 118 (55%) | 100 (47%) | 218 (51%) |
| Anti-TNF Therapy | 3 (1%) | 0 (0%) | 3 (1%) |
| Antibiotics | 27 (13%) | 19 (9%) | 46 (11%) |
| Immunosupressants | 83 (39%) | 81 (38%) | 164 (38%) |
| Steroids | 92 (43%) | 80 (37%) | 172 (40%) |

(Values in table above taken from Pages 932-955 of the CD303 Study Report.)

ENCORE (Study CD307)

Nearly all subjects (99%) in the ITT Population had received prior or concomitant therapy for CD. The majority of subjects (93%) had received prior or concomitant treatment with 5-ASA compounds or oral steroids, 74% had received prior or concomitant treatment with immunosuppressants, and 57% with antibiotics. See table below.

**Table 14. Subjects who Received Prior or Concomitant Medications for Crohn's Disease – Intent-to-Treat Population (Study CD307)**

| Medication | Placebo (n=250) N (%) | Natalizumab (n=259) N (%) | Overall (n=509) N (%) |
|---|---|---|---|
| Treatment Naive | 2 (1%) | 3 (1%) | 5 (1%) |
| 5-ASA Compounds | 232 (93%) | 241 (93%) | 473 (93%) |
| Steroids | 235 (94%) | 237 (92%) | 472 (93%) |
| Immunosuppressants | 182 (73%) | 194 (75%) | 376 (74%) |
| Antibiotics | 139 (56%) | 149 (58%) | 288 (57%) |

Note: Subjects defined as treatment naive if there was no prior exposure or concomitant exposure to 5-ASA compounds, steroids, immunosuppressants, and antibiotics, and no prior exposure to anti-TNF agents.
(Table above is taken from Page 116 of the Clinical Study Report for Study CD307)

Approximately 50% of the subjects had prior but not concomitant treatment with oral steroids, antibiotics, or anti-TNF agents, 44% with 5-ASA compounds, and 36% with immunosuppressants. At baseline (Week 0), 93% of subjects were receiving CD-related medications or diet: 49% were on 5-ASA compounds, 40% on oral steroids, 38% on immunosuppressants, 6% on antibiotics, and 1% on diet. See table below.

**Table 15. Subjects who Received Prior but not Concomitant Medications for Crohn's Disease – Intent-to-Treat Population (Study CD307)**

| Medication | Placebo (n=250) N (%) | Natalizumab (n=259) N (%) | Overall (n=509) N (%) |
|---|---|---|---|
| 5-ASA Compounds | 112 (45%) | 113 (44%) | 225 (44%) |
| Steroids | 140 (56%) | 127 (49%) | 267 (52%) |
| Immunosuppressants | 84 (34%) | 97 (37%) | 181 (36%) |
| Antibiotics | 123 (49%) | 130 (50%) | 253 (50%) |
| Anti-TNF Agents | 113 (45%) | 131 (51%) | 244 (48%) |

(Table above is taken from Page 116 of the Clinical Study Report for Study CD307)

Information on previous use of CD-related medications was captured in the CRFs at the Screening Visit, which included reasons for discontinuation or nonuse of the medications. The table below shows the reasons for which subjects discontinued their prior CD-related medications, grouped as "unresponsive" (which includes subjects that never responded as well as those that lost response over time), "AE/intolerant" and "other." For oral steroids, azathioprine or 6-MP or 6-TG, methotrexate, and other immunosuppressants, the category of "dependence" was included as well. The category of "other" included "disease in remission," "patient just stopped taking," "monetary," "pregnancy," "completed course" of treatment," "switched to …" other medication," and "stopped for surgery" among others.

**Table 16. Proportion of Subjects Previously Treated with Medications for Crohn's Disease but Discontinued Use Before Screening (Study CD307)**

| Medication Category | Placebo (n=250) N (%) | Natalizumab (n=259) N (%) | Overall (n=509) N (%) |
|---|---|---|---|
| 5-ASA Drugs | | | |
| Prior Use but Discontinued Before Screening | 112 (45%) | 115 (44%) | 227 (45%) |
| Reason for Discontinuation | | | |
| AE/Intolerant | 20 (18%) | 18 (16%) | 38 (17%) |
| Unresponsive | 74 (66%) | 73 (63%) | 147 (65%) |
| Other | 18 (16%) | 24 (21%) | 42 (19%) |
| Oral Steroids (other than Budesonide) | | | |
| Prior Use but Discontinued Before Screening | 155 (62%) | 153 (59%) | 308 (61%) |
| Reason for Discontinuation | | | |
| AE/Intolerant | 24 (15%) | 31 (20%) | 55 (18%) |
| Unresponsive | 28 (18%) | 34 (22%) | 62 (20%) |
| Dependence | 16 (10%) | 20 (13%) | 36 (12%) |
| Other | 87 (56%) | 68 (44%) | 155 (50%) |
| Budesonide | | | |
| Prior Use but Discontinued Before Screening | 64 (26%) | 61 (24%) | 125 (25%) |
| Reason for Discontinuation | | | |
| AE/Intolerant | 7 (11%) | 5 (8%) | 12 (10%) |
| Unresponsive | 39 (61%) | 38 (62%) | 77 (62%) |
| Dependence | 2 (3%) | 6 (10%) | 8 (6%) |
| Other | 16 (25%) | 12 (20%) | 28 (22%) |
| Azathioprine, 6-MP or 6-TG | | | |
| Prior Use but Discontinued Before Screening | 97 (39%) | 109 (42%) | 206 (40%) |
| Reason for Discontinuation | | | |
| AE/Intolerant | 53 (55%) | 60 (55%) | 113 (55%) |
| Unresponsive | 30 (31%) | 30 (28%) | 60 (29%) |
| Dependence | 0 (0%) | 1 (1%) | 1 (0%) |
| Other | 14 (14%) | 18 (17%) | 32 (16%) |
| Methotrexate | | | |
| Prior Use but Discontinued Before Screening | 29 (12%) | 39 (15%) | 68 (13%) |
| Reason for Discontinuation | | | |
| AE/Intolerant | 13 (45%) | 16 (41%) | 29 (43%) |
| Unresponsive | 13 (45%) | 18 (46%) | 31 (46%) |
| Dependence | 0 (0%) | 2 (5%) | 2 (3%) |
| Other | 3 (10%) | 3 (8%) | 6 (9%) |
| Other Immunosuppressants (i.e. Cyclosporine) | | | |
| Prior Use but Discontinued Before Screening | 8 (3%) | 12 (5%) | 20 (4%) |
| Reason for Discontinuation | | | |
| AE/Intolerant | 2 (25%) | 2 (17%) | 4 (20%) |
| Unresponsive | 2 (25%) | 9 (75%) | 11 (55%) |
| Dependence | 1 (13%) | 0 (0%) | 1 (5%) |
| Other | 3 (38%) | 1 (8%) | 4 (20%) |
| Anti-TNF Agents | | | |
| Prior Use but Discontinued Before Screening | 112 (45%) | 130 (50%) | 242 (48%) |
| Reason for Discontinuation | | | |
| AE/Intolerant | 35 (31%) | 35 (27%) | 70 (29%) |
| Unresponsive | 37 (33%) | 44 (34%) | 81 (33%) |
| Other | 40 (36%) | 51 (39%) | 91 (38%) |

(Table above is taken from Pages 118-120 of the Study CD307 Clinical Study Report.)

An overall analysis of treatment outcomes for prior use of medications for CD showed that 61% of subjects previously treated with oral steroids, other than budesonide, discontinued use of the medications: 20% discontinued treatment due to lack of response (unresponsive) and 12% due to dependency on the medication. Of those subjects treated previously with budesonide alone, approximately 62% of subjects in both treatment groups reported lack of response.

Subjects who were previously treated with azathioprine or 6-MP or 6-TG had the highest rate of discontinuation due to adverse events and/or intolerance (55% for both treatment groups). The rates of discontinuation due to adverse events and/or intolerance for other prior medications for CD in decreasing frequency were 43% (methotrexate), 29% (anti-TNF agents), 20% (other immunosuppressants, i.e., cyclosporine), 18% (oral steroids, other than budesonide), 17% (5-ASA compounds), 10% (budesonide alone), and 8% (antibiotics).

The table below shows the number and percentage of subjects who were receiving CD-related medications at the baseline visit. The majority of subjects (93%) were receiving treatment for Crohn's disease at baseline: 49% were on 5-ASA compounds, 40% on oral steroids, 38% on immunosuppressants, and 6% on antibiotics.

**Table 17. Concomitant CD-Related Medications Taken at Baseline – Intent-to-Treat Population (Study CD307)**

| Category | Placebo (n=250) N (%) | Natalizumab (n=259) N (%) | Overall (n=509) N (%) |
|---|---|---|---|
| Subjects with CD-Related Medications | 227 (91%) | 247 (95%) | 474 (93%) |
| 5-ASA compounds | 120 (48%) | 128 (49%) | 248 (49%) |
| Immunosuppressants | 96 (38%) | 97 (37%) | 193 (38%) |
| Steroids | 94 (38%) | 109 (42%) | 203 (40%) |
| Antibiotics | 13 (5%) | 17 (7%) | 30 (6%) |

(Values in table above are taken from Page 121 of the CD307 Study Report.)

### *Subject Disposition*

The subject disposition for each of the three studies is displayed in the figures below.

ENACT-1 (Study CD301)

**Table 18. Subject Disposition: Intent-to-Treat Population (Study CD301)**

| | Placebo (n=181) | Natalizumab (n=724) | Overall (n=905) |
|---|---|---|---|
| Population | N (%) | N (%) | N (%) |
| Subjects Randomized (ITT) | 181 (100%) | 724 (100%) | 905 (100%) |
| Subjects Treated with Study Drug (Safety) | 181 (100%) | 723 (100%) | 904 (100%) |
| Subjects with no Major Protocol Violations (Per Protocol) | 144 (80%) | 620 (86%) | 764 (84%) |
| Completed 10-Week Visit | 150 (83%) | 632 (87%) | 782 (86%) |
| Completed 12-Week Visit | 141 (78%) | 602 (83%) | 743 (82%) |
| Withdrawn Early | 40 (22%) | 122 (17%) | 162 (18%) |
| Primary Reason for Withdrawal | | | |
| Lost to Follow-Up | 3 (2%) | 8 (1%) | 11 (1%) |
| Adverse Event | 20 (11%) | 78 (11%) | 98 (11%) |
| Voluntary Withdrawal | 11 (6%) | 21 (3%) | 32 (4%) |
| Non-Compliance | 0 (0%) | 5 (1%) | 5 (1%) |
| Death | 0 (0%) | 1 (0%) | 1 (0%) |
| Other | 6 (3%) | 9 (1%) | 15 (2%) |
| Number of Infusions Prior to Withdrawal | | | |
| Zero | 0 (0%) | 1 (0%) | 1 (0%) |
| One | 19 (10%) | 52 (7%) | 71 (8%) |
| Two | 22 (12%) | 84 (12%) | 106 (12%) |
| Three | 140 (77%) | 587 (81%) | 727 (80%) |
| Subject status at the End of Treatment Phase | | | |
| Continued to CD301 Follow-Up Phase | 55 (30%) | 232 (32%) | 287 (32%) |
| Randomized to CD303 Study | 74 (41%) | 354 (49%) | 428 (47%) |
| Enrolled to CD351 (Open-label) Study | 11 (6%) | 32 (4%) | 43 (5%) |
| Not Continued in Any Further Study Visits | 29 (16%) | 81 (11%) | 110 (12%) |
| Other | 12 (7%) | 25 (3%) | 37 (4%) |
| Completed Week 32 Follow-Up Phase | 50 (28%) | 170 (23%) | 220 (24%) |
| Withdrawn Early Since Follow-Up Phase | 15 (8%) | 79 (11%) | 94 (10%) |
| Primary Reason for Withdrawal | | | |
| Lost to Follow-Up | 4 (2%) | 10 (1%) | 14 (2%) |
| Adverse Event | 0 (0%) | 4 (1%) | 4 (0%) |
| Voluntary Withdrawal | 1 (1%) | 7 (1%) | 8 (1%) |
| Non-Compliance | 0 (0%) | 0 (0%) | 0 (0%) |
| Death | 0 (0%) | 0 (0%) | 0 (0%) |
| Other | 10 (6%) | 58 (8%) | 68 (8%) |
| Subject Status at the End of Follow-Up Phase | | | |
| Enrolled to CD351 (Open-label) Study | 7 (4%) | 25 (3%) | 32 (4%) |
| Not Continued in Any Further Study Visits | 25 (14%) | 71 (10%) | 96 (11%) |
| Other | 18 (10%) | 74 (10%) | 92 (10%) |

(Table above is taken from Pages 247-249 of the Study CD301 Clinical Study Report.)

A total of 140 subjects in the natalizumab and placebo treatment groups (103 [14%] vs. 37 [20%], respectively) were excluded from the per protocol population due to protocol deviations.

These protocol deviations were grouped into five categories (see table below). The category "prohibited concomitant medications" excluded rescue medications.

**Table 19. Subjects Excluded From the Per Protocol Population by Category (Study CD301)**

| Category of Protocol Deviations | Number of Subjects with the Deviation | |
|---|---|---|
| | Natalizumab (n=724) N (%) | Placebo (n=181) N (%) |
| Prohibited concomitant medications | 82 (11%) | 21 (12%) |
| Eligibility criteria violation | 15 (2%) | 9 (5%) |
| Outside acceptable visit window | 6 (1%) | 6 (3%) |
| Missed, partial, or incorrect dosing | 1* (0.1%) | 0 (0%) |
| Other[#] | 3 (0.4%) | 3 (2%) |
| TOTAL | 103 (14%) | 37 (20%) |

Note: Subjects may be counted once for each criteria but are only counted once in the total.
* Subject CD552-004 did not receive the second infusion of study drug.
# Investigator was unblinded to lab results.
(Values in the table above are taken from Page 120 of the Study CD301 Clinical Study Report.)

## ENACT-2 (Study CD303)

**Table 20. Subject Disposition - Total Safety Population (Study CD303)**

| Population | Placebo (n=214) N (%) | Natalizumab (n=214) N (%) | Overall (n=428) N (%) |
|---|---|---|---|
| Subjects Randomized | 214 (100%) | 214 (100%) | 428 (100%) |
| Subjects Treated with Study Drug | 214 (100%) | 214 (100%) | 428 (100%) |
| Subjects with no Major Protocol Violations | 192 (90%) | 190 (89%) | 382 (89%) |
| Completed Month 15 Visit | 73 (34%) | 137 (64%) | 210 (49%) |
| Withdrawn Early | 141 (66%) | 77 (36%) | 218 (51%) |
| Primary Reason for Withdrawal | | | |
| Lost to Follow-Up | 1 (0%) | 3 (1%) | 4 (1%) |
| Adverse Event | 61 (29%) | 30 (14%) | 91 (21%) |
| Voluntary Withdrawal | 18 (8%) | 16 (7%) | 34 (8%) |
| Non-Compliance | 5 (2%) | 1 (0%) | 6 (1%) |
| Death | 0 (0%) | 0 (0%) | 0 (0%) |
| Other | 56 (26%) | 27 (13%) | 83 (19%) |
| Mean Number of Infusions Prior to Withdrawal/Completion of Study | | | |
| N | 214 | 214 | 428 |
| Mean | 7.1 | 9.2 | 8.2 |
| s.d. | 4.08 | 4.00 | 4.16 |
| Median | 6.0 | 12.0 | 11.0 |
| Min., Max. | 1,12 | 1,12 | 1,12 |

(Table above is taken from Page 114 of the CD303 Study Report)

A total of 45 subjects (23 [11%] natalizumab, 22 [10%] placebo) were excluded from per-protocol populations due to protocol deviations. A total of 15 (7%) natalizumab subjects and 18 (8%) placebo subjects who were randomized and received study drug in Study CD303 failed to meet protocol-specified entry criteria. Of these subjects, the majority (10 natalizumab, 12 placebo) failed to demonstrate a clinical response at Week 10 or Week 12 of Study CD301 and thus were omitted from the primary and contingent primary efficacy analyses. Other reasons

for ineligibility included receiving rescue treatment in Study CD301 (1 natalizumab, 4 placebo); ineligibility (CDAI < 220) at baseline of Study CD301 (2 natalizumab, 2 placebo); a lack of evidence of CD at baseline (1 natalizumab, 0 placebo); and a history of sickle cell anemia (1 natalizumab, 0 placebo). (See table below.)

**Table 21. Subjects Excluded From the Per Protocol Population by Category: Total Safety Population (Study CD303)**

| Category of Protocol Deviations | Number of Subjects with the Deviation | |
|---|---|---|
| | Natalizumab (n=214) | Placebo (n=214) |
| Eligibility criteria violation | 15 (7%) | 18 (8%) |
| Prohibited concomitant medications | 3 (1%) | 4 (2%) |
| Missed, partial, or incorrect dosing | 5 (2%) | 0 (0%) |
| Efficacy eval not performed or not valid | 1 (0.5%) | 0 (0%) |
| TOTAL | 24 (11%) | 22 (10%) |

(Values in the table above are taken from Page 960 of the CD303 Study Report.)

ENCORE (Study CD307)

**Table 22. Subject Disposition: Intent-to-Treat Population (Study CD307)**

| Variable Category | Placebo (n=250) N (%) | Natalizumab (n=259) N (%) | Overall (n=509) N (%) |
|---|---|---|---|
| Subjects Treated with Study Drug (a) | 250 (100%) | 260 (100%) | 510 (100%) |
| Subjects Randomized (ITT) | 250 (100%) | 259 (100%) | 509 (100%) |
| Subjects with no Major Protocol | 215 (86%) | 221 (85%) | 436 (86%) |
| Deviations | | | |
| Completed Week 4 Visit | 234(94%) | 247 (95%) | 481 (94%) |
| Completed Week 8 Visit | 228 (91%) | 249 (96%) | 477 (94%) |
| Completed Week 12 Treatment Phase (b) | 208 (83%) | 220 (85%) | 428 (84%) |
| Withdrawn from Treatment Phase | 42 (17%) | 39 (15%) | 81 (16%) |
| Primary Reason for Withdrawal | | | |
| Lost to Follow-Up | 0 (0%) | 1 (0%) | 1 (0%) |
| Subject Withdrew Consent | 3 (1%) | 4 (2%) | 7 (1%) |
| Adverse Event | 32 (13%) | 27 (10%) | 59 (12%) |
| Death | 0 (0%) | 0 (0%) | 0 (0%) |
| Investigator's Discretion | 2 (1%) | 1 (0%) | 3 (1%) |
| Sponsor's Discretion | 0 (0%) | 0 (0%) | 0 (0%) |
| Non-compliance | 0 (0%) | 3 (1%) | 3 (1%) |
| Other | 4 (2%) | 2 (1%) | 6 (1%) |
| Not Reported | 1 (0%) | 1 (0%) | 2 (0%) |
| Completed Week 20 Follow-up Phase | 3 (1%) | 6 (2%) | 9 (2%) |
| Withdrawn Early From Follow-up Phase | 4 (2%) | 5 (2%) | 9 (2%) |
| Primary Reason for Withdrawal | | | |
| Lost to Follow-Up | 1 (0%) | 1 (0%) | 2 (0%) |
| Subject Withdrew Consent | 1 (0%) | 2 (1%) | 3 (1%) |
| Adverse Event | 1 (0%) | 1 (0%) | 2 (0%) |
| Death | 0 (0%) | 0 (0%) | 0 (0%) |
| Investigator's Discretion | 1 (0%) | 0 (0%) | 1 (0%) |
| Sponsor's Discretion | 0 (0%) | 0 (0%) | 0 (0%) |
| Non-compliance | 0 (0%) | 0 (0%) | 0 (0%) |
| Other | 0 (0%) | 1 (0%) | 1 (0%) |
| Not Reported | 0 (0%) | 0 (0%) | 0 (0%) |

(a) Subject 621-712 received natalizumab, but was never randomized.
(b) Subjects who received all 3 infusions, completed all visits through Week 12, and did not have an Early Discontinuation visit
(Table above is taken from Page 105 of the CD307 Study Report.)

A total of 11 subjects (5 natalizumab and 6 placebo) and 12 subjects (8 natalizumab and 4 placebo) were erroneously enrolled into the trial despite the fact they did not meet protocol-specified inclusion and exclusion criteria, respectively. The description of the entry criteria and the number of subjects who did not meet the specified criteria are summarized in the table below.

**Table 23. Inclusion and Exclusion Criteria Deviations (Study CD307)**

| Inclusion and Exclusion Criteria Deviations | | |
|---|---|---|
| Description of Deviation | Subjects Who Failed Entry Criteria | |
| | Placebo | Natalizumab |
| Inclusion Criteria | | |
| Does the subject have clinical evidence of active (symptomatic) CD based on clinical history and radiologic or endoscopic findings within the previous 36 months? | 0 | 1 |
| Does the subject have a CDAI score >=220 and <=450 at Week 0? | 6 | 4 |
| TOTAL | (6) | (5) |
| Exclusion Criteria | | |
| Does the subject have a known active or draining fistulae? | 0 | 1 |
| Does the subject's concomitant medications for CD violate any of the 9 categories listed on the CRF? | 3 | 5 |
| Has the subject had a colostomy, ileostomy, or colectomy with ileorectal anastomosis? | 0 | 1 |
| Does the subject have history of neoplastic disease, except for basal cell carcinoma of the skin? | 1 | 0 |
| Does the subject have symptoms that are likely caused by factors other than inflammatory CD, including infection or irritable bowel syndrome (IBS) | 0 | 1 |
| TOTAL | (4) | (8) |
| Note 1: Subjects may be counted once for each criteria but are only counted once in the total.<br>2: Missing responses or responses of N/A (not applicable) are not counted. | | |

(Table above taken from page 107 of CSR CD307)

The Sponsor conducted a detailed review of all subjects, and the major protocol deviations or violations were identified during this blinded review of data prior to the Week 12 treatment phase database lock. A total of 39 (15%) natalizumab-treated and 35 (14%) placebo-treated subjects were excluded from the Per Protocol Population due to protocol deviations. These protocol deviations were grouped into eight categories (see table below). A hierarchy was used to determine the primary reason for exclusion in subjects with multiple reasons for exclusion and to ensure that subjects were counted only once in the table.

This review uncovered two additional subjects enrolled despite a lack of objective evidence of CD, one additional case of a subject randomized despite the presence of an active draining fistula, and 19 additional cases of concomitant medication at baseline violations. Thirty-one subjects were excluded from the Per Protocol Population because their CRP level dropped below 2.87 mg/L between the screening and baseline assessments. Six subjects whose investigator calculated baseline CDAI scores were outside of the ≥220 and ≤450 window qualified for the per protocol population based on recalculated CDAI scores using the hematocrit value from the baseline visit.

**Table 24. Number of Subjects Excluded from the Per Protocol Population by Primary Reason (Study CD307)**

| Primary Reason of Protocol Deviations | Number of Subjects with the Deviation | |
|---|---|---|
| | Placebo | Natalizumab |
| Lack of objective evidence of CD | 1 | 2 |
| Fistula | 1 | 1 |
| Concomitant medication violation | 12 | 15 |
| Baseline CDAI score either < 220 or > 450 | 2 | 2 |
| Baseline CRP < upper limit of normal | 17 | 14 |
| Significant prior or concomitant medical illness | 1 | 2 |
| Incomplete diary data available for efficacy assessment | 0 | 1 |
| Other | 1 | 2 |
| TOTAL | (35) | (39) |

Note: The hierarchy method was used to determine the primary reason of protocol deviation.
(Table above is taken from page 109 of the CD307 Study Report.)

## *Efficacy Results*

### ENACT-1 (Study CD301)

*ITT Population:*

The primary efficacy endpoint consists of the proportion of subjects achieving a clinical response (defined as ≥70-point decrease in CDAI score from baseline) at Week 10, the time point chosen for the primary efficacy analysis. For the ITT population, although treatment group differences were not statistically significant, a higher proportion of subjects in the natalizumab treatment group achieved a clinical response than those in the placebo treatment group at Week 10. This comprised 408 (56.4%) and 88 (48.6%) natalizumab and placebo subjects, respectively; (*p*-value = 0.051). The proportion of subjects achieving a clinical response at all visits for the ITT population is presented in the table below.

**Table 25. Subjects with a Clinical Response (≥ 70-Point Decrease from Baseline in CDAI): ITT Population (Study CD301)**

| Visit | Placebo (n=181) N (%) | Natalizumab (n=724) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 2 | 59 (32.6%) | 287 (39.6%) | 1.395 | (0.986, 1.974) | 0.060 |
| Week 4 | 81 (44.8%) | 371 (51.2%) | 1.324 | (0.953, 1.839) | 0.094 |
| Week 6 | 95 (52.5%) | 423 (58.4%) | 1.288 | (0.928, 1.787) | 0.130 |
| Week 8 | 91 (50.3%) | 410 (56.6%) | 1.316 | (0.948, 1.826) | 0.101 |
| **Week 10** | **88 (48.6%)** | **408 (56.4%)** | **1.385** | **(0.998, 1.921)** | **0.051** |
| Week 12 | 92 (50.8%) | 444 (61.3%) | 1.551 | (1.117, 2.153) | 0.009 |
| Any Time (b) | 132 (72.9%) | 555 (76.7%) | 1.238 | (0.854, 1.795) | 0.259 |
| Week 20 (c) | 20/ 44 (45.5%) | 99/176 (56.3%) | 1.308 | (0.782, 2.188) | 0.307 |

Note 1: Subjects with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10. Except for Week 20, LOCF was used to replace missing CDAI scores and all CDAI scores collected after rescue intervention. Similarly, subjects were classified as treatment failures after they were rescued.
2: Week 10 is the primary endpoint.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.
(b) Any time through Week 12
(c) For Week 20, the denominator for percentage (%) is the number of subjects who had Week 20 CDAI data.
(Table above is taken from Page 744 of the Study Report for Study CD301.)

Full summaries of the proportion of subjects in clinical remission at all visits for the ITT Population is presented in the table below.

**Table 26. Proportion of Subjects in Clinical Remission (CDAI Score < 150): ITT Population (Study CD301)**

| Visit | Placebo (n=181) N (%) | Natalizumab (n=724) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 2 | 18 (9.9%) | 100 (13.8%) | 1.397 | (0.814, 2.397) | 0.225 |
| Week 4 | 34 (18.8%) | 163 (22.5%) | 1.220 | (0.803, 1.855) | 0.351 |
| Week 6 | 41 (22.7%) | 236 (32.6%) | 1.630 | (1.106, 2.401) | 0.014 |
| Week 8 | 51 (28.2%) | 246 (34.0%) | 1.286 | (0.893, 1.851) | 0.177 |
| Week 10 | 55 (30.4%) | 267 (36.9%) | 1.320 | (0.927, 1.881) | 0.124 |
| Week 12 | 56 (30.9%) | 288 (39.8%) | 1.456 | (1.023, 2.073) | 0.037 |
| Any Time (b) | 79 (43.6%) | 391 (54.0%) | 1.503 | (1.075, 2.103) | 0.017 |
| Week 20 (c) | 8/ 44 (18.2%) | 45/176 (25.6%) | 1.443 | (0.666, 3.126) | 0.352 |

Note 1: Subjects with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10. Except for Week 20, LOCF was used to replace missing CDAI scores and all CDAI scores collected after rescue intervention. Similarly, subjects were classified as treatment failures after they were rescued.

2: Week 10 is the primary endpoint.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(b) Any time through Week 12

(c) For Week 20, the denominator for percentage (%) is the number of subjects who had Week 20 CDAI data.

(Table above is taken from Page 154 of the Study Report for Study CD301.)

*Post-Hoc Analysis in Elevated C-reactive Protein Subgroup:*

A subgroup of subjects with elevated C-reactive Protein (CRP) at baseline (defined as >2.87 mg/L) comprised 73% of the ITT population (526/724 [73%] natalizumab vs. 134/181 [74%] placebo). In this subgroup of subjects, a post-hoc analysis showed that significantly higher proportions in the natalizumab group achieved a clinical response at Week 10 and at all other time points measured compared to the placebo group (*p*-values <0.05); see table below.

**Table 27. Proportion of Subjects with a Clinical Response (≥ 70-Point Decrease in CDAI from BL): Elevated CRP Group (Post-hoc analysis) [Study CD301]**

| Visit | Placebo (n=134) N (%) | Natalizumab (n=526) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 2 | 42 (31.3%) | 221 (42.0%) | 1.617 | (1.077, 2.427) | 0.020 |
| Week 4 | 59 (44.0%) | 289 (54.9%) | 1.566 | (1.068, 2.296) | 0.022 |
| Week 6 | 66 (49.3%) | 328 (62.4%) | 1.713 | (1.169, 2.510) | 0.006 |
| Week 8 | 63 (47.0%) | 314 (59.7%) | 1.682 | (1.148, 2.465) | 0.008 |
| Week 10 | 60 (44.8%) | 303 (57.6%) | 1.685 | (1.149, 2.469) | 0.007 |
| Week 12 | 64 (47.8%) | 330 (62.7%) | 1.851 | (1.262, 2.714) | 0.002 |
| Any Time (b) | 92 (68.7%) | 412 (78.3%) | 1.654 | (1.086, 2.520) | 0.019 |
| Week 20 (c) | 16/ 34 (47.1%) | 67/110 (60.9%) | 1.093 | (0.609, 1.963) | 0.765 |

Note 1: Subjects with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10. Except for Week 20, LOCF was used to replace missing CDAI scores and all CDAI scores collected after rescue intervention. Similarly, subjects were classified as treatment failures after they were rescued.

2: Week 10 is the primary endpoint.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(b) Any time through Week 12

(c) For Week 20, the denominator for percentage (%) is the number of subjects who had Week 20 CDAI data.

(Table above is taken from Page 133 of the Study Report for Study CD301.)

A significantly higher proportion of natalizumab-treated subjects with elevated CRP at baseline achieved a clinical remission at Weeks 6, 10, and 12 compared to placebo-treated subjects (*p*-values <0.05); see table below.

**Table 28. Proportion of Subjects in Clinical Remission (CDAI < 150): Elevated CRP Group (Study CD301)**

| Visit | Placebo (n=134) N (%) | Natalizumab (n=526) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 2 | 13 (9.7%) | 75 (14.3%) | 1.488 | (0.787, 2.811) | 0.221 |
| Week 4 | 25 (18.7%) | 126 (24.0%) | 1.331 | (0.817, 2.168) | 0.251 |
| Week 6 | 30 (22.4%) | 186 (35.4%) | 1.883 | (1.197, 2.963) | 0.006 |
| Week 8 | 36 (26.9%) | 191 (36.3%) | 1.522 | (0.992, 2.336) | 0.054 |
| Week 10 | 37 (27.6%) | 208 (39.5%) | 1.69 | (1.110, 2.572) | 0.014 |
| Week 12 | 39 (29.1%) | 220 (41.8%) | 1.727 | (1.139, 2.618) | 0.01 |
| Any Time (b) | 56 (41.8%) | 295 (56.1%) | 1.763 | (1.191, 2.610) | 0.005 |
| Week 20 (c) | 8/34 (23.5%) | 31/110 (28.2%) | 0.989 | (0.443, 2.210) | 0.978 |

Note 1: Subjects with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10. Except for Week 20, LOCF was used to replace missing CDAI scores and all CDAI scores collected after rescue intervention. Similarly, subjects were classified as treatment failures after they were rescued.

2: Week 10 is the primary endpoint.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(b) Any time through Week 12

(c) For Week 20, the denominator for percentage (%) is the number of subjects who had Week 20 CDAI data.

(Table above is taken from Page 142 of the Study Report for Study CD301.)

*Additional Post-Hoc Analyses:*

*Concomitant Immunosuppressants:*

The number of subjects on immunosuppressants in the ITT population was 247 (34%) natalizumab and 53 (29%) placebo subjects (see table below). Immunosuppressants included azathioprine, 6-MP, and methotrexate (see Prior and Concomitant CD Therapies Across Studies). A significantly greater proportion of natalizumab-treated subjects receiving concomitant immunosuppressants achieved a clinical response than placebo-treated subjects at Week 10 (153 [62%] vs. 24 [45%], respectively; *p*-value = 0.027). Statistically significant differences were also observed between treatment groups at Week 6 (148 [60%] natalizumab vs. 23 [43%] placebo, *p*-value = 0.029), Week 8 (145 [59%] vs. 23 [43%], respectively; *p*-value = 0.043), and Week 12 (155 [63%] vs. 25 [47%], respectively; *p*-value = 0.037).

**Table 29. Proportion of Subjects with Clinical Response (≥ 70-Pt Decrease in CDAI from BL) on Immunosuppressants at BL (Study CD301)**

| Visit | Placebo (n=53) N (%) | Natalizumab (n=247) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 2 | 14 (26.4%) | 93 (37.7%) | 1.682 | (0.867, 3.263) | 0.124 |
| Week 4 | 23 (43.4%) | 125 (50.6%) | 1.336 | (0.735, 2.430) | 0.342 |
| Week 6 | 23 (43.4%) | 148 (59.9%) | 1.95 | (1.070, 3.552) | 0.029 |
| Week 8 | 23 (43.4%) | 145 (58.7%) | 1.854 | (1.018, 3.376) | 0.043 |
| Week 10 | 24 (45.3%) | 153 (61.9%) | 1.967 | (1.081, 3.579) | 0.027 |
| Week 12 | 25 (47.2%) | 155 (62.8%) | 1.887 | (1.038, 3.431) | 0.037 |
| Any Time (b) | 37 (69.8%) | 192 (77.7%) | 1.51 | (0.781, 2.917) | 0.22 |
| Week 20 (c) | 7/ 13 (53.8%) | 34/ 55 (61.8%) | 1.049 | (0.438, 2.513) | 0.915 |

Note 1: Subjects with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10. Except for Week 20, LOCF was used to replace missing CDAI scores and all CDAI scores collected after rescue intervention. Similarly, subjects were classified as treatment failures after they were rescued.

2: Week 10 is the primary endpoint.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(b) Any time through Week 12

(c) For Week 20, the denominator for percentage (%) is the number of subjects who had Week 20 CDAI data.

(Table above is taken from Page 135 of the Study Report for Study CD301.)

*Concomitant Immunosuppressants (Elevated CRP Group):*

Subgroup analysis of subjects with elevated baseline CRP and who were on concomitant immunosuppressants showed significantly higher response rates at Week 10 for natalizumab-treated (114 [62.0]) than placebo-treated (14 [36.8]) subjects, *p*-value = 0.005. In addition, statistical significance favoring natalizumab was achieved for clinical response at Weeks 2, 6, 8, and 12 (*p*-values <0.05); see table below.

**Table 30. Proportion of Subjects with Clinical Response (≥ 70-Pt Decrease in CDAI from BL) on Immunosuppressants at BL (Elevated CRP Group) [Study CD301]**

| Visit | Placebo (n=38) N (%) | Natalizumab (n=184) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 2 | 8 (21.1%) | 72 (39.1%) | 2.411 | (1.047, 5.552) | 0.039 |
| Week 4 | 14 (36.8%) | 98 (53.3%) | 1.953 | (0.951, 4.013) | 0.068 |
| Week 6 | 13 (34.2%) | 114 (62.0%) | 3.132 | (1.504, 6.520) | 0.002 |
| Week 8 | 12 (31.6%) | 112 (60.9%) | 3.370 | (1.599, 7.101) | 0.001 |
| Week 10 | 14 (36.8%) | 114 (62.0%) | 2.792 | (1.355, 5.754) | 0.005 |
| Week 12 | 16 (42.1%) | 117 (63.6%) | 2.401 | (1.180, 4.886) | 0.016 |
| Any Time (b) | 23 (60.5%) | 146 (79.3%) | 2.506 | (1.193, 5.262) | 0.015 |
| Week 20 (c) | 5/ 11 (45.5%) | 21/ 34 (61.8%) | 0.850 | (0.299, 2.417) | 0.761 |

Note 1: Subjects with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10. Except for Week 20, LOCF was used to replace missing CDAI scores and all CDAI scores collected after rescue intervention. Similarly, subjects were classified as treatment failures after they were rescued.

2: Week 10 is the primary endpoint.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(b) Any time through Week 12

(c) For Week 20, the denominator for percentage (%) is the number of subjects who had Week 20 CDAI data.

(Table above is taken from Page 136 of the Study Report for Study CD301.)

*Concomitant Immunosuppressants and Steroids (Elevated CRP Group):*

Clinical response rates were analyzed in a subpopulation of subjects with elevated CRP and receiving concomitant immunosuppressants and steroids. The proportions for the natalizumab-treated subjects were statistically significant at Weeks 8 (60/83 [72.3%] natalizumab vs. 5/17 [29.4%] placebo; *p*-value = 0.002) and 12 (60/83 [72.3%] vs. 8/17 [47.1%], respectively; *p*-value = 0.048) compared to the placebo-treated subjects. At Week 10, the difference between treatment groups was not significant (55 [66.3%] vs. 7 [41.2%], respectively; *p*-value = 0.058) (see table below).

**Table 31. Proportion of Subjects with Clinical Response (≥ 70-Pt Decrease in CDAI from BL) on Immunosuppressants and Steroids (Elevated CRP Group) [Study CD301]**

| Visit | Placebo (n=17) N (%) | Natalizumab (n=83) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 2 | 3 (17.6%) | 30 (36.1%) | 2.641 | (0.702, 9.937) | 0.151 |
| Week 4 | 7 (41.2%) | 44 (53.0%) | 1.612 | (0.560, 4.641) | 0.376 |
| Week 6 | 8 (47.1%) | 53 (63.9%) | 1.987 | (0.694, 5.693) | 0.201 |
| Week 8 | 5 (29.4%) | 60 (72.3%) | 6.261 | (1.985, 19.747) | 0.002 |
| Week 10 | 7 (41.2%) | 55 (66.3%) | 2.806 | (0.965, 8.161) | 0.058 |
| Week 12 | 8 (47.1%) | 60 (72.3%) | 2.934 | (1.010, 8.525) | 0.048 |
| Any Time (b) | 11 (64.7%) | 68 (81.9%) | 2.473 | (0.790, 7.740) | 0.120 |
| Week 20 (c) | 4/ 5 (80.0%) | 7/ 13 (53.8%) | 0.299 | (0.077, 1.168) | 0.083 |

Note 1: Subjects with missing CDAI scores at Week 10 or who were rescued prior to Week 10 were considered treatment failures at Week 10. Except for Week 20, LOCF was used to replace missing CDAI scores and all CDAI scores collected after rescue intervention. Similarly, subjects were classified as treatment failures after they were rescued.

2: Week 10 is the primary endpoint.

(d) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(e) Any time through Week 12

(f) For Week 20, the denominator for percentage (%) is the number of subjects who had Week 20 CDAI data.

(Table above is taken from Page 138 of the Study Report for Study CD301.)

### *Summary of ENACT-1 (Study CD301) Efficacy Results:*

Although a higher proportion of natalizumab-treated subjects than placebo subjects at the Week 10 timepoint experienced a clinical response (56% vs. 49%; p=0.051) and remission (37% vs. 30%; p=0.124), the treatment differences were not statistically significant in the ITT population.

In a post-hoc analysis of a subset of patients with CRP >2.87 mg/L (73% of the ITT population), a significantly higher proportion of natalizumab-treated subjects than placebo subjects at the Week 10 timepoint experienced a clinical response (58% vs. 45%; p=0.007) and remission (40% vs. 28%; p=0.014). Thus, the treatment difference appeared to be larger in the elevated CRP subpopulation; however, this was not a pre-specified statistical analysis.

In additional post-hoc analyses based on baseline medications as a possible surrogate of disease severity, a higher proportion of natalizumab-treated subjects than placebo subjects at the Week 10 timepoint experienced a clinical response as follows: (a) Immunosuppressants at baseline: 62% vs. 45% , p=0.027; (b) Immunosuppressants at baseline (elevated CRP group): 62% vs. 37% , p=0.005; (c) Immunosuppressants and steroids at baseline (elevated CRP group): 66% vs. 41%, p=0.058. Thus, the treatment difference appeared to be at least as large as for the overall study population; however, these were not pre-specified analyses.

ENACT-2 (Study CD303)

*Primary Efficacy Endpoint - Maintenance of Clinical Response:*

The table below presents a summary of subjects in the CD301 Natalizumab Responders Population who maintained clinical response over time in Study CD303.

A statistically significantly higher proportion of natalizumab-treated subjects maintained clinical response at each timepoint through Month 9 (i.e., after 6 months of treatment in Study CD303) compared to placebo-treated subjects (61% vs. 28%, $p < 0.001$). Statistically significant differences favoring the natalizumab treatment group were observed at every timepoint from Month 5 through Month 15 ($p = 0.007$ at Month 5; $p < 0.001$ at all subsequent timepoints).

By Month 6, only half of placebo-treated subjects had maintained clinical response, whereas the natalizumab group showed a 71% response rate. From Month 9 through Month 15, the difference in magnitude of the maintenance of response between treatment groups was > 30% favoring natalizumab at all timepoints.

**Table 32. Subjects in Clinical Response at Month 3 Who Maintained Clinical Response Over Time (CD301 Natalizumab Responders) [Study CD303]**

| Visit | Placebo (n=170) N (%) | Natalizumab (n=168) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Month 4 | 142 (83.5%) | 150 (89.3%) | 1.474 | (0.767, 2.834) | 0.244 |
| Month 5 | 105 (61.8%) | 129 (76.8%) | 1.935 | (1.196, 3.133) | 0.007 |
| Month 6 | 84 (49.4%) | 120 (71.4%) | 2.435 | (1.536, 3.862) | <0.001 |
| Month 7 | 70 (41.2%) | 112 (66.7%) | 2.753 | (1.743, 4.347) | <0.001 |
| Month 8 | 61 (35.9%) | 109 (64.9%) | 3.196 | (2.021, 5.055) | <0.001 |
| **Month 9** | **48 (28.2%)** | **103 (61.3%)** | **3.937** | **(2.468, 6.281)** | **<0.001** |
| Month 10 | 47 (27.6%) | 99 (58.9%) | 3.655 | (2.294, 5.824) | <0.001 |
| Month 11 | 46 (27.1%) | 99 (58.9%) | 3.782 | (2.367, 6.043) | <0.001 |
| Month 12 | 43 (25.3%) | 95 (56.5%) | 3.760 | (2.345, 6.029) | <0.001 |
| Month 13 | 38 (22.4%) | 94 (56.0%) | 4.312 | (2.668, 6.970) | <0.001 |
| Month 14 | 35 (20.6%) | 96 (57.1%) | 5.039 | (3.089, 8.219) | <0.001 |
| Month 15 | 34 (20.0%) | 90 (53.6%) | 4.516 | (2.764, 7.379) | <0.001 |

Note 1: A subject loses response at a specified timepoint if one or more of the following occurs at any time before the specified timepoint: 1) CDAI>=220 and increased >=70 points from Month 3, 2) rescued, 3) withdrew early, 4) has 50% or more missing CDAI scores, or 5) CDAI score at specified timepoint is missing.

2: Month 9 is the primary endpoint.

3: One subject (Placebo, CD074012) in the CD301 Natalizumab Responders Population was in remission at Month 3 but not in Response and is therefore removed from this analysis of response.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(Table above is taken form Page 124 of the CD303 Study Report.)

*Contingent Primary Efficacy Endpoint - Maintenance of Clinical Remission:*

The table below presents a summary of subjects in the CD301 Natalizumab Remission Population who maintained clinical remission over time in Study CD303.

A statistically significantly higher proportion of natalizumab-treated subjects maintained clinical remission at each timepoint through Month 9 (i.e., after 6 months of treatment in Study CD303) compared with placebo-treated subjects (44% vs. 26%, $p = 0.003$). Statistically significant differences favoring the natalizumab treatment group were observed at every timepoint from Month 5 through Month 15 ($p \leq 0.017$ through Month 9; $p < 0.001$ at all subsequent timepoints).

A substantial proportion of placebo-treated subjects lost remission early in the treatment phase of Study CD303; at Month 5, only 45% of placebo-treated subjects had retained clinical remission, compared to 64% of natalizumab-treated subjects. Maintenance of remission through Month 15 was achieved by more than twice as many natalizumab treated subjects compared with placebo-treated subjects (39% vs. 15%). From Month 10 through Month 15, the difference in magnitude of the maintenance of remission between treatment groups was > 20% favoring natalizumab at all timepoints.

**Table 33. Subjects in Clinical Remission at Month 3 Who Maintained Clinical Remission Over Time (CD301 Natalizumab Remission Population) [Study CD303]**

| Visit | Placebo (n=120) N (%) | Natalizumab (n=130) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Month 4 | 85 (70.8%) | 101 (77.7%) | 1.434 | (0.809, 2.544) | 0.217 |
| Month 5 | 54 (45.0%) | 83 (63.8%) | 2.172 | (1.298, 3.637) | 0.003 |
| Month 6 | 50 (41.7%) | 74 (56.9%) | 1.847 | (1.114, 3.065) | 0.017 |
| Month 7 | 41 (34.2%) | 69 (53.1%) | 2.196 | (1.310, 3.680) | 0.003 |
| Month 8 | 34 (28.3%) | 59 (45.4%) | 2.114 | (1.237, 3.610) | 0.006 |
| **Month 9** | **31 (25.8%)** | **57 (43.8%)** | **2.246** | **(1.307, 3.861)** | **0.003** |
| Month 10 | 28 (23.3%) | 58 (44.6%) | 2.665 | (1.533, 4.631) | <0.001 |
| Month 11 | 28 (23.3%) | 57 (43.8%) | 2.591 | (1.491, 4.503) | <0.001 |
| Month 12 | 25 (20.8%) | 54 (41.5%) | 2.741 | (1.552, 4.843) | <0.001 |
| Month 13 | 22 (18.3%) | 54 (41.5%) | 3.186 | (1.776, 5.713) | <0.001 |
| Month 14 | 17 (14.2%) | 54 (41.5%) | 4.34 | (2.322, 8.113) | <0.001 |
| Month 15 | 18 (15.0%) | 51 (39.2%) | 3.694 | (1.992, 6.852) | <0.001 |

Note 1: A subject loses response at a specified timepoint if one or more of the following occurs at any time before the specified timepoint: 1) CDAI>=220 and increased >=70 points from Month 3, 2) rescued, 3) withdrew early, 4) has 50% or more missing CDAI scores, or 5) CDAI score at specified timepoint is missing.

2: Month 9 is the primary endpoint.

3: One subject (Placebo, CD074012) in the CD301 Natalizumab Responders Population was in remission at Month 3 but not in Response and is therefore removed from this analysis of response.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process.

(Table above is taken form Page 126 of the CD303 Study Report.)

*Post-Hoc Analysis in Elevated C-reactive Protein Subgroup*

*Maintenance of Clinical Response:*

In natalizumab responders with elevated CRP at CD301 baseline, a statistically significantly higher proportion of natalizumab-treated subjects maintained clinical response at each timepoint through Month 9 (i.e., after 6 months of treatment in Study CD303) compared with placebo-treated subjects (61% vs. 26%, $p < 0.001$). The results were similar to those in the overall natalizumab responders population - 61% of the natalizumab-treated subjects maintained clinical response at each timepoint through Month 9 compared to 28% of the placebo-treated subjects ($p<0.001$). (See table below.)

**Table 34. Subjects in Clinical Response at Month 3 who Maintained Clinical Response Over Time (Natalizumab Responders with Elevated CRP at CD301 Baseline) [Study CD303]**

| Visit | Placebo N (%) | Natalizumab N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Natalizumab Responders (b) | N=170 | N=168 | | | |
| Month 9 | 48 (28.2%) | 103 (61.3%) | 3.937 | (2.468, 6.281) | <0.001 |
| Month 15 | 34 (20.0%) | 90 (53.6%) | 4.516 | (2.764, 7.379) | <0.001 |
| Natalizumab Responders with Elevated CRP at CD301 Baseline (b) | N=128 | N=129 | | | |
| Month 9 | 33 (25.8%) | 78 (60.5%) | 4.511 | (2.611, 7.796) | <0.001 |
| Month 15 | 24 (18.8%) | 69 (53.5%) | 5.027 | (2.836, 8.910) | <0.001 |

(a) The odds ratio, 95% CI, and p-value are from logistic regression.
(b) The logistic regression is adjusted by the stratification factors for randomization.
(Table above is taken from Page 158 of the CD303 Study Report.)

*Maintenance of Clinical Remission:*

In natalizumab remitters with elevated CRP at CD301 baseline, a statistically significantly higher proportion of natalizumab-treated subjects maintained clinical remission at each timepoint through Month 9 (i.e., after 6 months of treatment in Study CD303) compared with placebo-treated subjects (47% vs. 25%, $p = 0.002$). The results were similar to those in the overall natalizumab responders population - 44% of the natalizumab-treated subjects maintained clinical remission at each timepoint through Month 9 compared to 26% of the placebo-treated subjects ($p<0.001$). (See table below.)

**Table 35. Subjects in Clinical Remission at Month 3 who Maintained Clinical Remission Over Time (Natalizumab Remitters with Elevated CRP at CD301 Baseline) [Study CD303]**

| Visit | Placebo N (%) | Natalizumab N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Natalizumab Remitters (b) | N=120 | N=130 | | | |
| Month 9 | 31 (25.8%) | 57 (43.8%) | 2.246 | (1.307, 3.861) | 0.003 |
| Month 15 | 18 (15.0%) | 51 (39.2%) | 3.694 | (1.992, 6.852) | <0.001 |
| Natalizumab Remitters with Elevated CRP at CD301 Baseline (b) | N=94 | N=98 | | | |
| Month 9 | 23(24.5%) | 46 (46.9%) | 2.71 | (1.459, 5.032) | 0.002 |
| Month 15 | 13(13.8%) | 41 (41.8%) | 4.488 | (2.194, 9.179) | <0.001 |

(a) The odds ratio, 95% CI, and p-value are from logistic regression.
(b) The logistic regression is adjusted by the stratification factors for randomization.
(Table above is taken from Page 160 of the CD303 Study Report.)

*Additional Post-Hoc Analyses:*

*Concomitant Medications:*

For each of the exploratory populations analyzed, a statistically significantly higher proportion of natalizumab-treated subjects compared with placebo-treated subjects maintained clinical response through Month 9 and Month 15. (See table below.)

**Table 36. Subjects in Clinical Response at Month 3 who Maintained Clinical Response Over Time [Study CD303]**

| Natalizumab Responders Subgroup | | Placebo % (n/N) | Natalizumab % (n/N) | p-value (a) |
|---|---|---|---|---|
| Overall(b) | Mo. 9 | 28 % (48/170) | 61% (103/168) | <0.001 |
| | Mo. 15 | 20 % (34/170) | 54 % (90/168) | <0.001 |
| Immunosuppressant use at CD301 Baseline (b) | Mo. 9 | 28% (17/60)) | 65 % (40/62) | <0.001 |
| | Mo. 15 | 23% (14/60) | 52 % (32/62)) | 0.002 |
| Elevated CRP and Immunosuppressant use at CD301 Baseline (b) | Mo. 9 | 27% (13/49) | 61 % (30/49) | <0.001 |
| | Mo. 15 | 22% (11/49) | 51 % (25/49) | 0.004 |
| Elevated CRP, Immunosuppressant and Steroid use at CD301 Baseline (b) | Mo. 9 | 23% (6/26) | 56% (14/25) | 0.019 |
| | Mo. 15 | 19% (5/26) | 48% (12/25) | 0.034 |
| Steroid use at CD301 Baseline (b) | Mo. 9 | 25% (19/76) | 60% (40/67) | <0.001 |
| | Mo. 15 | 20% (15/76) | 52% (35/67) | <0.001 |
| Steroid and immunosuppressant use at CD301 Baseline (b) | Mo. 9 | 27% (9/33) | 61% (19/31) | 0.007 |
| | Mo. 15 | 21% (7/33) | 52% (16/31) | 0.013 |

(a) The p-value is from logistic regression.
(b) The logistic regression is adjusted by the stratification factors for randomization.
(Table above is taken from Pages 158 and 175-176 of the CD303 Study Report.)

For each of the exploratory populations analyzed, a higher proportion of natalizumab-treated subjects compared with placebo-treated subjects maintained clinical remission through Month 9 and Month 15. (See table below.)

**Table 37. Subjects in Clinical Remission at Month 3 who Maintained Clinical Remission Over Time [Study CD303]**

| Natalizumab Remitters Subgroup | Month | Placebo % (n/N) | Natalizumab % (n/N) | p-value (a) |
|---|---|---|---|---|
| Overall(b) | Mo. 9 | 26% (31/120) | 44% (57/130) | 0.003 |
| | Mo. 15 | 15% (18/120) | 39% (51/130) | <0.001 |
| Immunosuppressant use at CD301 Baseline (b) | Mo. 9 | 19% (8/43) | 49% (25/51) | 0.003 |
| | Mo. 15 | 14% (6/43) | 37% (19/51) | 0.014 |
| Elevated CRP and Immunosuppressant use at CD301 Baseline (b) | Mo. 9 | 19% (7/36) | 51% (20/39) | 0.005 |
| | Mo. 15 | 14% (5/36) | 38% (15/39) | 0.020 |
| Elevated CRP, Immunosuppressant and Steroid use at CD301 Baseline (b) | Mo. 9 | 20% (4/20) | 32% (7/22) | 0.388 |
| | Mo. 15 | 10% (2/20) | 18% (4/22) | 0.455 |
| Steroid use at CD301 Baseline (b) | Mo. 9 | 22% (12/55) | 33% (19/57) | 0.176 |
| | Mo. 15 | 15% (8/55) | 28% (16/57) | 0.086 |
| Steroid and immunosuppressant use at CD301 Baseline (b) | Mo. 9 | 17% (4/24) | 32% (9/28) | 0.205 |
| | Mo. 15 | 8% (2/24) | 21% (6/28) | 0.207 |

(a) The p-value is from logistic regression.
(b) The logistic regression is adjusted by the stratification factors for randomization.
(Table above is taken from Pages 160 and 176-177of the CD303 Study Report.)

*Investigator-Reported Inadequate Response to Prior Medications:*

For each of the exploratory populations analyzed, a higher proportion of natalizumab-treated subjects compared with placebo-treated subjects maintained clinical response through Month 9 and Month 15. (See table below.)

**Table 38. Subjects in Clinical Response at Month 3 who Maintained Clinical Response [Study CD303]**

| Natalizumab Responders Subgroup | Month | Placebo % (n/N) | Natalizumab % (n/N) | p-value (a) |
|---|---|---|---|---|
| Overall(b) | Mo. 9 | 28 % (48/170) | 61% (103/168) | <0.001 |
| | Mo. 15 | 20 % (34/170) | 54 % (90/168) | <0.001 |
| Investigator-Reported Inadequate Response to Prior anti-TNF (b) | Mo. 9 | 15% (5/34) | 54% (15/28) | 0.002 |
| | Mo. 15 | 18% (6/34) | 43% (12/28) | 0.034 |
| Investigator-Reported Inadequate Response to Prior Steroids (b) | Mo. 9 | 32% (35/109) | 60% (59/98) | <0.001 |
| | Mo. 15 | 21% (23/109) | 53% (52/98) | <0.001 |

(a) The p-value is from logistic regression.
(b) The logistic regression is adjusted by the stratification factors for randomization.
(Table above is taken from Pages 158 and 175-176 of the CD303 Study Report.)

For each of the exploratory populations analyzed, a higher proportion of natalizumab-treated subjects compared with placebo-treated subjects maintained clinical remission through Month 9 and Month 15. (See table below.)

**Table 39. Subjects in Clinical Remission at Month 3 who Maintained Clinical Remission [Study CD303]**

| Natalizumab Remitters Subgroup | Month | Placebo % (n/N) | Natalizumab % (n/N) | p-value (a) |
|---|---|---|---|---|
| Overall(b) | Mo. 9 | 26% (31/120) | 44% (57/130) | 0.003 |
| | Mo. 15 | 15% (18/120) | 39% (51/130) | <0.001 |
| Investigator-Reported Inadequate Response to Prior anti-TNF (b) | Mo. 9 | 9% (2/22) | 32% (7/22) | 0.077 |
| | Mo. 15 | 9% (2/22) | 27% (6/22) | 0.134 |
| Investigator-Reported Inadequate Response to Prior Steroids (b) | Mo. 9 | 28% (23/82) | 39% (32/83) | 0.154 |
| | Mo. 15 | 15% (12/82) | 34% (28/83) | 0.005 |

(a) The p-value is from logistic regression.
(b) The logistic regression is adjusted by the stratification factors for randomization.
(Table above is taken from Pages 158 and 175-176 of the CD303 Study Report.)

*Steroid Withdrawal Results*

*Subjects Not Taking Oral Steroids at Month 9:*

The table below summarizes subjects' oral steroid use over time for the subset of the CD301 Natalizumab Responders Population who were taking steroids at baseline of Study CD301.

Of the subjects in the CD301 Natalizumab Responders Population who were taking steroids at baseline of Study CD301, a total of 39 (58%) natalizumab-treated subjects were not taking oral steroids at Month 9, compared to 21 (28%) subjects in the placebo treatment group ($p < 0.001$). Statistically significant differences favoring the natalizumab treatment group were observed at every timepoint from Month 7 to Month 15 ($p \leq 0.004$), and the difference in magnitude between treatment groups at each of those timepoints was > 25%.

**Table 40. Number (%) of Subjects Not Taking Oral Steroids Over Time (CD301 Natalizumab Responders Using Baseline Steroids) [Study CD303]**

| Visit | Placebo (n=76) | | Natalizumab (n=67) | | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| Month 3 | 25 | 32.9 | 25 | 37.3 | 1.256 | (0.624, 2.526) | 0.523 |
| Month 4 | 45 | 59.2 | 39 | 58.2 | 0.847 | (0.425, 1.687) | 0.637 |
| Month 5 | 40 | 52.6 | 47 | 70.1 | 2.021 | (1.005, 4.064) | 0.049 |
| Month 6 | 38 | 50 | 46 | 68.7 | 1.962 | (0.965, 3.988) | 0.063 |
| Month 7 | 27 | 35.5 | 42 | 62.7 | 2.824 | (1.405, 5.678) | 0.004 |
| Month 8 | 24 | 31.6 | 40 | 59.7 | 2.968 | (1.458, 6.043) | 0.003 |
| **Month 9** | **21** | **27.6** | **39** | **58.2** | **3.448** | **(1.673, 7.106)** | **<0.001** |
| Month 10 | 21 | 27.6 | 39 | 58.2 | 3.448 | (1.673, 7.106) | <0.001 |
| Month 11 | 20 | 26.3 | 38 | 56.7 | 3.441 | (1.659, 7.136) | <0.001 |
| Month 12 | 18 | 23.7 | 35 | 52.2 | 3.239 | (1.555, 6.748) | 0.002 |
| Month 13 | 16 | 21.1 | 34 | 50.7 | 3.538 | (1.669, 7.498) | <0.001 |
| Month 14 | 15 | 19.7 | 34 | 50.7 | 3.863 | (1.804, 8.273) | <0.001 |
| Month 15 | 15 | 19.7 | 33 | 49.3 | 3.619 | (1.694, 7.732) | <0.001 |

Note 1: Results are frequency and percent AT each specified time point.
2: Visits occurring after Early Discontinuation or Rescue are counted as patient taking steroids.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process. (However, since the subset is limited to subjects taking steroids at CD301 baseline, the variable Steroid Use at CD301 Baseline was excluded from the model.)

(Table above is taken from Page 135 of the CD303 Study Report.)

*Subjects in Clinical Remission at Month 9 and Not Taking Oral Steroids at Month 9:*

The table below presents a summary of subjects in the CD301 Natalizumab Responders Population taking oral steroids at baseline of Study CD301 who were, at Month 9, in clinical remission and no longer taking oral steroids.

Among subjects in the CD301 Natalizumab Responders Population taking oral steroids at baseline of Study CD301, a statistically significantly higher proportion of natalizumab treated subjects compared with placebo-treated subjects were in clinical remission and not taking oral steroids at Month 9 (45% vs. 22%, $p = 0.014$). Statistically significant differences in incidence of steroid-free remission favoring the natalizumab treatment group were observed at every timepoint from Month 9 through Month 15 ($p \leq 0.014$), and the difference in magnitude between treatment groups at each of those timepoints was > 20%.

**Table 41. Number (%) of Subjects in Clinical Remission and Not Taking Oral Steroids Over Time (CD301 Natalizumab Responders Using Baseline Steroids) [Study CD303]**

| Visit | Placebo (n=76) | | Natalizumab (n=67) | | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| Month 3 | 16 | 21.1 | 19 | 28.4 | 1.211 | (0.542, 2.702) | 0.64 |
| Month 4 | 31 | 40.8 | 26 | 38.8 | 0.742 | (0.364, 1.508) | 0.409 |
| Month 5 | 24 | 31.6 | 33 | 49.3 | 1.925 | (0.962, 3.849) | 0.064 |
| Month 6 | 28 | 36.8 | 33 | 49.3 | 1.463 | (0.733, 2.919) | 0.28 |
| Month 7 | 22 | 28.9 | 31 | 46.3 | 1.916 | (0.947, 3.876) | 0.071 |
| Month 8 | 19 | 25 | 28 | 41.8 | 1.914 | (0.916, 3.995) | 0.084 |
| **Month 9** | **17** | **22.4** | **30** | **44.8** | **2.537** | **(1.208, 5.322)** | **0.014** |
| Month 10 | 17 | 22.4 | 31 | 46.3 | 2.707 | (1.285, 5.701) | 0.009 |
| Month 11 | 15 | 19.7 | 34 | 50.7 | 3.846 | (1.784, 8.292) | 0.001 |
| Month 12 | 13 | 17.1 | 31 | 46.3 | 3.805 | (1.715, 8.441) | 0.001 |
| Month 13 | 14 | 18.4 | 30 | 44.8 | 3.234 | (1.475, 7.086) | 0.003 |
| Month 14 | 12 | 15.8 | 28 | 41.8 | 3.481 | (1.561, 7.759) | 0.002 |
| Month 15 | 11 | 14.5 | 28 | 41.8 | 3.876 | (1.713, 8.763) | 0.001 |

Note 1: Results are frequency and percent AT each specified time point.
2: Visits occurring after Early Discontinuation or Rescue are counted as patient taking steroids.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for the stratification factors used in the randomization process. (However, since the subset is limited to subjects taking steroids at CD301 baseline, the variable Steroid Use at CD301 Baseline was excluded from the model.)

(Table above is taken from Page 137 of the CD303 Study Report.)

### *Summary of ENACT-2 (Study CD303) Efficacy Results:*

A significantly higher proportion of natalizumab-treated subjects than placebo subjects maintained clinical response through an additional six months (61% vs. 28%; p<0.001); also, a significantly higher proportion of natalizumab-treated subjects than placebo subjects maintained clinical remission through an additional six months (44% vs. 26%; p=0.003).

In a post-hoc analysis of the subset of patients from with elevated CRP at baseline of CD301, a significantly higher proportion of natalizumab-treated subjects than placebo subjects maintained clinical response through an additional six months (61% vs. 26%; p<0.001); also, in a post-hoc analysis of the subset of patients from with elevated CRP at baseline of CD301, a significantly higher proportion of natalizumab-treated subjects than placebo subjects maintained clinical remission through an additional six months (47% vs. 25%; p=0.002). Thus, the treatment difference appeared to be similar in the elevated CRP subpopulation; however, this was not a pre-specified statistical analysis.

In additional post-hoc analyses based on investigator-reported inadequate response, a higher proportion of natalizumab-treated subjects than placebo subjects maintained clinical response through an additional six months as follows: (a) investigator-reported inadequate response to steroids: 60% vs. 32% , p<0.001; (b) investigator-reported inadequate response to anti-TNF: 54% vs. 15%, p=0.002. Thus, the treatment difference in these subgroups appeared to be about as large as for the overall study population; however, these were not pre-specified analyses.

In additional post-hoc analyses based on Study CD301 baseline medication use, a higher proportion of natalizumab-treated subjects than placebo subjects maintained clinical response through an additional six months as follows: (a) Steroids at baseline: 60% vs. 25% , p<0.001; (b) Immunosuppressants at baseline: 65% vs. 28% , p<0.001; (c) Steroids and immunosuppressants at baseline: 61% vs. 27%, p=.007. Thus, the treatment difference in these subgroups appeared to be about as large as for the overall study population; however, these were not pre-specified analyses.

Of subjects in the CD301 natalizumab responders population that were taking steroids at the baseline of Study CD301, a total of 58% of natalizumab-treated subjects were not taking oral steroids at Month 9, compared to 28% of subjects in the placebo treatment group (p < 0.001); and a statistically significantly higher proportion of natalizumab treated subjects compared with placebo-treated subjects were in clinical remission and not taking oral steroids at Month 9 (45% vs. 22%, p = 0.014).

ENCORE (Study CD307)

*ITT Population:*

***Clinical Response (≥70-point Decrease from Baseline in CDAI score) at Weeks 8 and 12***

The primary efficacy endpoint consists of the proportion of subjects achieving a clinical response (defined as ≥ 70-point decrease from baseline [Week 0] in CDAI score) at both Weeks 8 and 12. The table below shows the results over time for the ITT Population.

**Table 42. Proportion of Subjects with a Clinical Response (≥ 70-point decrease from baseline in CDAI) – ITT Population (Study CD307)**

| Visit | Placebo (n=250) N (%) | Natalizumab (n=259) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 4 | 92 (36.8%) | 133 (51.4%) | 1.801 | (1.262, 2.570) | 0.001 |
| Week 8 | 99 (39.6%) | 146 (56.4%) | 1.969 | (1.382, 2.805) | <0.001 |
| Week 12 | 109 (43.6%) | 155 (59.8%) | 1.953 | (1.370, 2.783) | <0.001 |
| Weeks 4 & 8 | 62 (24.8%) | 109 (42.1%) | 2.191 | (1.500, 3.202) | <0.001 |
| **Weeks 8 & 12** | **81 (32.4%)** | **124 (47.9%)** | **1.924** | **(1.341, 2.760)** | **<0.001** |
| Any Time (b) | 146 (58.4%) | 192 (74.1%) | 2.049 | (1.406, 2.987) | <0.001 |

Note 1: Subjects were classified as treatment failures at any visit after rescue, early withdrawal, or discontinuing use of study drug due to adverse event. If CDAI score was missing for a given time point, the subject was considered a treatment failure for that time point.
2: Response at Weeks 8 & 12 is the primary endpoint.

(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for disease severity (CDAI < 330 vs. >= 330) at baseline.

(b) Any time through Week 12.

(Table above is taken from Page 123 of the Clinical Study Report for Study CD307)

The primary analysis was on the ITT Population. For this population, a statistically significantly higher proportion of natalizumab-treated subjects showed a clinical response compared to placebo-treated subjects at both Weeks 8 and 12 (124 [47.9%] natalizumab vs. 81 [32.4%] placebo, p-value <0.001).

### *Clinical Remission (CDAI Score ≤ 150) at Weeks 8 and 12*

The table below presents a summary of natalizumab-treated and placebo-treated subjects in the ITT Population who achieved a clinical remission (CDAI score <150) over time.

**Table 43. Proportion of Subjects in Clinical Remission (CDAI < 150) – ITT Population (Study CD307)**

| Visit | Placebo (n=250) N (%) | Natalizumab (n=259) N (%) | Odds Ratio (a) | 95% CI of Odds Ratio (a) | p-value (a) |
|---|---|---|---|---|---|
| Week 4 | 39 (15.6%) | 62 (23.9%) | 1.838 | (1.164, 2.902) | 0.009 |
| Week 8 | 52 (20.8%) | 83 (32.0%) | 1.904 | (1.264, 2.869) | 0.002 |
| Week 12 | 63 (25.2%) | 97 (37.5%) | 1.912 | (1.292, 2.829) | 0.001 |
| Weeks 4 & 8 | 22 (8.8%) | 48 (18.5%) | 2.529 | (1.464, 4.369) | <0.001 |
| **Weeks 8 & 12** | **40 (16.0%)** | **68 (26.3%)** | **2.011** | **(1.285, 3.146)** | **0.002** |
| Any Time (b) | 86 (34.4%) | 121 (46.7%) | 1.806 | (1.247, 2.614) | 0.002 |

Note: Subjects were classified as treatment failures at any visit after rescue, early withdrawal, or discontinuing use of study drug due to adverse event. If CDAI score was missing for a given time point, the subject was considered a treatment failure for that time point.
(a) The adjusted odds ratio, 95% CI, and p-value are from logistic regression adjusting for disease severity (CDAI < 330 vs. >= 330) at baseline.
(b) Any time through Week 12.
(Table above is taken from Page 125 of CSR study CD307)

A higher proportion of subjects in the natalizumab treatment group than those in the placebo group were in clinical remission at both Weeks 8 and 12. The difference was statistically significant (68 [26.3%] natalizumab vs. 40 [16.0%] placebo, p-value = 0.002.

*Exploratory Analyses in Subgroups:*

Exploratory analyses of the effects of certain demographic and baseline characteristics also were performed on this primary endpoint using the ITT Population.

*Prior Medication Use*

The table below shows subgroup analyses based on prior medication use of the proportion of subjects showing clinical response at both Weeks 8 and 12 in the ITT population.

**Table 44. Subgroup Analysis (Prior Medications) of Proportion of Subjects Showing Clinical Response at both Weeks 8 and 12 - ITT Population (Study CD307)**

| Variable Category | Placebo n/N (%) | Natalizumab n/N (%) | p-value (a) |
|---|---|---|---|
| Response at both Weeks 8 and 12 [(b)] | 81/250 (32.4%) | 124/259 (47.9%) | <0.001 |
| Prior Use of Oral Steroids | | | |
| No | 38/110 (34.5%) | 63/131 (48.1%) | 0.034 |
| Yes | 43/140 (30.7%) | 61/127 (48.0%) | 0.004 |
| Prior Use of Immunosuppressants | | | |
| No | 61/166 (36.7%) | 81/162 (50.0%) | 0.016 |
| Yes | 20/ 84 (23.8%) | 43/ 97 (44.3%) | 0.004 |
| Prior Use of Oral Steroids or Immunosuppressants | | | |
| No | 28/ 75 (37.3%) | 40/ 77 (51.9%) | 0.071 |
| Yes | 53/175 (30.3%) | 84/181 (46.4%) | 0.002 |
| Prior Use of Antibiotics | | | |
| No | 49/126 (38.9%) | 62/127 (48.8%) | 0.112 |
| Yes | 31/123 (25.2%) | 60/130 (46.2%) | <0.001 |
| Prior Use of 5-ASA | | | |
| No | 49/136 (36.0%) | 71/144 (49.3%) | 0.025 |
| Yes | 31/112 (27.7%) | 53/113 (46.9%) | 0.003 |
| Prior Use of Anti-TNF Agents | | | |
| No | 56/136 (41.2%) | 75/128 (58.6%) | 0.005 |
| Yes | 24/113 (21.2%) | 49/131 (37.4%) | 0.007 |

Note 1: Subjects were classified as treatment failures at any visit after rescue, early withdrawal, or discontinuing use of study drug due to adverse event or if the CDAI score was missing.
2: The n/N is expressed as the number of subjects with a clinical response at both Weeks 8 and 12 by the number of subjects in each subgroup analysis.
3: Countries that enrolled at least 15 subjects in either treatment group.
(a) The p-value is from logistic regression.
(b) The p-value is from logistic regression adjusting for baseline disease severity (CDAI < 330 vs. CDAI >= 330).
(Table above is taken from Page 159 of Study CD307 Clinical Study Report)

*Concomitant Medication Use*

The table below shows subgroup analyses based on concomitant medication use of the proportion of subjects showing clinical response at both Weeks 8 and 12 in the ITT population.

**Table 45. Subgroup Analysis (Baseline Medications) of Proportion of Subjects Showing Clinical Response at both Weeks 8 and 12 - ITT Population (Study CD307)**

| Variable Category | Placebo n/N (%) | Natalizumab n/N (%) | p-value (a) |
|---|---|---|---|
| Response at both Weeks 8 and 12 [(b)] | 81/250 (32.4%) | 124/259 (47.9%) | <0.001 |
| Baseline Steroids | | | |
| No | 48/156 (30.8%) | 75/148 (50.7%) | <0.001 |
| Yes | 33/ 94 (35.1%) | 49/111 (44.1%) | 0.189 |
| Baseline Immunosuppressants | | | |
| No | 49/153 (32.0%) | 81/162 (50.0%) | 0.001 |
| Yes | 32/ 97 (33.0%) | 43/ 97 (44.3%) | 0.106 |
| Baseline Steroids or Immunosuppressants | | | |
| No | 30/ 98 (30.6%) | 46/ 90 (51.1%) | 0.005 |
| Yes | 51/152 (33.6%) | 78/169 (46.2%) | 0.022 |
| Baseline Antibiotics | | | |
| No | 78/230 (33.9%) | 113/238 (47.5%) | 0.003 |
| Yes | 3/ 20 (15.0%) | 11/ 21 (52.4%) | 0.017 |
| Baseline 5-ASA Compounds | | | |
| No | 42/130 (32.3%) | 60/129 (46.5%) | 0.020 |
| Yes | 39/120 (32.5%) | 64/130 (49.2%) | 0.008 |

Note 1: Subjects were classified as treatment failures at any visit after rescue, early withdrawal, or discontinuing use of study drug due to adverse event or if the CDAI score was missing.
2: The n/N is expressed as the number of subjects with a clinical response at both Weeks 8 and 12 by the number of subjects in each subgroup analysis.
3: Countries that enrolled at least 15 subjects in either treatment group.
(a) The p-value is from logistic regression.
(b) The p-value is from logistic regression adjusting for baseline disease severity (CDAI < 330 vs. CDAI >= 330).
(Table above is taken from Page 160 of Study CD307 Clinical Study Report)

*Other Exploratory Analyses:*

Other exploratory analyses included those based on baseline CDAI, disease site, prior surgery, geographical region, country, age group, gender, baseline weight, baseline BMI, and smoking status. No signal suggesting that one subgroup benefits more than another was found except for site of disease. Subjects with ileocolonic/colonic disease appeared to have a more pronounced clinical response than subjects with disease confined to the ileum; the reason for this difference is unclear. (See table below.)

**Table 46. Subgroup Analysis (Disease Site) of Proportion of Subjects Showing Clinical Response at both Weeks 8 and 12 - ITT Population (Study CD307)**

| Variable Category | Placebo n/N (%) | Natalizumab n/N (%) | p-value (a) |
|---|---|---|---|
| Response at both Weeks 8 and 12 [(b)] | 81/250 (32.4%) | 124/259 (47.9%) | <0.001 |
| Disease Site | | | |
| Colonic | 17/ 65 (26.2%) | 36/ 69 (52.2%) | 0.002 |
| Ileocolonic | 38/120 (31.7%) | 68/134 (50.7%) | 0.002 |
| Ileum | 26/ 65 (40.0%) | 20/ 56 (35.7%) | 0.628 |

Note 1: Subjects were classified as treatment failures at any visit after rescue, early withdrawal, or discontinuing use of study drug due to adverse event or if the CDAI score was missing.
2:The n/N is expressed as the number of subjects with a clinical response at both Weeks 8 and 12 by the number of subjects in each subgroup analysis.
3:Countries that enrolled at least 15 subjects in either treatment group.
(c) The p-value is from logistic regression.
The p-value is from logistic regression adjusting for baseline disease severity (CDAI < 330 vs. CDAI >= 330).

***Summary of ENCORE (Study CD307) Efficacy Results:***

A significantly higher proportion of natalizumab-treated subjects than placebo subjects at the Weeks 8 and 12 timepoints experienced a clinical response (48% vs. 32%; $p<0.001$) and remission (26% vs. 16%; $p<0.001$).

In exploratory analyses based on prior medications, a higher proportion of natalizumab-treated subjects than placebo subjects at the Weeks 8 and 12 timepoints experienced a clinical response as follows: (1) prior steroids: 48% vs. 31% , p=0.004; (2) prior immunosuppressants: 44% vs. 24%, p=0.004 ; (3) prior steroids or immunosuppressants: 46% vs. 30% , p=0.002 ; (4) prior anti-TNFs: 37% vs. 21 % , p=0.007. Thus, the treatment difference in these subgroups appeared to be about as large as for the overall study population; however, these were not pre-specified analyses.

In exploratory analyses based on baseline medications, a higher proportion of natalizumab-treated subjects than placebo subjects at the Weeks 8 and 12 timepoints experienced a clinical response as follows: (1) baseline steroids: 44% vs. 35%, p=0.189; (2) baseline immunosuppressants: 44% vs. 33% , p=0.106; (3) baseline steroids or immunosuppressants: 46% vs. 34% , p=0.022. Thus, the treatment difference in these subgroups appeared to be slightly less than that of the overall study population; however, these were not pre-specified analyses.

**Additional Results**

***Summary of Clinical Pharmacology Findings***

The findings of the population PK in CD patients (N = 1194) from five phase II studies and three phase III studies were similar to those obtained for MS patients. In both patient populations, an (unexplained) time dependency of CL was found to reduce CL by 25% with repeated administration. Persistent (defined as positive at two or more time points separated by at least 42 days) anti-natalizumab antibodies occurring in approximately 10% of the patients were found to increase CL by 15%. Body weight, age, ALT, AST, bilirubin, and creatinine clearance had no relevant influence on the PK of natalizumab suggesting that a fixed dosing regimen is appropriate.

# Review of Safety

In addition to a discussion of deaths and serious adverse events (SAEs), this summary of safety is focused on infections, hypersensitivity events, and carcinogenicity as these were identified as non-PML potential safety concerns by the previous review of June 2006. In addition, this summary of safety is focused on categories of concomitant medication use with regard to exposure, and with regard to assessment of adverse events (AEs), particularly infections, to determine if there is a possible relationship of categories of concomitant medication use with AEs and if there is a relationship with duration of co-exposure of natalizumab and concomitant medications with AEs.

No additional safety concerns have been raised from the current review but the final review is pending and there are a number of information requests from the sponsor. Many of these information requests are related to assessment of AEs with concomitant medication use. (See Outstanding Items.)

**Progressive Multifocal Leukoencephalopathy (PML)**

Three known, confirmed cases of PML have been associated with natalizumab treatment. These cases have been reported in the literature (see Kleinschmidt-DeMasters 2005, Langer-Gould 2005, and Van Assche 2005); this briefing package includes copies of these articles. The three cases are briefly summarized below; however, the reader is referred to the articles for a comprehensive description of each case.

In addition, a detailed review of subjects (a total of 3116 patients that included 1869 MS patients and 1247 CD or rheumatoid arthritis [RA] patients) who received natalizumab during drug development took place and is described in the literature (see Yousry 2006). The review included physical examination findings, neurological examination findings, brain magnetic resonance imaging (MRI) scans, JC viral DNA analyses (plasma and CSF), and results of cases reviewed by the Independent Adjudication Committee. The objective was to identify any additional cases of PML in order to better characterize the risk associated with natalizumab administration. The procedures are briefly summarized below, but the reader is referred to the article for a comprehensive description of the detailed review. Their review suggests a risk of PML of roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9 months, and that the risk associated with longer treatment is not known.

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

This was a 46 year-old woman with RRMS that was participating in Study 1802 (the Avonex add-on study) when she died from PML. The patient's MS symptoms began in 1999 and treatment with Avonex was initiated in February 2000. The patient began receiving natalizumab 300 mg IV every 4 weeks on April 12, 2002, and received her last dose on January 18, 2005. This patient received a total of 37 natalizumab infusions. Also, this patient had three times received methylprednisolone intermittently for five days at a time March 16-20, 2002, December 15-19, 2004, and January 5-9, 2005. Symptoms of PML began in November 2004 with increased difficulty with eye-hand coordination and problems with her speech. These

symptoms progressively worsened and she was treated with methylprednisolone twice (as described above) because she was initially thought to have worsening MS. Significant MRI changes were seen in mid-December 2004; the last natalizumab treatment she received was in January 2005. This patient continued to decline; she eventually had a positive CSF JCV DNA in [redacted]. She died later that month. An autopsy was conducted which confirmed PML.

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

This was a 46 year-old man with RRMS who was also in Study 1802 (the Avonex add-on study). This patient was on Avonex and had received a total of 28 natalizumab infusions. It should be noted that 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 it had not been immediately recognized as such. This patient was noted to have atypical behavior during a visit to a doctor one month later. By mid-December, this patient had developed worsening symptoms; a repeat brain MRI revealed new lesions consistent with PML. Natalizumab was stopped in mid-December. In February, JCV DNA in serum and CSF were positive, as was a brain biopsy for PML. Avonex was stopped in February 2005. This patient continued to decline despite being treated with multiple medications, but eventually stabilized, and improved, but remains severely disabled.

***PML Case 3 (reported by Van Assche)***

This was a 60 year-old Crohn's disease patient who had been treated intermittently with natalizumab and immunosuppressive agents who died from what was initially thought to be an astrocytoma, but was retrospectively on pathology specimen determined to be PML. This patient had a significant history of immunosuppressive use. Beginning in March 2002, this patient received three doses of natalizumab given concomitantly with azothioprine. The patient then entered the placebo arm of a continuation study, and stopped natalizumab. The patient was on placebo and azothioprine until November 2002, when he had to stop the azothioprine due to pancytopenia. The patient was off of immunosuppressive agents altogether until February 2003 when the patient began open-label treatment with natalizumab infusions. In July 2003, after five consecutive natalizumab doses (total of eight doses), the patient presented with a one week history of cognitive decline. A brain MRI revealed a frontal lesion for which the patient underwent partial resection and was diagnosed with anaplastic astrocytoma, WHO Grade III. The patient was treated with steroids and anticonvulsants, but died in [redacted]. The sponsor re-evaluated the pathology slides and found that the patient actually had PML. Retrospective analysis of stored serum samples from the patient demonstrated detectable JCV DNA two months before clinical presentation. It was noted that the serum JC DNA increased in number over the time leading up to clinical presentation.

***Risk of PML with Natalizumab Administration***

Shortly after the discovery of three cases of PML in patients that had received natalizumab, the sponsor worked with the FDA to design a new study to determine the true incidence of PML associated with natalizumab administration. The main objective was to re-examine subjects

that had received natalizumab in the past, in particular the subjects who had participated in Phase 3 studies, in order to look for additional cases of PML or other atypical infections. The study included a comprehensive evaluation of patients for clinical symptoms or signs, laboratory findings, or MRI consistent with PML. In addition, plasma and CSF samples for assessment of JC viremia were collected from asymptomatic natalizumab-treated patients from past clinical trials. These samples were compared to samples taken from a control group that consisted of naïve MS patients, patients with non-inflammatory neurological diseases, and those without neurological diseases. The sponsor also collected plasma and CSF samples to determine whether serum JCV testing could be used in surveillance to predict PML occurrence.

The detailed review of possible cases of PML in patients exposed to natalizumab in clinical trials is described in the literature (Yousry 2006) and suggests a risk of PML of roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9 months, and that the risk associated with longer treatment is not known.

## Natalizumab Exposure and Description of Data Sources

### *Overall*

In the CD program, 1,639 subjects have received natalizumab with a total of 1,897 person-years of exposure. In the completed MS program, 2,321 subjects received natalizumab with a total of 3,805 person-years of exposure. Combined, there were 5,702 person-years exposure based on 3,960 individuals. Total natalizumab exposure is summarized in the table below.

**Table 47. Total Natalizumab Exposure (MS & CD Studies)**

| | No. Subjects Exposed | Person-Years of Exposure |
|---|---|---|
| MS Studies | 2321 subjects | 3805 person-yrs |
| CD Studies | 1639 subjects | 1897 person-yrs |
| Combined | 3960 subjects | 5702 person-yrs |

(Values in the table above are taken from Page 513 of the Summary of Clinical Safety.)

The table below summarizes exposure to natalizumab at a 300 mg fixed dose in the MS and CD development programs.

**Table 48. Exposure to Natalizumab at a 300 mg Fixed Dose**

| | MS | CD* | Total |
|---|---|---|---|
| Total Number Exposed | 1937 | 1378 | 3315 |
| ≥ 1/2 year | 1631 (84%) | 775 (56%) | 2406 (73%) |
| ≥ 1 year | 1240 (64%) | 599 (43%) | 1839 (55%) |
| ≥ 2 years | 1121 (58%) | 250 (18% ) | 1371 (41%) |

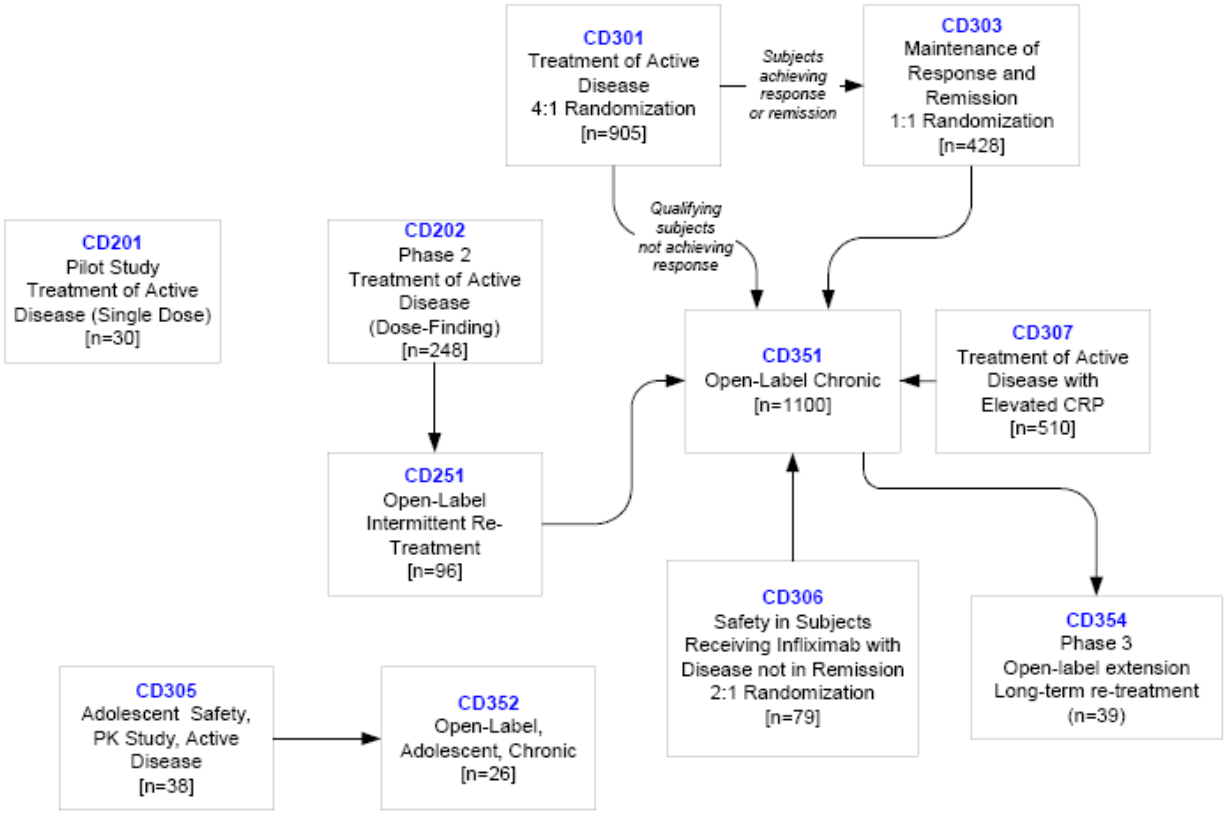
Values in the table above were taken from the Review by Drs. Susan McDermott and Alice Hughes for Natalizumab in MS (5/18/06)

Approximately 7,000 MS pts were treated while natalizumab was on the market from November 2004 to February 2005. The majority received only one or two doses.

Additional subjects exposed in clinical trials included 201 healthy volunteers, 10 subjects with Ulcerative Colitis, and 305 subjects with Rheumatoid Arthritis (RA).

### *CD Development Program*

**Figure 3. Clinical Development of Natalizumab in Crohn's Disease**




(Figure above is taken from Page 10 of the Sponsor's Clinical Overview)

Short-term Placebo-controlled Treatment Studies of Active CD

Studies CD201, CD202, CD301, and CD307 are collectively referred to as "Short-term placebo-controlled treatment studies of active CD." See table below and figure above.

**Table 49. Short-term Placebo-controlled Treatment Studies of Active CD**

| Study | Phase | Number Dosed | |
|---|---|---|---|
| | | Natalizumab | Placebo |
| CD201 | 2 | 18 | 12 |
| CD202 | 2 | 181 | 63 |
| CD301 | 3 | 723 | 181 |
| CD307 | 3 | 260 | 250 |
| Total | -- | 1182 | 506 |

Of the 1182 CD patients treated with natalizumab in short-term placebo-controlled studies of active CD, 72% (i.e., 846 CD patients) received three infusions of natalizumab, the maximum number allowed in these short-term studies.

*Concomitant Medications*

Of the 1,182 subjects who received natalizumab on the short-term placebo-controlled treatment studies, 373 (32%) received it as monotherapy, 340 (29%) received natalizumab in combination with steroids, 205 (17%) received natalizumab in combination with other immunosuppressants, and 264 (22%) received natalizumab in combination with steroids and other immunosuppressants. (See table below.)

**Table 50. Short-term Placebo-Controlled Treatment Studies of Active CD: Concomitant Medications**

| Category | Placebo (n=506 ) | Natalizumab (n=1182) |
|---|---|---|
| Monotherapy* | 154 (30%) | 373 (32%) |
| Concomitant Immunosuppressants[#] | 89 (18%) | 205 (17%) |
| Concomitant Steroids[†] | 154 (30%) | 340 (29%) |
| Concomitant Immunosuppressants and Steroids | 109 (22%) | 264 (22%) |

* Monotherapy is defined as taking neither concomitant immunosuppressants nor concomitant steroids.
[#] Concomitant immunosuppressants is defined as not taking steroids.
[†] Concomitant steroids is defined as not immunosuppressants.
(Values in table above are taken from Table 5-21 – pages 428-439 in the Summary of Clinical Safety)

Pending Information Request: The sponsor was requested to include two additional categories of concomitant medication use, "concomitant immunosuppressants with or without steroids", and "concomitant steroids with or without immunosuppressants" in summarizing proportions of subjects on categories of concomitant medications (see Outstanding Items).

Short and Long Term Dosing in CD

The short-term placebo-controlled treatment studies of active CD, the extension and maintenance studies (Studies CD251, CD303, CD351, and CD352), and the study in adolescents (CD305) are collectively referred to as "Short and Long Term Dosing in CD"; this includes all the CD studies shown in the figure above except CD354 and CD306. Of the 1,563 CD subjects enrolled in short and long-term dosing CD studies, 518 (33%) have been exposed to natalizumab for at least 52 weeks and 288 (18%) have been treated for at least 102 weeks (see table below). In this population of 1,563 natalizumab-treated subjects, 1,343 received at least one infusion with a fixed dose of 300 mg natalizumab.

*Concomitant Medications*

The table below summarizes the overall exposure duration and concomitant medication use for during specified time intervals for the short and long-term dosing in CD group.

**Table 51. Overall* Exposure Durations (CD) and Concomitant Medications for Specified Time Intervals**

| Exposure* to Natalizumab | | | | | | |
|---|---|---|---|---|---|---|
| Duration | <6 mo | ≥6 mo | ≥1 yr | ≥1.5 yr | ≥2 yr | ≥2.5 yr |
| No. Doses | ≥1 | ≥7 | ≥13 | ≥19 | ≥25 | ≥31 |
| No. Subjects | 1563 | 742 | 518 | 427 | 294 | 81 |
| Concomitant Medications[#] During Time Interval | | | | | | |
| Time Interval | 0-6 mo | 6-12mo | 1-1.5yr | 1.5-2yr | 2-2.5yr | 2.5 yr+ |
| Any[†] | 99% | 100% | 99% | 100% | 99% | 96% |
| Steroid | 64% | 54% | 53% | 51% | 52% | 52% |
| Immunosuppressant | 48% | 47% | 48% | 53% | 54% | 57% |

* Short- & Long-term Dosing in CD: All CD studies but CD354 (n=40) and CD306 (n=79) included. (Number of subjects exposed for specified time intervals determined from Table 1-7 of the Summary of Clinical Safety.)

[†] "Any" refers to all categories of concomitant medications, not only those for treatment of CD.

[#] Values in table above by concomitant medications are based on preliminary calculations based on a listing of concomitant medications (Table S3.1 in the Summary of Clinical Safety), and must be confirmed by Biogen Idec. (Information Request Letter dated June 14, 2007, has been sent to Biogen Idec.)

Pending Information Request: The sponsor was requested to provide numbers of subjects taking concomitant medications by categories of concomitant medications (see Outstanding Items). Percent of subjects with "Steroid" and "Immunosuppressant" use during time intervals in the table above were estimated by this reviewer based on a listing of concomitant medications that was not categorized by class of medication. In addition, the sponsor was requested to provide analyses of infections, serious infections, upper respiratory tract infections, and lower respiratory tract infections by number of natalizumab infusions and by category of concomitant medications as in the table above.

### *Data and Methods*

On February 28, 2005 dosing was suspended in all ongoing natalizumab clinical trials, and those trials were considered complete on March 30, 2005. Eligible subjects were subsequently assessed as part of a safety amendment to all ongoing studies, and these assessments (Dose Suspension Safety Assessments) were considered complete by 30 September 2005.

The data included in the submission from Biogen Idec are summarized in the table below.

**Table 52. Studies and Data Cut-off Dates for Safety Review**

| Studies | Data Cut-off Dates |
|---|---|
| Randomized trials of MS | All trials were completed on or before 28 February 2005, and all data were included in the Biogen Idec submission. |
| Open label trials of MS | An additional analysis of adverse events from all MS patients exposed to natalizumab was included in the Biogen Idec submission. |
| Short-term, placebo-controlled treatment studies of active CD | All trials were complete on or before 30 March 2005, and all data are included in the Biogen Idec submission. |
| Short- and long-term dosing of CD | All trials were complete on or before 30 March 2005, and all data are included in the Biogen Idec submission. |
| Dose Suspension Safety Assessment data | All safety evaluations were completed on or before 30 September 2005, and all data are included in the Biogen Idec submission. |
| Serious Adverse Events (SAE)s of interest | Selected SAEs reported after 30 March 2005 and prior to 30 June 2006 are summarized in narrative form in the Biogen Idec submission. |

(Information in the table above was summarized by this reviewer from page 74 of the Sponsor's Summary of Clinical Safety.)

Analysis of safety was conducted by conventional parameters. Another aspect of the safety evaluation was to highlight potential mechanism-based toxicity or those adverse events that may relate to the protein composition of the drug. These included the following:

- infusion reactions
- hypersensitivity-like reactions
- the risk of infection
- the risk of malignancy
- possible effects of anti-natalizumab antibodies on the safety profile of natalizumab
- potential effects on hematopoiesis

For the placebo-controlled MS studies, the incidence of adverse events has been presented based on subjects' exposure until the end of a subject's participation in a study.

For all studies in Crohn's disease, the time of follow-up has been truncated at 12 weeks following the last or previous dose or at the time of study withdrawal or study completion (March 30, 2005), whichever was earlier, for two reasons: (1) Many subjects with Crohn's disease in short-term placebo-controlled studies may not have received any drug for long periods prior to entering an extension or continuation study; (2) The mean elimination half-life of natalizumab is approximately 8-10 days and so drug is expected to be cleared within 12 weeks after a dose. This 12-week rule does not apply to serious adverse events.

All treatment-emergent serious adverse events and selected serious adverse events collected through June 30, 2006, are presented. In incidence tables, a subject who had the same event more than once is counted only once in the incidence for that event. All adverse events recorded on subjects' case report forms (CRFs) were coded using the Medical Dictionary of Regulatory Activities (MedDRA), Version 6.0.

Since a significant number of CD subjects enrolled in continuation or extension studies, their dosing experience can take the form of:

1. placebo alone (CD201, CD202, CD301, CD301 to CD303 placebo only, CD307),
2. natalizumab alone (CD201, CD202, CD202 to CD251 and/or CD351, CD301, CD301 to CD303 and/or CD351 natalizumab only, CD307, CD307 to CD351, CD305, CD305 to CD352),
3. placebo then natalizumab (CD202 placebo to CD251 and/or CD351, CD301 placebo to CD303 natalizumab and/or CD351, CD301 and CD303 placebo to CD351 natalizumab, CD307 placebo to CD351 natalizumab),
4. natalizumab then placebo (CD301 natalizumab to CD303 placebo),
5. natalizumab then placebo then natalizumab (CD301 natalizumab to CD303 placebo to CD351 natalizumab).

Therefore, many subjects (categories 3 to 5) have experience on both natalizumab and placebo. In order to account for prolonged periods on placebo and to elicit potential delayed effects from natalizumab, the classification outlined was adopted for analyzing SAEs. These categories are mutually exclusive so a subject can appear in one and only one category. In the tables, however, categories 4 and 5 have been combined.

## Demographic and Baseline Characteristics

### *Short-term Placebo-controlled Studies in CD*

In the short-term placebo-controlled treatment studies of active CD (see table below), treatment groups were well matched with respect to demographic and baseline disease characteristics. In the natalizumab group, ages ranged from 18 to 84 years (median 36) with 2% aged 65 and over, 57% were women, and 95% were white. Seven percent of the natalizumab group weighed less than 50 kg, and 6% weighed more than 100 kg. Time since diagnosis ranged from those recently diagnosed to those diagnosed 56 years prior to study entry (median 7.8 years). Baseline CDAI score ranged from 122 to 496 (median 290).

**Table 53. Short-Term Placebo-Controlled Treatment Studies of Active CD: Demographic and Baseline Disease Characteristics**

| | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 506 (100%) | 1182 (100%) |
| Age (years) | | |
| Median | 35 | 36 |
| Min.,Max. | 18, 83 | 18, 84 |
| Gender | | |
| Male | 210 (42%) | 504 (43%) |
| Female | 296 (58%) | 678 (57%) |
| Race | | |
| White | 481 (95%) | 1123 (95%) |
| Black | 10 (2%) | 26 (2%) |
| Other | 15 (3%) | 33 (3%) |
| Body Weight (kg) | | |
| Median | 68.2 | 68 |
| Min.,Max. | 36.0, 151.0 | 38.0, 180.2 |
| Time Since Diagnosis | | |
| Median (yrs) | 6.7 | 7.8 |
| Min.(yrs), Max.(yrs) | 0, 45 | 0, 56 |
| Baseline CDAI | | |
| <220 | 25 (5%) | 49 (4%) |
| >=220, <330 | 323 (64%) | 780 (66%) |
| >=330, <=450 | 144 (28%) | 331 (28%) |
| >450 | 6 (1%) | 13 (1%) |
| Median | 286.5 | 290 |
| Min.,Max. | 149, 518 | 122, 496 |

NOTE: Numbers in parentheses are percentages
(Values in table above are taken from Pages 40-41 of the Summary of Clinical Safety.)

### *Short and Long-term Dosing in CD*

The demographics and baseline characteristics of the CD population who participated in treatment and/or extension studies with increasing exposure did not vary significantly from that of the short-term placebo controlled studies (see table below).

Table 54. **Short- and Long-Term Dosing in CD: Demographic and Baseline Disease Characteristics**

| | Subjects Who Received 1 or More Infusions | Subjects Who Received 7 or More Infusions | Subjects Who Received 13 or More Infusions | Subjects Who Received 19 or More Infusions | Subjects Who Received 25 or More Infusions | Subjects Who Received 31 or More Infusions |
|---|---|---|---|---|---|---|
| No. of Subjects Dosed | 1563 (100%) | 681 (100%) | 509 (100%) | 427 (100%) | 294 (100%) | 81 (100%) |
| Age (years) | | | | | | |
| Median | 35 | 36 | 36 | 35 | 35 | 32 |
| Min.,Max. | 11, 84 | 12, 76 | 12, 75 | 12, 75 | 12, 75 | 14, 74 |
| Gender | | | | | | |
| Male | 678 (43%) | 318 (47%) | 236 (46%) | 197 (46%) | 138 (47%) | 40 (49%) |
| Female | 885 (57%) | 363 (53%) | 273 (54%) | 230 (54%) | 156 (53%) | 41 (51%) |
| Race | | | | | | |
| White | 1478 (95%) | 640 (94%) | 476 (94%) | 396 (93%) | 276 (94%) | 75 (93%) |
| Black | 38 (2%) | 21 (3%) | 15 (3%) | 15 (4%) | 8 (3%) | 4 (5%) |
| Other | 47 (3%) | 20 (3%) | 18 (4%) | 16 (4%) | 10 (3%) | 2 (2%) |
| Body Weight (kg) | | | | | | |
| Median | 67.9 | 69.1 | 69 | 69 | 69 | 69 |
| Min.,Max. | 29.2, 180.2 | 29.2, 167.8 | 29.2, 167.8 | 29.2, 167.8 | 29.2, 167.8 | 38.0, 121.3 |
| Time Since Diagnosis | | | | | | |
| Median | 87 | 94 | 86 | 83.5 | 82 | 82 |
| Min.,Max. | 0, 672 | 0, 480 | 0, 456 | 0, 456 | 1, 456 | 4, 362 |
| Baseline CDAI (a) | | | | | | |
| <220 | 63 (4%) | 26 (4%) | 19 (4%) | 13 (3%) | 10 (3%) | 2 (2%) |
| >=220, <330 | 1007 (64%) | 444 (65%) | 341 (67%) | 290 (68%) | 205 (70%) | 56 (69%) |
| >=330, <=450 | 426 (27%) | 176 (26%) | 120 (24%) | 100 (23%) | 65 (22%) | 20 (25%) |
| >450 | 17 (1%) | 6 (<1%) | 5 (<1%) | 3 (<1%) | 2 (<1%) | 0 |
| Median | 289 | 289 | 288 | 288 | 288.5 | 283.5 |
| Min.,Max. | 122, 518 | 171, 496 | 171, 496 | 171, 468 | 171, 468 | 202, 430 |

(a) CD305 subjects were not available for presentation and the percentages were calculated based on the available data.
NOTE: Numbers in parentheses are percentages
(Values in table above are taken from Pages 42-44 of the Summary of Clinical Safety.)

## Deaths

### *Clinical Studies*

There have been 18 deaths in the natalizumab development program. Fourteen of these deaths occurred in natalizumab-treated patients and four occurred in placebo-treated patients. Deaths are summarized below by study populations and by whether subjects were treated with natalizumab or placebo. Of the natalizumab-treated patients, there were 6 deaths in MS studies, 6 in CD studies, and 2 in RA studies.

Deaths in Placebo-controlled Studies

In CD placebo-controlled studies, there were two deaths in the natalizumab group (2/1182; 0.17%) and zero deaths in the placebo group. There were 4 additional deaths in CD extension studies. In MS placebo-controlled studies, there were two deaths among patients who received natalizumab (2/1617; 0.12%) and three deaths among patients who received placebo (3/1135; 0.26%). There were four additional deaths among patients who received natalizumab in open-label MS 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. Deaths in MS and CD Placebo-Controlled Studies are summarized in the table below.

**Table 55. Deaths in MS and CD Placebo-Controlled Studies**

| MS | | CD | |
|---|---|---|---|
| Placebo | Natalizumab | Placebo | Natalizumab |
| 0.26% (3/1135) | 0.12% (2/1617) | 0 (0/506) | 0.17% (2/1182) |

* Values in table taken from BLA Review 125104/15 Alice Hughes, M.D. and Susan S. McDermott, M.D. (5/18/06); values same as no new deaths in placebo-controlled studies as per submission.

Deaths were balanced in the MS placebo-controlled studies between patients who received placebo and patients who received natalizumab. In CD placebo-controlled studies, deaths were more frequent in natalizumab-treated patients compared to placebo-treated patients.

Deaths in Natalizumab-treated Subjects

Regarding natalizumab-treated patients that died, the causes of death and a brief description are shown below. Six died of infections, one of a malignancy, and seven of other causes.

Infections

(1) PML: 46 year old female (MS study 1808) died of PML after 37 natalizumab infusions. [discussed in Progressive Multifocal Leukoencephalopathy (PML) section]
(2) PML: 60 year old male (CD351) died of PML after receiving eight natalizumab infusions. [discussed in Progressive Multifocal Leukoencephalopathy (PML) section]
(3) Multi-organ system failure: 73 year old male (CD351) died of multi-organ system failure after duodenal ulcer perforation requiring laparotomy and a hospital course complicated by peritonitis and pulmonary aspergillosis; he had received a total of 10 natalizumab infusions.
(4) Respiratory failure: 53 year old female (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.
(5) Multi-organ system failure: 69 year old male (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 infusions of natalizumab.

(6) Multi-organ system failure: 49 year old female (CD301) with a history of nephrotic syndrome pre-dating natalizumab treatment died of sepsis and multi-organ system failure following admission to the hospital with a severe CD exacerbation requiring hemicolectomy 20 days after her third natalizumab infusion.

Malignancies

(1) Malignant melanoma: 38 year old male (MS study 1801) died of metastatic malignant melanoma approximately two years after receiving five natalizumab infusions. He had noticed the lesion on his left shoulder that was ultimately diagnosed as malignant melanoma at the time of his first or second natalizumab infusion.

Other

(1) Alcohol poisoning: 49 year old female (MS study 1801) with a history of anxiety died as a result of alcohol poisoning (autopsy-confirmed) 23 days after her 25$^{th}$ natalizumab infusion.
(2) Suicide: 27 year old male (MS Study 1808) committed suicide 23 weeks after his 31$^{st}$ natalizumab infusion.
(3) Acute arrhythmia/seizure: 51 year old female (MS study 1808 Dose Suspension Safety Assessment Period) died of acute arrhythmia/seizure 6 months after 31 natalizumab infusions. Concomitant medications included Baclofen, Avonex, Ditropan, amitryptiline, and citalopram. Toxicology was unremarkable except for elevated level of citalopram.
(4) MS progression: 5 year old female (compassionate-use protocol 1804) died of respiratory distress secondary to progression of MS approximately 5 months after her tenth natalizumab infusion.
(5) Carbon dioxide asphyxiation: 42 year old male (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).
(6) Acute MI: 67 year old male (CD351) died of acute myocardial infarction complicated by left ventricular rupture, hemopericardium, cardiac tamponade, and cardiogenic shock 2 months after his 22$^{nd}$ natalizumab infusion.
(7) Rheumatoid pulmonary disease: 59 year old female (RA251) died of end-stage rheumatoid pulmonary disease (per autopsy) one month after her first natalizumab infusion.

***Post-marketing Reports***

Ten deaths have been reported in the post-marketing setting (through the efficacy supplement cut-off date of March 31, 2006) among the estimated 7000 patients who are estimated to have received natalizumab between its approval (November 23, 2004) and market suspension (February 28, 2005).

Deaths – Brief Description

The causes of death and a brief description are shown below. Three died of infections, one of a malignancy, and six of other or unknown causes.

Infections

(1) Herpes encephalitis: 54-year-old male with a 20-year history of MS developed Herpes encephailits after one dose of natalizumab.

(2) Urinary tract infection: 52-year old female with 15 year history of urinary tract infections was hospitalized two weeks after her first natalizumab infusion.
(3) Multiple sclerosis relapse : 26y yr old female progression of MS (patient had an aggressive form of MS); proximate cause of death was a GI infection followed by sepsis and pneumonia

Malignancies

(1) Ovarian cancer: 68 year old female on Avonex® for approximately four years was hospitalized and subsequently diagnosed with ovarian cancer one month after her first dose of natalizumab.

Other/unknown

(1) Suicide: female age not known, number of doses not known.
(2) Not known (Pancytopenia or car accident?): 50+ female with 15 year history of MS and congenital hypogammaglobulinemia and panyctopenia dies after ambulance crashed on way home from the hospital.
(3) Amyotrophic lateral sclerosis: female age not known – progression of amyotprophic lateral sclerosis (ALS); subject had history of ALS and MS. (1 dose)
(4) Paralysis: 66 year old female number of doses not stated – reported by consumer (patients sister) – patient had been previously paralyzed from breast down and the paralysis spread up her neck and down her arms and fingers.
(5) Not known (myocardial infarction or stroke): 49 year old female after one dose (reported by consumer)
(6) Cause of death not specified: 28 year old female – number of doses not known. No details provided. (reported by consumer)

***Summary of Deaths***

Regarding deaths in five natalizumab-treated patients due to infections in the clinical trial setting (the two cases of PML, the case of E.Coli sepsis, the case of pulmonary aspergillosis, and the case of pneumocystis carinii pulmonary infections) and the three cases in the postmarketing setting (the cases of Herpes encephalitis, urinary tract infection, and multiple sclerosis relapse) are concerning for a possible association with natalizumab. However, for the case of the patient that had a severe CD exacerbation requiring hemicoloectomy, the sepsis was almost definitely due to fecal peritonitis and an association with natalizumab appears unlikely.

Regarding the deaths due to malignancies, a causal role for natalizumab is highly doubtful in each of the cases. For the metastatic malignant melanoma patient, a causal role is unlikely because the patient had noticed the lesion at the time of the first or second study drug infusion. Similarly the case of ovarian cancer was diagnosed just one month after the patient's first natalizumab infusion, and a causal role for natalizumab is unlikely given the short duration of exposure.

A possible association between natalizumab and mood disorders is raised by the death due to alcohol poisoning and the death due to suicide in clinical trials and by the death in the post-marketing setting due to suicide.

Thus, potential safety signals raised by a review of deaths in the natalizumab development program and in the post-marketing setting are for infections and mood disorders.

## Serious Adverse Events

### *Short-term Placebo-controlled Studies in CD*

As shown in the table below, 14.9% of natalizumab-treated subjects and 14.0% of those who received placebo experienced at least one serious adverse event in a short-term placebo controlled treatment study of active CD. The most common SAEs were gastrointestinal in nature (9.8% natalizumab *vs.* 9.9% placebo), the most common being Crohn's disease (5.9% natalizumab *vs.* 8.7% placebo). Serious infections and infestations were seen in 2.4% of both natalizumab-treated subjects and those who received placebo, the most common being perianal abscess (0.6% in both natalizumab and placebo treated subjects). All other SAEs occurred at an incidence less than 1.0%, and many events were experienced by only one subject. (See also table in Appendix 5.)

SAEs with ≥1% incidence in natalizumab group in short-term placebo-controlled studies in CD are summarized in the table below.

**Table 56. Short-term Placebo-controlled Studies in CD (SAEs with ≥1% incidence in natalizumab group)**

| Serious Adverse Event | Placebo (n=506) | Natalizumab (n=1182) |
|---|---|---|
| All SAEs | 71 (14.0%) | 176 (14.9%) |
| Gastrointestinal disorders* | 50 (9.9%) | 116 (9.7%) |
| Crohn's Disease* | 44 (8.7%) | 70 (5.9%) |
| All serious infections and infestations | 12 (2.4%) | 28 (2.4%) |

* Crohn's disease (exacerbation) accounted for most of the gastrointestinal disorders.
Table above summarized from pages 91-96 of the sponsor's Summary of Clinical Safety.

The incidence of serious infections and infestations was similar in placebo- and natalizumab-treated patients (2.4% in each group).

A table of SAEs occurring in ≥ 0.2 % of natalizumab-treated subjects and more frequently than in placebo-treated subjects in CD placebo-controlled studies is provided in Appendix 5.

## Concomitant Medications

The tables below show the incidence of SAEs by categories of concomitant medications.

**Table 57. SAEs in Placebo Group of Short-term Placebo-Controlled Studies of CD (Monotherapy versus Immunosuppressants and/or Steroids): Incidence > 0.2% in Total**

| Placebo treated group | | | | | |
|---|---|---|---|---|---|
| SAE – Preferred Term | Total | Mono-therapy* | Concomitant Immunosuppressants[#] | Concomitant Steroids[†] | Concomitant Immunosuppressants and Steroids |
| No. Subjects Dosed | 506 (100%) | 154 (100%) | 89 (100%) | 154 (100%) | 109 (100%) |
| No. Subjects with a SAE | 71 (14.0%) | 13 (8.4%) | 6 (6.7%) | 24 (15.6%) | 28 (25.7%) |
| Crohn's disease | 44 (8.7%) | 4 (2.6%) | 1 (1.1%) | 19 (12.3%) | 20 (18.3%) |
| Small intestinal obstruction NOS | 2 (0.4%) | 0 | 0 | 1 (0.6%) | 1 (0.9%) |
| Abdominal pain NOS | 2 (0.4%) | 1 (0.6%) | 0 | 1 (0.6%) | 0 |
| Intestinal obstruction NOS | 3 (0.6%) | 1 (0.6%) | 0 | 1 (0.6%) | 1 (0.9%) |
| Perianal abscess | 3 (0.6%) | 1 (0.6%) | 0 | 1 (0.6%) | 1 (0.9%) |
| Pregnancy NOS | 2 (0.4%) | 0 | 2 (2.2%) | 0 | 0 |
| Pyrexia | 2 (0.4%) | 1 (0.6%) | 0 | 1 (0.6%) | 0 |
| Depression | 3 (0.6%) | 2 (1.3%) | 0 | 0 | 1 (0.9%) |
| Dehydration | 2 (0.4%) | 0 | 0 | 0 | 2 (1.8%) |
| Abortion spontaneous NOS | 2 (0.4%) | 0 | 1 (1.1%) | 1 (0.6%) | 0 |
| Rectal abscess | 2 (0.4%) | 0 | 0 | 1 (0.6%) | 1 (0.9%) |

* Monotherapy is defined as taking neither concomitant immunosuppressants nor concomitant steroids.
[#] Concomitant immunosuppressants is defined as not taking steroids.
[†] Concomitant steroids is defined as not immunosuppressants.
(Values in table above are taken from Table 5-21 – pages 428-439 in the Summary of Clinical Safety)

**Table 58. SAEs in Natalizumab Group of Short-term Placebo-Controlled Studies of CD (Monotherapy versus Immunosuppressants and/or Steroids): Incidence > 0.2% in Total**

| Natalizumab treated group | | | | | |
|---|---|---|---|---|---|
| SAE – Preferred Term | Total | Mono-therapy* | Concomitant Immunosuppressants[#] | Concomitant Steroids[†] | Concomitant Immunosuppressants and Steroids |
| No. Subjects Dosed | 1182 (100%) | 373 (100%) | 205 (100%) | 340 (100%) | 264 (100%) |
| No. Subjects with a SAE | 176 (14.9%) | 32 (8.6%) | 28 (13.7%) | 54 (15.9%) | 62 (23.5%) |
| Crohn's disease | 70 (5.9%) | 7 (1.9%) | 4 (2.0%) | 26 (7.6%) | 33 (12.5%) |
| Small intestinal obstruction NOS | 9 (0.8%) | 2 (0.5%) | 1 (0.5%) | 4 (1.2%) | 2 (0.8%) |
| Abdominal pain NOS | 8 (0.7%) | 1 (0.3%) | 0 | 3 (0.9%) | 4 (1.5%) |
| Intestinal obstruction NOS | 8 (0.7%) | 0 | 5 (2.4%) | 1 (0.3%) | 2 (0.8%) |
| Perianal abscess | 7 (0.6%) | 0 | 3 (1.5%) | 4 (1.2%) | 0 |
| Intestinal stenosis NOS | 6 (0.5%) | 0 | 2 (1.0%) | 2 (0.6%) | 2 (0.8%) |
| Anaemia NOS | 4 (0.3%) | 0 | 0 | 1 (0.3%) | 3 (1.1%) |
| Cholelithiasis | 4 (0.3%) | 2 (0.5%) | 0 | 1 (0.3%) | 1 (0.4%) |
| Pregnancy NOS | 4 (0.3%) | 2 (0.5%) | 1 (0.5%) | 0 | 1 (0.4%) |
| Pyrexia | 4 (0.3%) | 0 | 1 (0.5%) | 1 (0.3%) | 2 (0.8%) |
| Vomiting NOS | 4 (0.3%) | 2 (0.5%) | 0 | 0 | 2 (0.8%) |
| Abdominal abscess NOS | 3 (0.3%) | 1 (0.3%) | 1 (0.5%) | 1 (0.3%) | 0 |
| Abscess NOS | 1 (<0.1%) | 1 (0.3%) | 0 | 0 | 0 |
| Abdominal adhesions | 3 (0.3%) | 0 | 1 (0.5%) | 0 | 2 (0.8%) |
| Arthralgia | 3 (0.3%) | 0 | 0 | 1 (0.3%) | 2 (0.8%) |
| Hypersensitivity NOS | 3 (0.3%) | 0 | 0 | 1 (0.3%) | 2 (0.8%) |
| Intestinal fistula | 3 (0.3%) | 1 (0.3%) | 1 (0.5%) | 1 (0.3%) | 0 |

* Monotherapy is defined as taking neither concomitant immunosuppressants nor concomitant steroids.
[#] Concomitant immunosuppressants is defined as not taking steroids.
[†] Concomitant steroids is defined as not immunosuppressants.
(Values in table above are taken from Table 5-21 – pages 428-439 in the Summary of Clinical Safety)

Pending Information Request: The sponsor was requested to include two additional categories of concomitant medication use, "concomitant immunosuppressants with or without steroids", and "concomitant steroids with or without immunosuppressants" in analyzing SAEs on categories of concomitant medications to further clarify this issue (see Outstanding Items).

Based on the incidence of SAEs by categories of concomitant medications provided, the incidences of overall SAEs comparing natalizumab group and placebo group were similar across categories of concomitant medications except for higher incidence of SAEs in the natalizumab group with concomitant immunosuppressants than the placebo group (13.7% [28/205] versus 6.7% [6/89]). The reason for this difference is not clear. Additional information requested regarding SAE incidence by categories of concomitant medications may help to clarify this.

The most common SAE in both the natalizumab and placebo groups was Crohn's disease; the incidence appeared to be highest with concomitant immunosuppressants and steroids (18.3%

placebo and 12.5% natalizumab). The higher incidence of Crohn's disease in subjects receiving either natalizumab or placebo in conjunction with both immunosuppressants and steroids may reflect a more severe patient population (e.g., requiring concomitant immunosuppressants and steroids) than the other subgroups.

***Short and Long-term Dosing in CD***

The individuals in the short and long-term dosing in CD population consisted of 163 subjects who received placebo only, 1,041 who received natalizumab only, 343 who received placebo then natalizumab, and 179 who received natalizumab followed by placebo, of whom 153 restarted treatment with natalizumab. (See Data and Methods section.)

SAEs occurred in 28.1% and 23.3% of the natalizumab only and placebo only groups, respectively. The most common SAE was gastrointestinal disorders with 18.2% of subjects who received natalizumab only versus 16.0% of those who received placebo only. The most common gastrointestinal event was Crohn's disease: 10.8% of those who received natalizumab only versus 12.9% of those who received placebo only.

In the cohort who received placebo then natalizumab, 6.7% had serious events of CD while receiving placebo and 5.2% while receiving natalizumab.

***Placebo-controlled Studies of MS***

In MS placebo-controlled studies, the overall incidence of SAEs was higher in the placebo group than the natalizumab group. Of the 1,617 natalizumab-treated subjects, 251 (15.5%) experienced at least one SAE; of the 1,135 subjects who received placebo, 214 (18.9%) experienced at least one serious event.

The most common SAEs were nervous system disorders (5.9% natalizumab vs. 10.2% placebo) with MS relapse contributing significantly to this incidence (4.7% natalizumab vs. 9.0% placebo). The incidence of serious infections and infestations was similar in each treatment group (2.4% natalizumab vs. 2.2% placebo) with appendicitis (0.4 vs. 0.3%) and urinary tract infection NOS (0.4 vs. 0.2%) being the most common. Injuries and poisoning and procedural complications were seen slightly more often in the natalizumab group than in placebo (1.7 vs. 0.9%), as were gastrointestinal disorders (1.2 vs. 0.8%). All other SAEs in natalizumab-treated subjects occurred at an incidence less than 1.0%. (See the table below and the table in Appendix 4.)

**Table 59. SAEs in Placebo-controlled Studies of MS with ≥1% Incidence in Natalizumab group**

| Serious Adverse Event | Placebo (n=1135)<br>N (% ) | Natalizumab (n=1617)<br>% (No.) |
|---|---|---|
| All | 214 (18.9% ) | 251 (15.5%) |
| Infections and infestations | 25 (2.2%) | 39 (2.4%) |
| Nervous system disorders | 116 (10.2% ) | 95 (5.9%) |
| Multiple Sclerosis Relapse | 102 (9.0%) | 76 (4.7%) |
| Injury, poisoning and procedural complications | 10 (0.9%)) | 28 (1.7%) |
| Gastrointestinal disorders | 9 (0.8%) | 19 (1.2%) |

(Values in the table above are taken from Pages 82-89 of the Summary of Clinical Safety.)

***Summary of SAEs***

In short-term placebo-controlled CD studies, the overall incidence of SAEs was higher in the natalizumab group than the placebo group (natalizumab 14.9% vs. placebo 14.0%), whereas in MS placebo-controlled studies, the overall incidence of SAEs was higher in the placebo group than the natalizumab group (placebo 18.9% vs. natalizumab 15.5%).

The most common SAE in natalizumab and placebo groups was CD, and was highest with concomitant immunosuppressants and steroids, and may reflect a more severe patient population (e.g., requiring concomitant immunosuppressants and steroids) than the other subgroups.

Serious infections and infestations were in the same proportion of natalizumab and placebo group subjects (2.4% in both placebo and natalizumab) in short-term placebo-controlled CD studies, but were slightly higher in the natalizumab group than the placebo group (Natalizumab 2.4% vs. Placebo 2.2%) in placebo-controlled MS studies..

Other SAEs with high frequency in the short term placebo controlled CD studies and the short term placebo controlled MS studies were mainly gastrointestinal disorders and nervous system disorders, respectively. Each of these were more common in the respective placebo groups and was most frequently due to MS relapse for the MS studies, and Crohn's disease exacerbation for the CD studies.

**Common AEs**

In short-term placebo-controlled CD studies, 87.4% (1033) of natalizumab-treated subjects and 85.6% (433) of placebo-treated subjects experienced at least one adverse event. The most common adverse events experienced by natalizumab-treated subjects were the following:

- Headache: 30.8% of natalizumab group vs. 24.3% of placebo group
- Nausea: 16.2% of natalizumab group vs. 15.0% of placebo group
- Nasopharyngitis: 13.4% of natalizumab group vs. 9.7% of placebo group

In placebo-controlled MS studies, 96.0% (1552) of natalizumab-treated subjects and 97.3% of placebo-treated subjects experienced at least one adverse event. The most common adverse events experienced by natalizumab-treated subjects were the following:

- Headache: 39.2% of natalizumab group vs. 38.4% of placebo group
- Multiple sclerosis relapse: 32.1% of natalizumab group vs. 54.8% of placebo group
- Nasopharyngitis: 29.5% of natalizumab group vs. 30.0% of placebo group
- Fatigue: 27.5% of natalizumab group vs. 26.9% of placebo group.

Review of all adverse events experienced by at least 1% of subjects in short-term CD placebo-controlled studies and in MS placebo-controlled studies did not identify new safety signals that were not apparent during the BLA review that preceded natalizumab's return to market in June 2006 or that are not discussed elsewhere in this safety review.

**AEs Associated with Dropouts**

*Short-term Placebo-controlled CD Studies*

In short-term placebo-controlled studies of active CD, AEs leading to discontinuation occurred in 9.1% (108) of subjects in the natalizumab group and in 11.3% (57) of subjects in the placebo group. The most frequently reported AE leading to discontinuation of natalizumab [3.7% (44)] was Crohn's disease; however, subjects in the placebo group discontinued study drug due to this AE more frequently [7.9% (40)].

The other events most frequently leading to discontinuation that led to discontinuation more frequently in natalizumab-treated subjects than in placebo-treated subjects were the following: urticaria (discontinuation of 0.8% of natalizumab group versus 0.2% of placebo group), dyspnea (0.3% versus 0), flushing (0.3% versus 0), nausea (0.3% versus 0.2%), pruritus (0.3% versus 0.2%), hypersensitivity (0.3% versus 0), infusion-related reaction (0.3% versus 0), rigors (0.3% versus 0), and tremor (0.3% versus 0). Other AEs each led to discontinuation of natalizumab in two subjects or less.

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

*Placebo-controlled MS Studies*

In placebo-controlled MS studies, AEs leading to discontinuation occurred in 5.8% (93) of subjects receiving natalizumab and in 4.8% (54) of subjects receiving placebo. The most frequently reported adverse event leading to discontinuation of natalizumab was urticaria. Seventeen subjects (1.1%) discontinued natalizumab due to urticaria compared to four (0.4%) of placebo-treated subjects.

In natalizumab-treated subjects, the other events most frequently leading to discontinuation were hypersensitivity (led to discontinuation in 0.4% of natalizumab group vs. 0 in placebo group), nausea (0.3% vs. 0), and anaphylactic reaction (0.2% vs. 0). Other adverse events that led to discontinuation of natalizumab each occurred in three or less subjects. Subjects were required by study protocol to discontinue study drug if they developed urticaria, anaphylaxis, angioedema, serum sickness, or biopsy-proven vasculitis.

**Laboratory Findings, Vital Signs, and Electrocardiograms (ECGs)**

*Hematology*

An increase in circulating leukocytes, except neutrophils, is a known pharmacodynamic effect of natalizumab. Such an increase was seen in subjects taking natalizumab; this appears to be reversible with stopping of the medication. The sponsor also included information regarding the potential for natalizumab to decrease red blood cells and cause anemia; although found to occur in the natalizumab group, it does not appear to be a significant safety issue as the effect on red cells appears to be reversible. With regard to platelet counts or prothrombin, no significant associated safety signals were identified.

*Other Laboratory Data*
No new safety signals were identified upon review of other laboratory data that included urinalysis, liver functions tests, kidney function tests, electrolytes, and other blood chemistries.

**Special Safety Issues by Organ or Syndrome**

Non-PML safety issues identified in the review by the Division of Neurology Products (Review by Dr.'s Susan McDermott and Alice Hughes for Natalizumab in MS; 5/18/06) and presented in the Advisory Committee (March 7-8, 2006) are summarized below. No new safety issues were identified.

Each of the issues below will be discussed.

1. Infections other than PML: concern of Herpes infections, lower respiratory tract infections (especially atypical pathogens), viral meningitides
2. Immunogenicity: approximately 10%
3. Hypersensitivity: associated with immunogenicity
4. Carcinogenicity: no clear increase in risk; in placebo-controlled studies, overall malignancies balanced in MS, but higher in CD

***Infections Other Than PML***

Short-term Placebo-Controlled CD Studies

*Infections*
In short-term placebo-controlled trials in CD, the rates of infection were somewhat higher in natalizumab-treated CD subjects compared to subjects receiving placebo (i.e., 1.67 per person-year in the natalizumab-treated group compared to 1.45 per person-year in placebo-treated subjects). Also, the overall incidence of infection was somewhat higher in natalizumab-treated CD subjects, 40.4%, compared to subjects receiving placebo, 36.2%. The overall incidence of upper respiratory tract infection and pneumonia was somewhat higher in natalizumab-treated subjects (natalizumab *vs.* placebo: 26.6 *vs.* 21.5% upper respiratory tract infection and 0.3 vs. 0.2% pneumonia) while the incidence of lower respiratory tract infection was similar (3.1 *vs.* 3.4%. (See tables below.)

**Table 60. Short-Term Placebo-Controlled Treatment Studies of Active CD: Infections with an Incidence of ≥1%**

| | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 506 (100%) | 1182 (100%) |
| Number of Subjects with an Infection | 183 (36.2%) | 477 (40.4%) |
| Event | | |
| Nasopharyngitis | 50 (9.9%) | 158 (13.4%) |
| Upper respiratory tract infection NOS | 19 (3.8%) | 50 (4.2%) |
| Influenza | 23 (4.5%) | 46 (3.9%) |
| Sinusitis NOS | 12 (2.4%) | 37 (3.1%) |
| Viral infection NOS | 8 (1.6%) | 34 (2.9%) |
| Urinary tract infection NOS | 7 (1.4%) | 31 (2.6%) |
| Gastroenteritis NOS | 10 (2.0%) | 26 (2.2%) |
| Pharyngitis viral NOS | 4 (0.8%) | 23 (1.9%) |
| Herpes simplex | 4 (0.8%) | 15 (1.3%) |
| Perianal abscess | 4 (0.8%) | 13 (1.1%) |
| Upper respiratory tract infection viral NOS | 3 (0.6%) | 13 (1.1%) |
| Gastroenteritis viral NOS | 7 (1.4%) | 10 (0.8%) |
| Bronchitis NOS | 10 (2.0%) | 9 (0.8%) |
| Oral candidiasis | 6 (1.2%) | 4 (0.3%) |

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.
(Values in the table above are taken from Page 192 of the Summary of Clinical Safety.)

**Table 61. Short-term Placebo-controlled Treatment Studies of Active CD: Incidence of Upper Respiratory Tract Infections**

| Preferred Term | Placebo | Natalizumab |
|---|---|---|
| No. Subjects Dosed | 506 (100%) | 1182 (100%) |
| No. Subjects with an Upper Respiratory Tract Infection | 109 (21.5%) | 315 (26.6%) |
| Event | | |
| Nasopharyngitis | 50 (9.9%) | 158 (13.4%) |
| Upper respiratory tract | 19 (3.8%) | 50 (4.2%) |
| infection NOS | | |
| Influenza | 23 (4.5%) | 46 (3.9%) |
| Sinusitis NOS | 12 (2.4%) | 37 (3.1%) |
| Pharyngitis viral NOS | 4 (0.8%) | 23 (1.9%) |
| Upper respiratory tract | 3 (0.6%) | 13 (1.1%) |
| infection viral NOS | | |
| Pharyngitis | 2 (0.4%) | 8 (0.7%) |
| Tonsillitis | 0 | 7 (0.6%) |
| Rhinitis infective | 0 | 4 (0.3%) |
| Laryngitis viral NOS | 1 (0.2%) | 3 (0.3%) |
| Pharyngitis streptococcal | 1 (0.2%) | 1 (<0.1%) |
| Rhinolaryngitis | 0 | 1 (<0.1%) |
| Sinusitis acute NOS | 2 (0.4%) | 1 (<0.1%) |

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.
(Values in the table above are taken from Page 3414 of the Summary of Clinical Safety Source Tables.)

**Table 62. Short-term Placebo-controlled Treatment Studies of Active CD: Incidence of Pneumonia**

| Preferred Term | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 506 (100.0%) | 1182 (100.0%) |
| Number of Subjects with an Event | 1 (0.2%) | 6 (0.5%) |
| Pneumonia NOS | 1 (0.2%) | 4 (0.3%) |
| Bronchopneumonia NOS | 0 | 2 (0.2%) |

(Values in the table above are taken from Page 3419 of the Summary of Clinical Safety Source Tables.)

**Table 63. Short-term Placebo-controlled Treatment Studies of Active CD: Incidence of Lower Respiratory Tract Infections**

| Preferred Term | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 506 (100%) | 1182 (100%) |
| Number of Subjects with a Lower Respiratory Tract Infection | 17 (3.4%) | 37 (3.1%) |
| Event | | |
| Bronchitis NOS | 10 (2.0%) | 9 (0.8%) |
| Bronchitis bacterial NOS | 0 | 6 (0.5%) |
| Bronchitis viral | 1 (0.2%) | 5 (0.4%) |
| Respiratory tract infection NOS | 1 (0.2%) | 5 (0.4%) |
| Pneumonia NOS | 1 (0.2%) | 4 (0.3%) |
| Bronchitis acute NOS | 1 (0.2%) | 3 (0.3%) |
| Bronchopneumonia NOS | 0 | 2 (0.2%) |
| Lower respiratory tract infection NOS | 4 (0.8%) | 2 (0.2%) |
| Respiratory tract infection viral NOS | 0 | 1 (<0.1%) |

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.
(Values in the table above are taken from Page 3415 of the Summary of Clinical Safety Source Tables.)

*Serious infections*

The incidence of serious infection was 2.5% and 2.4% in the natalizumab and placebo groups, respectively (see table below).

Among the serious infections there were 16 (1.4%) reports of abscess in the natalizumab treatment group and 8 (1.6%) in the placebo treatment group. The most common serious infection was perianal abscess (natalizumab *vs.* placebo: 0.6 *vs.* 0.6%). In the natalizumab group, there were three reports of abdominal abscess NOS and one report each of abscess NOS, abscess intestinal, appendiceal abscess, psoas abscess, vaginal abscess, and vulval abscess. In the placebo group, there were 2 reports of rectal abscess and one report each of abdominal abscess NOS, peritoneal abscess, and tooth abscess.

There were 2 (0.2%) cases of viral meningitis in the natalizumab group. The first case was a 52 year old female hospitalized for viral meningitis 20 days after her first infusion of natalizumab; the second case was a 31 year old male hospitalized for viral meningitis 30 days after his second infusion of natalizumab. Both cases resolved. (Details of each of the cases are provided in the Clinical Briefing Document by Drs. Alice Hughes and Susan S. McDermott for the March 7 to March 8, 2006 Advisory Committee.)

One serious atypical infection (cytomegalovirus [CMV] colitis) occurred in a natalizumab-treated subject (after two doses) but no cases occurred in placebo-treated subjects. That subject was a 32 year old female that was also receiving azathioprine. CMV rarely causes colitis in immunocompetent subjects. (Details of this case are provided in the Clinical Briefing Document by Drs. Alice Hughes and Susan S. McDermott for the March 7 to March 8, 2006 Advisory Committee.)

**Table 64. Short-Term Placebo-Controlled Treatment Studies of Active CD: Incidence of Serious Infections**

| Preferred Term | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 506 (100%) | 1182 (100%) |
| Number of Subjects with a Serious Infection | 12 (2.4%) | 29 (2.5%) |
| Event | | |
| Perianal abscess | 3 (0.6%) | 7 (0.6%) |
| Abdominal abscess NOS | 1 (0.2%) | 3 (0.3%) |
| Gastroenteritis NOS | 1 (0.2%) | 2 (0.2%) |
| Meningitis viral NOS | 0 | 2 (0.2%) |
| Urinary tract infection NOS | 0 | 2 (0.2%) |
| Abscess NOS | 0 | 1 (<0.1%) |
| Abscess intestinal | 0 | 1 (<0.1%) |
| Appendiceal abscess | 0 | 1 (<0.1%) |
| Appendicitis | 0 | 1 (<0.1%) |
| Bacteraemia | 0 | 1 (<0.1%) |
| Bronchopneumonia NOS | 0 | 1 (<0.1%) |
| Cytomegalovirus infection | 0 | 1 (<0.1%) |
| Gastroenteritis viral NOS | 1 (0.2%) | 1 (<0.1%) |
| Prostatitis | 0 | 1 (<0.1%) |
| Psoas abscess | 0 | 1 (<0.1%) |
| Purulent discharge | 0 | 1 (<0.1%) |
| Salpingitis NOS | 0 | 1 (<0.1%) |
| Septic shock | 0 | 1 (<0.1%) |
| Staphylococcal sepsis | 0 | 1 (<0.1%) |
| Vaginal abscess | 0 | 1 (<0.1%) |
| Vulval abscess | 0 | 1 (<0.1%) |
| Cellulitis | 1 (0.2%) | 0 |
| Herpes simplex | 1 (0.2%) | 0 |
| Peritoneal abscess | 1 (0.2%) | 0 |
| Rectal abscess | 2 (0.4%) | 0 |
| Sepsis NOS | 2 (0.4%) | 0 |
| Tooth abscess | 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.
(Values in the table above are taken from Page 193 of the Summary of Clinical Safety.)

*Concomitant Medications*

With regard to concomitant medications, overall infections and serious infections were summarized by category of concomitant medication use for the short-term placebo-controlled CD population, but not for the short and long term CD population. An information request is pending for the sponsor to summarize infections and serious infections for the short and long term CD population by class of concomitant medication use. (See Outstanding Items.)

*Infections*

In the natalizumab group, the incidence of infections by concomitant medication use was as follows: 41.3% (monotherapy), 39.4% (steroids), 40.0% (immunosuppressants), and 40.5% (steroids and immunosuppressants); in the placebo group, the incidence of infection by concomitant medication use was 33.8% (monotherapy), 37.0% (steroids), 37.1% (immunosuppressants), and 37.6% (steroids and immunosuppressants). Thus, no clear relation of overall infections and concomitant medication use was found. However, an information request is pending to provide adverse events by additional categories of concomitant medication use. (See Outstanding Items.)

The most common infection in the natalizumab group, nasopharyngitis, was experienced by concomitant medication groups as follows: 14.2% (monotherapy), 14.1% (steroids), 10.7% (immunosuppressants), and 13.3% (steroids and immunosuppressants). A slightly higher incidence of influenza was seen in subjects who received drug with steroids compared to as monotherapy, and with immunosuppressants compared to with immunosuppressants and steroids; the incidence of influenza by concomitant medications was as follows: 3.8% (monotherapy), 4.4% (immunosuppressants), 4.7% (steroids), and 2.7% (immunosuppressants and steroids). No clear relation was found with concomitant medications for either of these infection AEs.

*Serious Infections*

The tables below show the incidence of serious infections by categories of concomitant medication use. Serious infections appeared to occur at a slightly higher rate in subjects receiving natalizumab with concomitant medications (3.9% [immunosuppressants], 2.6% [steroids], 1.9% [steroids+immunosuppressants] than in those receiving natalizumab monotherapy (1.9%). However, no clear relation between concomitant medication use and serious infections was found.

The two viral meningitis cases, and the case of CMV each were in combination with concomitant medications (see the table below). The sponsor was requested to provide additional categories of concomitant medication use; that is pending and may elucidate the incidences of serious infections by concomitant medication use.

**Table 65. Placebo Group - Short-Term Placebo-Controlled Treatment Studies of Active CD: Incidence of Serious Infections in Monotherapy and in Combination with Immunosuppressants and Steroids**

| Placebo Group | | | | | |
|---|---|---|---|---|---|
| Preferred Term | All | Monotherapy (a) | Concomitant Immunosupp (b) | Concomitant Steroids (c) | Concomitant Immunosupp + Steroids (d) |
| No. Subjects Dosed | 506 (100%) | 154 (100%) | 89 (100%) | 154 (100%) | 109 (100%) |
| No. Subjects with a Serious Infection | 12 (2.4%) | 2 (1.3%) | 1 (1.1%) | 2 (1.3%) | 7 (6.4%) |
| Perianal abscess | 3 (0.6%) | 1 (0.6%) | 0 | 1 (0.6%) | 1 (0.9%) |
| Abdominal abscess NOS | 1 (0.2%) | 0 | 0 | 0 | 1 (0.9%) |
| Gastroenteritis NOS | 1 (0.2%) | 0 | 0 | 0 | 1 (0.9%) |
| Gastroenteritis viral NOS | 1 (0.2%) | 1 (0.6%) | 0 | 0 | 0 |
| Cellulitis | 1 (0.2%) | 0 | 0 | 0 | 1 (0.9%) |
| Herpes simplex | 1 (0.2%) | 0 | 0 | 0 | 1 (0.9%) |
| Peritoneal abscess | 1 (0.2%) | 0 | 0 | 0 | 1 (0.9%) |
| Rectal abscess | 2 (0.4%) | 0 | 0 | 1 (0.6%) | 1 (0.9%) |
| Sepsis NOS | 2 (0.4%) | 0 | 1 (1.1%) | 1 (0.6%) | 0 |
| Tooth abscess | 1 (0.2%) | 0 | 0 | 0 | 1 (0.9%) |

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 placebo-controlled Natalizumab group.

(a) Without concomitant use of steroids or immunosuppressants.
(b) With concomitant use of immunosuppressants, but without concomitant use of steroids.
(c) With concomitant use of steroids, but without concomitant use of immunosuppressants.
(d) With concomitant use of immunosuppressants, with concomitant use of steroids.
(Values in table above taken from Page 451 of the Summary of Clinical Safety.)

**Table 66. Natalizumab Group - Short-Term Placebo-Controlled Treatment Studies of Active CD: Incidence of Serious Infections in Monotherapy and in Combination with Immunosuppressants and Steroids**

| Natalizumab Group | | | | | |
|---|---|---|---|---|---|
| Preferred Term | All | Monotherapy (a) | Concomitant Immunosupp (b) | Concomitant Steroids (c) | Concomitant Immunosupp + Steroids (d) |
| No. Subjects Dosed | 1182 (100%) | 373 (100%) | 205 (100%) | 340 (100%) | 264 (100%) |
| No. Subjects with a Serious Infection | 29 (2.5%) | 7 (1.9%) | 8 (3.9%) | 9 (2.6%) | 5 (1.9%) |
| Perianal abscess | 7 (0.6%) | 0 | 3 (1.5%) | 4 (1.2%) | 0 |
| Abdominal abscess NOS | 3 (0.3%) | 1 (0.3%) | 1 (0.5%) | 1 (0.3%) | 0 |
| Gastroenteritis NOS | 2 (0.2%) | 0 | 2 (1.0%) | 0 | 0 |
| Meningitis viral NOS | 2 (0.2%) | 0 | 0 | 0 | 2 (0.8%) |
| Urinary tract infection NOS | 2 (0.2%) | 2 (0.5%) | 0 | 0 | 0 |
| Abscess NOS | 1 (<0.1%) | 1 (0.3%) | 0 | 0 | 0 |
| Abscess intestinal | 1 (<0.1%) | 0 | 0 | 1 (0.3%) | 0 |
| Appendiceal abscess | 1 (<0.1%) | 0 | 0 | 0 | 1 (0.4%) |
| Appendicitis | 1 (<0.1%) | 1 (0.3%) | 0 | 0 | 0 |
| Bacteraemia | 1 (<0.1%) | 0 | 0 | 1 (0.3%) | 0 |
| Bronchopneumonia NOS | 1 (<0.1%) | 0 | 0 | 0 | 1 (0.4%) |
| Cytomegalovirus infection | 1 (<0.1%) | 0 | 1 (0.5%) | 0 | 0 |
| Gastroenteritis viral NOS | 1 (<0.1%) | 0 | 1 (0.5%) | 0 | 0 |
| Prostatitis | 1 (<0.1%) | 1 (0.3%) | 0 | 0 | 0 |
| Psoas abscess | 1 (<0.1%) | 0 | 0 | 1 (0.3%) | 0 |
| Purulent discharge | 1 (<0.1%) | 0 | 0 | 0 | 1 (0.4%) |
| Salpingitis NOS | 1 (<0.1%) | 1 (0.3%) | 0 | 0 | 0 |
| Septic shock | 1 (<0.1%) | 0 | 0 | 1 (0.3%) | 0 |
| Staphylococcal sepsis | 1 (<0.1%) | 0 | 0 | 0 | 1 (0.4%) |
| Vaginal abscess | 1 (<0.1%) | 0 | 0 | 1 (0.3%) | 0 |
| Vulval abscess | 1 (<0.1%) | 1 (0.3%) | 0 | 0 | 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 placebo-controlled Natalizumab group.
(a) Without concomitant use of steroids or immunosuppressants.
(b) With concomitant use of immunosuppressants, but without concomitant use of steroids.
(c) With concomitant use of steroids, but without concomitant use of immunosuppressants.
(d) With concomitant use of immunosuppressants, with concomitant use of steroids.
(Values in table above taken from Page 452-453 of the Summary of Clinical Safety.)

## Short- and Long-term Dosing in CD

In the short- and long-term dosing in CD population, there were five serious atypical lower respiratory tract infections (pneumonia with lung abscess, pulmonary aspergillosis, pneumocystis carinii pneumonia, mycobacterium avium intracellulare complex pneumonia, and a Burkholderia cepacia lower respiratory tract infection). (Details of these cases are provided in

the Clinical Briefing Document by Drs. Alice Hughes and Susan S. McDermott for the March 7 to March 8, 2006 Advisory Committee.)

There were six serious herpes infections including a case of varicella pneumonia and two cases of herpes zoster. The CMV colitis case (discussed in the Infection-Short-term Placebo-Controlled CD Studies section above) and the varicella pneumonia case each developed in subjects that did not have diseases that predisposed to immunodeficiency; this is notable as each of these infections are generally considered opportunistic infections. The possibility of a compromise in cell-mediated immunity is indicated by each of these infections.

Placebo-controlled Studies in MS

The rates of infection were similar between natalizumab-treated and placebo-treated MS subjects (1.54 infections per person-year for natalizumab-treated subjects vs. 1.50 infections per person-year for placebo-treated subjects). The incidence of infections was well balanced between natalizumab-treated and placebo-treated subjects (73.7% of natalizumab-treated subjects vs. 73.9% of placebo-treated subjects; see Table 67.)

Specific infection types that occurred more frequently in natalizumab-treated subjects than placebo-treated subjects included lower respiratory tract infections, herpes simplex and herpes zoster infections, vaginal fungal infections, tooth infections, and gingival infections.

The incidence of serious infections was 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 (see Table 68). One opportunistic infection was reported; this was a cryptosporidial gastroenteritis in a 31 year old male that had received 16 infusions of natalizumab.

**Table 67. Placebo-Controlled Studies of MS: Infections With an Incidence of 1% or More**

| Preferred Term | Placebo | Natalizumab |
|---|---|---|
| No. Subjects Dosed | 1135 (100.0%) | 1617 (100.0%) |
| No. Subjects with an Infection | 839 (73.9%) | 1192 (73.7%) |
| Event | | |
| Nasopharyngitis | 340 (30.0%) | 477 (29.5%) |
| Upper respiratory tract infection NOS | 169 (14.9%) | 247 (15.3%) |
| Urinary tract infection NOS | 179 (15.8%) | 245 (15.2%) |
| Influenza | 146 (12.9%) | 225 (13.9%) |
| Sinusitis NOS | 122 (10.7%) | 184 (11.4%) |
| Upper respiratory tract infection viral NOS | 88 (7.8%) | 134 (8.3%) |
| Pharyngitis | 59 (5.2%) | 125 (7.7%) |
| Bronchial infection | 71 (6.3%) | 95 (5.9%) |
| Gastroenteritis viral NOS | 80 (7.0%) | 88 (5.4%) |
| Herpes simplex | 53 (4.7%) | 80 (4.9%) |
| Vaginosis fungal NOS | 40 (3.5%) | 64 (4.0%) |
| Gastroenteritis NOS | 21 (1.9%) | 56 (3.5%) |
| Rhinitis infective | 39 (3.4%) | 51 (3.2%) |
| Tonsillitis | 23 (2.0%) | 51 (3.2%) |
| Bladder infection NOS | 16 (1.4%) | 38 (2.4%) |
| Ear infection NOS | 28 (2.5%) | 38 (2.4%) |
| Tooth infection | 22 (1.9%) | 37 (2.3%) |
| Tooth abscess | 25 (2.2%) | 36 (2.2%) |
| Conjunctivitis infective | 25 (2.2%) | 35 (2.2%) |
| Herpes zoster | 16 (1.4%) | 33 (2.0%) |
| Lower respiratory tract infection NOS | 18 (1.6%) | 33 (2.0%) |
| Upper respiratory tract infection bacterial | 29 (2.6%) | 33 (2.0%) |
| Cystitis NOS | 19 (1.7%) | 32 (2.0%) |
| Respiratory tract infection NOS | 15 (1.3%) | 30 (1.9%) |
| Tooth caries NOS | 20 (1.8%) | 27 (1.7%) |
| Vaginitis | 12 (1.1%) | 25 (1.5%) |
| Bronchitis NOS | 24 (2.1%) | 22 (1.4%) |
| Viral infection NOS | 15 (1.3%) | 21 (1.3%) |
| Pharyngitis viral NOS | 9 (0.8%) | 19 (1.2%) |
| Gingival infection | 6 (0.5%) | 18 (1.1%) |
| Pharyngitis streptococcal | 20 (1.8%) | 18 (1.1%) |
| Pneumonia NOS | 10 (0.9%) | 18 (1.1%) |
| Urinary tract infection bacterial | 18 (1.6%) | 18 (1.1%) |
| Laryngopharyngitis NOS | 12 (1.1%) | 16 (1.0%) |
| Pharyngitis bacterial | 14 (1.2%) | 12 (0.7%) |

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column within each system organ class.
(Values in the table above are taken from page 187 of the Summary of Clinical Safety)

**Table 68. Placebo-Controlled Studies of MS: Incidence of Serious Infections**

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

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the Natalizumab column within each system organ class.
(Values in the table above are taken from page 188 of the Summary of Clinical Safety)

Post-Marketing

The post-marketing reports of serious infections are shown in the table below.

**Table 69. Frequency of Serious Infections by Infection Type in Post-Marketing**

| Type of infection | HCP Cases | Consumer Cases | Total Cases |
|---|---|---|---|
| Pneumonia | 3 | 5 | 8 |
| Urinary tract infection | 4 | 1 | 5 |
| 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 |
| Pyelonephritis | 1 | 0 | 1 |
| Blister | 1 | 0 | 1 |
| Ovarian cyst | 1 | 0 | 1 |
| Cystitis | 0 | 1 | 1 |
| Gangrene | 0 | 1 | 1 |
| Infection | 0 | 1 | 1 |
| Herpes simplex | 0 | 1 | 1 |
| Ceullulitis | 0 | 1 | 1 |
| **Total** | **19** | **11** | **30** |
| **Cases Mentioning PML** | **4** | **0** | **4** |

HCP: Health Care Provider

Pneumonia was the most common serious infection reported for patients who received natalizumab-in the post-marketing setting. Pneumonias were reported for 0.11% (8/7000) 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. Organisms were not reported for any of the urinary tract infection cases.

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 were provided in the Clinical Briefing Document by Drs. Alice Hughes and Susan S. McDermott for the March 7 to March 8, 2006 Advisory Committee.)

Summary of Infections

Overall infection incidence was higher in the natalizumab-treated group than the placebo-treated group (40.4% vs. 36.2%) in CD short-term placebo-controlled studies, but was balanced in the MS placebo-controlled studies (73.7% vs. 73.9%).

Serious infections occurred at approximately the same rate in both the short term placebo controlled CD studies (natalizumab 2.5% vs. placebo 2.4%) and the in the placebo-controlled MS studies (natalizumab 2.4% vs. placebo 2.3%).

Atypical infections reported in CD studies included a CMV colitis case, and opportunistic pulmonary infections (mycobacterium avium intracellulare, pneumocystis carinii, aspergillus, and burkholderia cepacia). In addition, two cases of viral meningitis, a varicella pneumonia, and two cases of herpes zoster were reported in CD studies. A cryptosporidial gastroenteritis case was reported in an MS study. Two reports of herpes meningitis/ encephalitis occurred in the postmarketing setting.

No clear relation of the incidence of overall infections, serious infections, or atypical infections was found with the number of infusions or with concomitant immunosuppressant and/or steroid use.

*Immunogenicity*

A screening ELISA assay was used followed by a cell-based blocking assay in those who were screening antibody positive and had no detectable natalizumab in the serum. In general, blood was drawn for determination of anti-natalizumab antibodies every 12 weeks in the Phase 3 MS and CD studies.

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% (130/1258) of subjects assessed had anti-natalizumab antibodies at one or more time points, and 8.5%% (107/1258) of subjects were characterized as persistently positive (positive at two or more time points separated by at least 42 days or at the last time point tested), for anti-natalizumab antibodies.

*Antibody Development by Concomitant Medications – Studies CD301 & CD307*

Antibody development in Study CD301 and Study CD307 was higher in subjects receiving monotherapy versus those receiving concomitant steroids or concomitant immunosuppressants.

**Table 70. Anti-Natalizumab Antibody Development* by Concomitant Medications (CD301 and CD307)**

| | Monotherapy | Concomitant Steroids | Concomitant Immunosuppressants |
|---|---|---|---|
| CD301 ITT | 12% (39/315) | 5 % (8/161) | 2 % ( 6/247) |
| CD307 ITT | 13% (11/85) | 10 % (7/67) | 5 % (4/88) |

* any visit after Baseline to Week 12
(Values in table above for CD301 taken from Page 2699 of Study CD301 Report; values in table above for CD307, taken from Page 232 of Study CD307 Report.)

Clinical response appeared to be decreased in those with positive antibodies.

**Table 71. Clinical Response by Antibody Status (CD301 and CD307)**

| Study | Antibody (+) | Antibody(-) |
|---|---|---|
| CD301 ITT: Clinical Response Wk 10 | 43% (17/40) | 58% (349/599) |
| CD307 ITT: Clinical Response Wks 8 & 12 | 41% ( 9/22) | 50% (108/218) |

(Values in table above for Study CD301 taken from Page 850 of Study CD301 Report; values in table above for Study CD307 taken from Page 654 of Study CD307 Report).

The sponsor monitored the formation of anti-natalizumab antibody formation in selected CD studies and assessed the impact of anti-natalizumab antibody formation on AEs, focusing on infusion reactions and hypersensitivity reactions. Antibodies were characterized as being either present or absent, with no distinction between persistent and transient positivity. In Studies CD301 and CD307, 9.0% (81/899) subjects who were dosed and had an ELISA assay, tested positive for screening anti-natalizumab antibodies. (No distinction was made between persistent and transient positivity; antibodies were characterized as being either present or absent.)

Most common AEs (antibody-positive vs. antibody-negative) were: Crohn's disease (17.3 vs. 7.9%), pruritus (7.4 vs. 2.6%), rash NOS (7.4 vs. 3.7%), urticaria (7.4 vs. 1.0%), rigors (6.2 vs. 1.7%), chest pain (6.2 vs. 2.1%), peripheral edema (6.2 vs. 2.4%), and flushing (4.9 vs. 1.0%). The higher incidence of Crohn's disease in those that are antibody-positive suggests that presence of anti-natalizumab antibody may decrease the therapeutic effect of natalizumab.

Infusion reactions in CD Studies 301 and 307 were strongly associated with anti-natalizumab antibody formation. Infusion reactions were reported in 35.8% (29/81) of subjects who tested positive for anti-natalizumab antibodies compared to 8.8% (72/818) of antibody-negative subjects. The most commonly reported infusion reactions, all of which occurred substantially more frequently in antibody-positive patients compared to antibody-negative patients, were urticaria NOS (7.4% of anti-natalizumab antibody-positive patients vs. 0.7% of antibody-negative patients), pruritus (7.4% vs. 0.5%), nausea (6.2% vs. 1.1%), flushing (4.9% vs. 0.4%), and dyspnea (5.0% vs. 0.4%).

Hypersensitivity NOS was reported in 2 (2.5%) anti-natalizumab antibody-positive patients, compared to 0.5% (4) of antibody-negative patients. One anaphylactic reaction was reported in 1 patient (1.2%) who tested positive for anti-natalizumab antibodies versus none in those who tested negative.

MS Studies

In the combined Phase 3 MS studies, similar results were found to those of the CD studies. Of the 1210 evaluated natalizumab-treated subjects, 127 (10.5%) had a positive anti-natalizumab antibody titer at least once during the studies of whom 75 (6.2%) subjects had persistently positive titers.

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

Most common AEs in the persistently positive subjects were MS relapse (57.3 vs. 34.7% antibody negative), headache (40.0 vs. 40.0%), nasopharyngitis (37.3 vs. 35.4%), fatigue (30.7 vs. 29.3%), back pain (28.0 vs. 20.8%), nausea (25.3 vs. 14.7%), arthralgia (24.0 vs. 19.9%), rigors (22.7 vs. 2.3%), and pain in extremity (20.0 vs. 18.8%). The higher incidence of MS relapse and neurological symptoms in subjects persistently positive for anti-natalizumab antibodies could reflect diminished therapeutic effect of natalizumab in these subjects.

Six of the 7 subjects with the preferred term hypersensitivity NOS were persistently antibody positive and the remaining subject was antibody negative. The hypersensitivity systemic reactions reported as anaphylactic/anaphylactoid reactions occurred in 5 (0.4%) natalizumab-treated subjects of whom 4 were persistently antibody positive and one transiently antibody positive.

The infusion reactions by preferred term with a higher incidence in the persistently antibody-positive group include, in addition to those already reported, headache (persistently antibody-positive vs. overall: 16.0 vs. 4.7%), flushing (10.7 vs. 1.2%), dizziness (6.7 vs. 2.9%), tremor (5.3 vs. 0.3%), tachycardia NOS (5.3 vs. 0.4%), hypotension (4.0 vs. 0.6%), dyspnea (5.3 vs. 0.3%), nausea (17.3 vs. 2.3%), vomiting (6.7 vs. 0.5%), urticaria (13.3 vs. 1.4%), pruritus (6.7 vs. 1.2%), rigors (20.0 vs. 1.4%), pyrexia (4.0 vs. 0.7%), feeling cold (5.3 vs. 0.3%), back pain (4.0 vs. 0.4%), and chest pain (4.0 vs. 0.4%) .

Summary of Immunogenicity

Anti-natalizumab antibody positivity occurred at approximately 10%, based on at least once every 12 weeks testing. In Studies CD301 and CD307, antibody development appeared to be higher in subjects receiving monotherapy versus those receiving concomitant steroids or concomitant immunosuppressants. Clinical response appeared to be decreased in subjects with positive antibodies.

In both the MS and CD study populations, anti-natalizumab antibody positivity was associated with infusion reactions (such as headache, nausea, urticaria, flushing, pruritus, and fatigue) at a higher incidence than in those that were antibody-negative. In both the MS and CD study populations, anti-natalizumab antibody positivity was also associated with hypersensitivity reactions and with anaphylactic/anaphylactoid reactions at a higher incidence than in those that were antibody-negative.

*Hypersensitivity*

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. Hypersensitivity events occurring within the 2-hour infusion reaction window were defined in the study protocols as acute hypersensitivity reactions.

Overall, the incidence of hypersensitivity in the placebo controlled CD trials (CD301 and CD307) was 3.5% and the rate in the MS placebo controlled trials (1801, 1802 and 1803) was 4.2%. 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). In the CD placebo-controlled studies, urticaria occurred as an infusion reaction in 1.2% of natalizumab-treated subjects and 0.2% of placebo-treated subjects.

Anaphylactic reactions in CD placebo-controlled studies occurred in <0.1% (1) natalizumab-treated and in no placebo-treated subjects; one additional case occurred during the first infusion in CD251 (approximately 300 days after receiving four infusions in the prior CD study). Anaphylactic reactions in MS placebo-controlled studies occurred in 0.4% (6) of natalizumab-treated and 0.2% (2) of placebo-treated subjects; symptoms in all the cases resolved with appropriate therapy without clinical sequelae.

*Carcinogenicity*

Because natalizumab interferes with lymphocyte trafficking and because tumor immunosurveillance is mediated by T lymphocytes, there is the potential for natalizumab to increase the risk for malignancies. Also, immunosuppressant agents such as azathioprine and 6-MP have been shown to increase the risk for malignancy.

CD Studies

A total of 7 (0.6%) malignancies occurred in natalizumab-treated CD subjects in contrast to 1 (0.2%) in the placebo-treated (see tables below).

**Table 72. Short-Term Placebo-Controlled Treatment Studies of Active CD: Rate of Malignancies**

| | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 506 | 1182 |
| Number of Subjects with a Malignancy | 1 | 7 |
| Total Person-Years | 166.28 | 438.3 |
| Annualized Rate* | 0.60 | 1.60 |
| Event | | |
| Lung adenocarcinoma NOS | 0 | 2 (0.46) |
| Bladder cancer NOS | 0 | 1 (0.23) |
| Breast cancer NOS | 0 | 1 (0.23) |
| Breast cancer invasive NOS | 0 | 1 (0.23) |
| Colon cancer NOS | 0 | 1 (0.23) |
| Malignant melanoma | 0 | 1 (0.23) |
| Uterine cancer NOS | 1 (0.60) | 0 |

* Annualized Rate: per 100 person-years

NOTE 1: Entries are no. of events (event rate). Event rate = (total no. of events / total person-years) x 100.
2: Preferred terms are presented by decreasing rate in the Natalizumab column.

(Values in the table above are taken from Page 231 of the Summary of Clinical Safety.)

In the short-term placebo-controlled CD study population, natalizumab-treated subjects had a higher incidence of malignancies than placebo-treated subjects (incidence: natalizumab 0.6% vs. placebo 0.2%) and a higher rate of malignancies (rate: natalizumab 1.60 events per 100 person-years vs. placebo 0.60 events per 100 person-years).

An additional nine malignancies were diagnosed in subjects who received natalizumab in long term dosing studies in CD as follows: basal cell carcinoma of the skin (3 cases), squamous cell carcinoma of the skin (2), uterine carcinoma (2), breast ductal carcinoma in situ (1), clear cell

renal cell carcinoma (1), metastatic rectal carcinoma (1). A long term control group was not available for comparison. No clear relation with number of infusions was found.

MS Studies

The incidence and rate of malignancies in placebo-controlled studies of MS are shown in the tables below.

**Table 73. Placebo-Controlled Studies of MS: Rate of Malignancies**

| Preferred Term | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 1135 | 1617 |
| Number of Subjects with an Event | 15 | 11 |
| Total Person-Years | 2060.36 | 2910.37 |
| Annualized Rate* | 0.73 | 0.38 |
| Event | | |
| Basal cell carcinoma | 4 (0.19) | 4 (0.14) |
| Breast cancer NOS | 3 (0.15) | 3 (0.10) |
| Breast cancer in situ | 1 (0.05) | 1 (0.03) |
| Cervical carcinoma stage 0 | 0 | 1 (0.03) |
| Colon cancer NOS | 0 | 1 (0.03) |
| Metastatic malignant melanoma | 0 | 1 (0.03) |
| Breast cancer metastatic | 1 (0.05) | 0 |
| Breast cancer stage III | 1 (0.05) | 0 |
| Malignant melanoma | 2 (0.10) | 0 |
| Malignant pleural effusion | 1 (0.05) | 0 |
| Secretory adenoma of pituitary | 1 (0.05) | 0 |
| Squamous cell carcinoma of skin | 1 (0.05) | 0 |

* Annualized Rate: per 100 person-years
NOTE
1: Entries are no. of events (event rate). Event rate = (total no. of events / total person-years) x 100.
2: Preferred terms are presented by decreasing rate in the Natalizumab column.
(Values in the table above are taken from page 224 of the Summary of Clinical Safety.)

The incidence and rate of malignancies were balanced across the treatment groups in the MS study population. In the placebo-controlled MS study population, incidence of malignancies in the natalizumab group was 0.7% and in the placebo group was 1.3%; rate of malignancies in the natalizumab group was 0.38 per 100 person-years and in the placebo group was 0.73 per 100 person-years.

Pooled MS and Active CD (Placebo-Controlled Studies)

The incidence and rate of malignancies in the pooled placebo-controlled studies of MS and placebo-controlled studies of active CD is shown in the table below.

**Table 74. Placebo-Controlled Studies of MS and of Treatment Studies of Active CD: Rate of Malignancies**

| Preferred Term | Placebo | Natalizumab |
|---|---|---|
| Number of Subjects Dosed | 1641 | 2799 |
| Number of Subjects with a Malignancy | 16 | 18 |
| Total Person-Years | 2226.64 | 3348.66 |
| Annualized Rate* | 0.72 | 0.54 |
| Event | | |
| Basal cell carcinoma | 4 (0.18) | 4 (0.12) |
| Breast cancer NOS | 3 (0.13) | 4 (0.12) |
| Colon cancer NOS | 0 | 2 (0.06) |
| Lung adenocarcinoma NOS | 0 | 2 (0.06) |
| Bladder cancer NOS | 0 | 1 (0.03) |
| Breast cancer in situ | 1 (0.04) | 1 (0.03) |
| Breast cancer invasive NOS | 0 | 1 (0.03) |
| Cervical carcinoma stage 0 | 0 | 1 (0.03) |
| Malignant melanoma | 2 (0.09) | 1 (0.03) |
| Metastatic malignant melanoma | 0 | 1 (0.03) |
| Breast cancer metastatic | 1 (0.04) | 0 |
| Breast cancer stage III | 1 (0.04) | 0 |
| Malignant pleural effusion | 1 (0.04) | 0 |
| Secretory adenoma of pituitary | 1 (0.04) | 0 |
| Squamous cell carcinoma of skin | 1 (0.04) | 0 |
| Uterine cancer NOS | 1 (0.04) | 0 |

* Annualized Rate: per 100 person-years
NOTE
1: Entries are number of events (event rate). Event rate = (total no. of events / total person-years) x 100.
2: Preferred terms are presented by decreasing rate in the Natalizumab column.
(Values in the table above are taken from Page 240 of the Summary of Clinical Safety.)

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.

Concomitant Medications

No clear relationship between malignancies and concomitant steroids and/or immunosuppressants in the natalizumab-treated group of short-term placebo-controlled CD studies was found. Of the total of seven malignancies in the natalizumab-treated group, two were treated with monotherapy, two with concomitant immunosuppressants, two with concomitant steroids, and one with concomitant immunousppressants and steroids. However, the number of subjects in each of the subgroups is small, making a determination difficult.

Post-marketing

The table below shows the frequency of malignancies by malignancy type in the post-marketing setting.

**Table 75. Frequency of Malignancies By Malignancy Type in Post-Marketing**

| Cancer type | HCP Cases | Consumer Cases | Total Cases |
|---|---|---|---|
| Ovarian cancer | 1 | 0 | 1 |
| Melanoma | 0 | 1 | 1 |
| Skin cancer | 1 | 1 | 2 |
| **Total** | **2** | **2** | **4** |

HCP: Health Care Professional
(Table above is taken from Page 499 of the Summary of Clinical Safety.)

The first was a case of ovarian cancer that was discussed in the Deaths section; the case of ovarian cancer was diagnosed just one month after the patient's first natalizumab infusion. Each of the cases occurred shortly before market suspension, and with concomitant Avonex® therapy. The second case was of melanoma of the left knee that was removed. The case of skin cancer was a cancerous mole on the belly button region that resolved with outpatient surgery to remove the mole. The other skin cancer was of the face that has not yet resolved; that patient had an outpatient colonoscopy that revealed a pre-cancerous polyp in the colon. The very short treatment periods of TYSABRI® due to its market suspension make a causal relationship with the drug in the development of each of the malignancies unlikely.

Summary of Carcinogenicity

The rates of malignancies were higher in the natalizumab-treated group than in the placebo-treated group in short-term placebo-controlled CD studies (natalizumab: 1.60 per 100 person-years vs. placebo: 0.60 per 100 person-years), but the rates in the placebo-controlled MS studies were balanced across treatment groups (natalizumab: 0.38 per 100 person-years vs. placebo: 0.73 per 100 person-years), and the rates in the pooled MS and active CD placebo-controlled studies were balanced across treatment groups (natalizumab: 0.54 per 100 person-years vs. placebo: 0.72 per 100 person-years). No clear increase in risk of malignancy was found with natalizumab treatment; however, the effects of natalizumab exposure beyond two years are unknown in the clinical trial setting, and there may be effects that may require longer periods of time to occur.

No clear relation between malignancies and concomitant immunosuppressant and/or steroid use was appreciated; however, the analyses are limited by the small numbers of subjects with malignancies in each of the concomitant medication categories.

# Discussion and Conclusions

## Efficacy Summary

Induction

In the first induction study (Study CD301), the proportion of patients experiencing a clinical response (CDAI decrease ≥70) at Week 10 was 7.8% higher for natalizumab than for placebo, but statistical significance was not reached (56.4% vs. 48.6%; p=0.051). In a post-hoc analysis of a subset of patients with CRP >2.87 mg/L (73% of the ITT population), the proportion that experienced a clinical response at Week 10 was 12.8% higher for natalizumab than for placebo (57.6% vs. 44.8%; nominal p=0.007). (The Sponsor's rationale for using elevated CRP levels was that CRP is a marker for ongoing inflammation.)

In the second induction study (Study CD307), an elevated CRP population was prospectively selected to confirm the results of CD301. The proportion attaining a clinical response at Weeks 8 and 12 was 15.5% higher for natalizumab than for placebo (47.9% vs. 32.4%; p<0.001).

Maintenance

In the maintenance study (Study CD303), responders from Study CD301 were re-randomized to natalizumab or placebo; the proportion of patients maintaining clinical response through an additional six months was 33% higher for natalizumab than for placebo (61.3% vs. 28.2%; p<0.001). In a post-hoc analysis of the subset of patients that had an elevated CRP at baseline of Study CD301, the results were similar: the proportion of patients maintaining clinical response through an additional six months was 35% higher for natalizumab than for placebo (60.5% vs. 25.8%; p<0.001).

Subgroup analyses

Subgroup analyses were done in each of the studies based on baseline medication use, prior medication use, and reported response to prior therapies. In general, the treatment effects appeared to be fairly similar to that of the respective overall study population. This suggests that the treatment effect would be expected to be preserved for these subgroups, but the analyses were all post-hoc. Also, analyses of clinical response in subgroups defined as "failures" or "inadequate response to prior therapies" need to be interpreted with caution because these cases were identified only by report and without prospective criteria for an adequate therapeutic trial.

**Safety Summary**

Progressive Multifocal Leukoencephalopathy (PML)
Natalizumab administration has been associated with three cases of PML. Although the two PML cases in MS patients occurred with a concomitant interferon agent, the PML case in the CD patient occurred with azathioprine use eight months prior and a history of deficient hematopoiesis; thus, the data are insufficient to determine whether the risk of PML is limited to patients with concomitant immunosuppressive therapies.

Based on the detailed review of possible cases of PML in patients exposed to natalizumab in clinical trials in the dose suspension safety assessments described by Yousry et al., the risk of PML is roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9 months.

As no new cases of PML have been found in the dose suspension safety assessments, one focus of this safety review has been to determine if infections, particularly serious infections, are increased with natalizumab treatment versus placebo or with cumulative natalizumab dosing. The safety databases used were the short-term placebo controlled CD study database (natalizumab n=1182; placebo n=506), and the short and long term studies in CD database (n=1563 exposed to natalizumab).

Other Infections
In the database of short-term placebo-controlled active CD studies, infections overall were higher in the natalizumab group than the placebo group (40% vs. 36%), but serious infections were nearly the same between the two groups (2.5% natalizumab vs. 2.4% placebo). Natalizumab administration appeared to be associated with an increased incidence of atypical and serious infections; these included viral meningitis, herpes infections, and atypical pulmonary and gastrointestinal infections.

Concomitant Immunosuppressants and/or Steroids
Based on the short-term placebo controlled CD study database and the short- and long-term studies in CD database, no clear association was found between concomitant immunosuppressant and/or steroid use and infections or other AEs. In the short and long-term dosing in CD population, a number of opportunistic pulmonary infections (mycobacterium avium intracellulare, pneumocystis carinii, aspergillus, and burkholderia cepacia) were found. No clear relation of these infections to number of infusions or to concomitant immunosuppressant or steroid use was found.

Other safety issues
Hypersensitivity and infusion reactions were associated with natalizumab use, and are described in the currently approved labeling. There was no clear increase in risk in carcinogenicity. However, long-term follow-up data would be necessary to reliably assess the risk of carcinogenicity.

**Benefit-Risk Considerations**

When originally approved for the MS indication, there was an unprecedented treatment effect in that population. Although the cases of PML changed the benefit-risk considerations, return to market occurred largely because of the large treatment effect; a key decision on approval was that natalizumab be returned to market as monotherapy based on the concern that PML risk increases with increasing immunosuppression. The indication for monotherapy was supported by the fact that one of the two pivotal MS studies was a monotherapy study.

The benefit and risk considerations in the CD population are considerably different from those in the MS population. The treatment effect in the CD population (13% to 16% in induction, 33% to 35% in maintenance) was not as high as that in the MS population (absolute treatment effect of 42% to 49%) nor is it clearly distinguished from approved CD therapies. With regard to risk, CD patients are more likely to be on chronic immunosuppressant and/or steroid therapy than MS patients.

The sponsor's proposed indication is limited to those that are failures of prior conventional therapies (where conventional therapies include mesalamine, immunosuppressants and steroids).

An attempt was made to identify subgroups within the overall population for whom the benefit to risk ratio may be more favorable.

First, subgroups for who the risks might be more acceptable might include those with prior medication use or those with inadequate response to prior therapies. These patients would likely be more severe and/or refractory than other patients. Across the categories based on prior medication use and investigator-reported inadequate response to prior therapies (where prior therapies included immunosuppressants, steroids, and/or anti-TNFs) the proportions demonstrating clinical response were similar to those in the overall population, although no subgroup demonstrated a strikingly higher clinical response.

Second, with regard to risk, it was not possible to identify characteristics with certainty that may predict the development of PML as there were only three cases. Incidence of infections, in particular opportunistic infections, were used as a surrogate for PML risk and were analyzed across categories of concomitant medication use (monotherapy versus steroids and/or immunosuppressants); no clear relation of infections to concomitant therapies was found.

Although a relationship between immunosuppressant and/or steroid use with infections was not found, there remains the concern that the risk of infections and of PML might be higher with concomitant therapies. The clinical response proportions across categories of concomitant medication use were similar to the overall proportions suggesting that restrictions on concomitant medication use could be considered an approach to reduce risks while maintaining efficacy. However, that strategy has not been investigated prospectively.

Additional considerations relate to clinical practice.

Cases of PML often present with neurological symptoms and signs; and may be identified more readily in a neurology practice than in a gastroenterology practice. However, the background rate of neurological signs and symptoms would be considerably less in a CD patient than in an MS patient, allowing for easier detection of PML cases in CD patients.

The role of CRP in treating patients must be determined. In the maintenance study (CD303), a post-hoc analysis of patients with baseline elevated CRP level showed similar efficacy to the overall population. In one induction study (CD301), a subgroup selected based on elevated baseline CRP was associated with greater efficacy but that was a post-hoc analysis. In the other induction study (CD307), only patients with elevated baseline CRP were enrolled, so further information was not gained on patients that do not have elevated baseline CRP.

Because CD patients may have flares while on therapy with natalizumab, and these may require long-term therapy with steroids and/or immunosuppressants (whereas MS relapses are more likely to require pulse steroids), it may be harder to attain a goal of strict monotherapy in CD patients.

The role of brain MRIs, neurological exams by neurologists, JC virus testing and/or other evaluations that may potentially decrease the risk of PML must be determined.

# Outstanding Items

The Division of Scientific Investigations inspection of selected sites is pending at the time this Briefing Document was written.

Items below are pending at the time this Briefing Document was written; these items were included in an Information Request Letter dated June 14, 2007.

1. Prior Medication Use
   - Clarify criteria used to define inadequate response to a prior medication.
   - Clarify terms used to categorize prior medication use.
   - Add combination categories of prior medication use (i.e., "immunosuppressants or anti-TNF", and "immunosuppressants and anti-TNF").

2. Concomitant Medication Use
   - Provide numbers of subjects by category of medication (not only medication name).
   - Add additional categories (i.e., "steroids with or without immunosuppressants", and "immunosuppressants with or without steroids")

3. Subgroup Analyses of Clinical Response
   - Based on prior and/or concomitant medication use (for each of the Phase 3 studies).
   - By severity of disease at baseline (based on baseline CDAI).
   - Based on baseline CRP.

4. Safety Analyses by Concomitant Medication Use
   - Selected AEs (SAEs, infections, and serious infections) by concomitant medication categories.
   - Selected AEs (infections and serious infections) by concomitant medication use and by number of infusions.

5. Other Requests
   - Analyze results of Study CD303 with stratification based on smoking status as there is a baseline imbalance.
   - Explain why subjects with ileocolonic/colonic disease appeared to have a more pronounced clinical response than subjects with disease confined to the ileum in Study CD307.
   - Explain variation in clinical response rates by world region.
   - Among subjects in Study CD301 who were eligible to participate in Study CD303, summarize and compare characteristics for those who chose to participate and for those who chose not to.
   - Provide age-adjusted mortality rates for a general CD population and for a population of comparable severity to those exposed to natalizumab in the CD studies.

# Appendix 1

## Crohn's Disease Activity Index (CDAI)

**Figure 4. CDAI Score Calculation**

**CROHN'S DISEASE ACTIVITY INDEX (CDAI)**

| Variable | Weighting factor |
|---|---|
| Total number of diarrheal stools for each of previous 7 days | × 2 |
| Abdominal pain for each of previous 7 days<br>None = 0<br>Mild = 1<br>Moderate = 2<br>Severe = 3 | × 5 |
| General well-being for each of previous 7 days<br>Well = 0<br>Below par = 1<br>Poor = 2<br>Very poor = 3<br>Terrible = 4 | × 7 |

All other indices will be assessed by the Doctor at outpatient visit as follows:

| | |
|---|---|
| Clinical signs during the previous 7 days<br>Arthritis or arthralgia = 1<br>Skin or mouth lesions = 1<br>Iritis or uveitis = 1<br>Anorectal lesion = 1<br>Other fistulae = 1<br>Fever over 38°C during the week = 1 | × 20 |
| Lomotil or other anti-diarrheal<br>No = 0, yes = 1 | × 30 |
| Abdominal mass<br>None = 0<br>Questionable = 2<br>Definite = 5 | × 10 |
| Anemia defined by hematocrit less than:<br>For males: 47% – HCT value<br>For females: 42% – HCT value | × 6 |
| $\left(\frac{\text{(Standard weight (kg)* — Actual weight (kg)}}{\text{Standard weight* (kg)}} \times \frac{1}{100}\right)$ x | × 1<br>Note: Maximum correction value is -10 |
| Crohn's disease Activity Index (CDAI) Total | = |

* Obtain from the Standard Height and Weight Tables, which will be provided.

(Figure above is taken from page 88 of the Clinical Study Report for Study CD307)

# Appendix 2

## Study CD301 (Selected Study Results)

The tables below include the following information on previous medications for CD: (1) response to initial treatment; (2) loss of response with continued treatment; (3) dependence on treatment, and (4) reasons for discontinuation due to treatment

**Table 76. 5-ASA Compounds: Response, Dependence, and Reason for Discontinuation – N (%)**

| Variable Statistics | Placebo (n=181) | | Natalizumab (n=724) | | Overall (n=905) | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| Responded to Initial Treatment | 121 (67) | 26 (14) | 496 (69) | 137 (19) | 617 (68) | 163 (18) |
| Lost Response with Continued Treatment | 56 (31) | 91 (50) | 266 (37) | 366 (51) | 322 (36) | 457 (50) |
| Became Dependent on Treatment | 29 (16) | 118 (65) | 116 (16) | 517 (71) | 145 (16) | 635 (70) |
| Discontinued Due to Adverse Events | 25 (14) | 122 (67) | 87 (12) | 546 (75) | 112 (12) | 668 (74) |
| Discontinued Due to Infusion Reaction* | 0* | 10 (6) | 0* | 44 (6) | 0* | 54 (6) |
| * "Discontinued Due to Infusion Reaction"categorized as "(NA)" for 137 (76), 590 (81), and 727 (80) subjects in placebo, natalizumab, and overall groups, respectively, based on marking of "NA" category on Case Report Form for question "Discontinue due to Infusion Reaction". | | | | | | |

(Values in table above are taken from Page 295 of the Study Report for Study CD301.)

**Table 77. Immunosuppressants: Response, Dependence, and Reason for Discontinuation – N (%)**

| Variable Statistics | Placebo (n=181) | | Natalizumab (n=724) | | Overall (n=905) | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| Responded to Initial Treatment | 85 (47) | 35 (19) | 349 (48) | 133 (18) | 434 (48) | 168 (19) |
| Lost Response with Continued Treatment | 34 (19) | 85 (47) | 154 (21) | 329 (45) | 188 (21) | 414 (46) |
| Became Dependent on Treatment | 16 (9) | 103 (57) | 80 (11) | 402 (56) | 96 (11) | 505 (56) |
| Discontinued Due to Adverse Events | 45 (25) | 75 (41) | 185 (26) | 298 (41) | 230 (25) | 373 (41) |
| Discontinued Due to Infusion Reaction* | 0* | 9 (5) | 0* | 34 (5) | 0* | 43 (5) |
| * "Discontinued Due to Infusion Reaction"categorized as "NA" for 111 (61), 450 (62), and 561 (62) subjects in the placebo, natalizumab, and overall groups, respectively, based on marking of "NA" category on Case Report Form for question "Discontinue due to Infusion Reaction?". | | | | | | |

(Values in table above are taken from Page 295 of the Study Report for Study CD301.)

**Table 78. Steroids: Response, Dependence, and Reason for Discontinuation – N (%)**

| Variable Statistics | Placebo (n=181) | | Natalizumab (n=724) | | Overall (n=905) | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| Responded to Initial Treatment | 151 (83) | 7 (4) | 616 (85) | 27 (4) | 767 (85) | 34 (4) |
| Lost Response with | 46 (25) | 111 (61) | 219 (30) | 423 (58) | 265 (29) | 534 (59) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Continued Treatment | | | | | | |
| Became Dependent on Treatment | 60 (33) | 97 (54) | 258 (36) | 385 (53) | 318 (35) | 482 (53) |
| Discontinued Due to Adverse Events | 21 (12) | 137 (76) | 83 (11) | 560 (77) | 104 (11) | 697 (77) |
| Discontinued Due to Infusion Reaction* | 0 (0)* | 14 (8) | 1 (0)* | 57 (8) | 1 (0)* | 71 (8) |
| * "Discontinued Due to Infusion Reaction"categorized as "(NA)" for 145 (80), 585 (81), and 730 (81) subjects in the placebo, natalizumab, and overall groups, respectively, based on marking of "NA" category on Case Report Form for question "Discontinue due to Infusion Reaction". | | | | | | |

(Values in table above are taken from Page 296 of the Study Report for Study CD301.)

**Table 79. Anti-TNF Therapy: Response, Dependence, and Reason for Discontinuation – N (%)**

| Variable Statistics | Placebo (n=181) | | Natalizumab (n=724) | | Overall (n=905) | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| Responded to Initial Treatment | 54 (30) | 15 (8) | 225 (31) | 66 (9) | 279 (31) | 81 (9) |
| Lost Response with Continued Treatment | 279 (31) | 81 (9) | 96 (13) | 192 (27) | 119 (13) | 236 (26) |
| Became Dependent on Treatment | 2 (1) | 67 (37) | 13 (2) | 277 (38) | 15 (2) | 344 (38) |
| Discontinued Due to Adverse Events | 13 (7) | 56 (31) | 50 (7) | 240 (33) | 63 (7) | 296 (33) |
| Discontinued Due to Infusion Reaction* | 9 (5)* | 55 (30) | 35 (5)* | 212 (29) | 44 (5)* | 267 (30) |
| * "Discontinued Due to Infusion Reaction" categorized as "(NA)" for 5 (3), 44 (6), and 49 (5) subjects in the placebo, natalizumab, and overall groups, respectively, based on marking of "NA" category on Case Report Form for question "Discontinue due to Infusion Reaction". | | | | | | |

(Values in table above are taken from Page 296 of the Study Report for Study CD301.)

**Table 80. Antibiotics: Response, Dependence, and Reason for Discontinuation – N (%)**

| Variable Statistics | Placebo (n=181) | | Natalizumab (n=724) | | Overall (n=905) | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| Responded to Initial Treatment | 64 (35) | 16 (9) | 241 (33) | 58 (8) | 305 (34) | 74 (8) |
| Lost Response with Continued Treatment | 18 (10) | 62 (34) | 80 (11) | 219 (30) | 98 (11) | 281 (31) |
| Became Dependent on Treatment | 1 (1) | 78 (43) | 15 (2) | 284 (39) | 16 (2) | 362 (40) |
| Discontinued Due to Adverse Events | 15 (8) | 65 (36) | 39 (5) | 261 (36) | 54 (6) | 326 (36) |
| Discontinued Due to Infusion Reaction* | 0 (0)* | 7 (4) | 2 (0)* | 22 (3) | 2 (0)* | 29 (3) |
| * "Discontinued Due to Infusion Reaction" categorized as "(NA)" for 74 (41), 276 (38), and 350 (39) subjects in the placebo, natalizumab, and overall groups, respectively, based on marking of "NA" category on Case Report Form for question "Discontinue due to Infusion Reaction". | | | | | | |

(Values in table above are taken from Page 297 of the Study Report for Study CD301.)

# Appendix 3

## Study CD303 (Selected Study Features)

Primary Endpoint - Contingent Sequential Analysis:

The contingent sequential analysis first tested the hypothesis of the primary endpoint at the 0.05 significance level. If the primary endpoint was significant, the hypothesis of the contingent primary endpoint was to be tested at the 0.05 level. If the primary endpoint was not significant, the hypothesis related to clinical remission was not to be tested as a contingent primary endpoint.

Steroid Taper Algorithm:

All subjects receiving oral steroids are required to undergo a taper immediately upon entry into Study CD303 (i.e., at Week 10 Study CD301) using the following algorithm:

- Subjects on doses equivalent to > 10 mg of prednisolone will begin their taper at a rate of 5 mg every 7 days until they reach a dose of 10 mg. If the patient is receiving 11–14 mg the dose should be reduced to the equivalent of 10 mg prednisolone for 7 days, followed by the standard taper schedule below;
- Subjects on doses equivalent to ≤ 10 mg of prednisolone will be tapered at a rate of 2.5 mg every 7 days until they are completely withdrawn.
- Subjects taking budesonide should be tapered at a rate of 3 mg every 3 weeks until they are completely withdrawn.

Subjects whose symptoms worsen significantly may interrupt their taper by either halting the dose decreases or by having their dose re-increased up to their baseline level. All subjects who interrupt the taper must re-start within 4 weeks, continuing according to the algorithm outlined above.

Subjects who re-increase their dose above baseline levels, which is considered rescue intervention, or whose CDAI increases to ≥ 220 AND there is ≥ 70 point increase in the CDAI score from the baseline (Week 12), will be considered treatment failures.

# Appendix 4

## SAEs in Placebo-controlled Studies of MS

[Values in the table below are taken from the BLA Review 125104/15 Alice Hughes, M.D. and Susan S. McDermott, M.D. (5/18/06) and confirmed with values in table found on pages 82-89 of the Summary of Clinical Safety]

**Table 81. SAEs in Placebo-controlled Studies of MS - SAEs that Occurred in ≥ 0.1% of Natalizumab-treated Patients (and at Greater Frequency than in Placebo-treated Patients)**

| Serious Adverse Event | Placebo (n=1135) % (No.) | Natalizumab (n=1617) % (No.) |
|---|---|---|
| All | 18.9% (214) | 15.5% (251) |
| Infections and infestations | 2.2% (25) | 2.4% (39) |
| Urinary tract infection (UTI)* | 0.5% (6) | 0.6% (10) |
| Pneumonia* | 0.2% (2) | 0.4% (6) |
| Appendicitis | 0.3% (3) | 0.4% (6) |
| Urinary tract infection NOS | 0.2% (2) | 0.4% (6) |
| Viral infection NOS | 0 | 0.2% (3) |
| Infection NOS | <0.1% (1) | 0.1% (2) |
| Pyelonephritis NOS | <0.1% (1) | 0.1% (2) |
| Sinusitis NOS | <0.1% (1) | 0.1% (2) |
| Urosepsis | <0.1% (1) | 0.1% (2) |
| Blood and lymphatic system disorders | 0.2% (2) | 0.3% (5) |
| Thrombocytopenia | 0 | 0.1% (2) |
| Immune system disorders | 0.2% (2) | 0.8% (13) |
| Anaphylactic reaction | 0.2% (2) | 0.3% (5) |
| Anaphylactoid reaction | 0 | 0.1% (2) |
| Hypersensitivity NOS | 0 | 0.2% (4) |
| Metabolism and nutrition disorders | | |
| Dehydration | <0.1% (1) | 0.2% (3) |
| Nervous system disorders | | |
| Grand mal convulsion | <0.1% (1) | 0.1% (2) |
| Gastrointestinal disorders | 0.8% (9) | 1.2% (19) |
| Abdominal pain NOS | 0 | 0.2% (4) |
| Appendicitis perforated | 0 | 0.1% (2) |
| Colitis NOS | 0 | 0.1% (2) |
| Gastritis NOS | 0 | 0.1% (2) |
| Nausea | 0 | 0.1% (2) |
| Hepatobiliary disorders | | |
| Cholelithiasis | 0.3% (3) | 0.6% (9) |
| Cholecystitis NOS | 0 | 0.1% (2) |
| Skin and subcutaneous tissue disorders | | |
| Rash NOS | <0.1% (1) | 0.1% (2) |
| Urticaria NOS | <.1% (1) | 0.1% (2) |
| Musculoskeletal and connective tissue disorders | | |
| Localised osteoarthritis | <0.1% (1) | 0.1% (2) |
| Renal and urinary disorders | 0.3% (3) | 0.4% (7) |
| Reproductive system and breast disorders | 0.5% (6) | 0.7% (12) |
| Ovarian cyst | 0 | 0.2% (4) |
| Cervical dysplasia | 0 | 0.1% (2) |

| | | |
|---|---|---|
| General disorders and administrative site conditions | 0.7% (8) | 0.8% (13) |
| Asthenia | 0 | 0.1% (2) |
| Fatigue | 0 | 0.1% (2) |
| Injury, poisoning and procedural complications | 0.9% (10) | 1.7% (28) |
| Fall | <0.1% (1) | 0.3% (5) |
| Overdose NOS | 0 | 0.2% (3) |
| Road traffic accident | <0.1% (1) | 0.2% (3) |
| Alcohol poisoning | <0.1% (1) | 0.1% (2) |
| Closed head injury | 0 | 0.1% (2) |
| Head injury | <0.1% (1) | 0.1% (2) |
| Hip fracture | 0 | 0.1% (2) |
| Post-procedural pain | 0 | 0.1% (2) |
| Thermal burn | 0 | 0.1% (2) |

NOTE (1) A subject was counted only once within each system organ class/preferred term.
(2) Preferred terms are presented by decreasing incidence in the Natalizumab column within each system organ class.

# Appendix 5

## SAEs in CD Placebo-Controlled Studies

**Table 82. SAEs Occurring in ≥ 0.2% of Natalizumab-treated Subjects and More Frequently than in Placebo-treated Subjects (Short-term Placebo controlled Studies of CD)**

| Serious Adverse Event | Placebo (n=506) % (No.) | Natalizumab (n=1182) % (No.) |
|---|---|---|
| All | 14.0% (71) | 14.9% (176) |
| Infections and infestations | | |
| Abdominal abscess NOS | 0.2% (1) | 0.3% (3) |
| Meningitis viral NOS | 0 | 0.2% (2) |
| Urinary tract infection NOS | 0 | 0.2% (2) |
| Neoplasms | 0.2% (1) | 0.7% (8) |
| Lung adenocarcinoma NOS | 0 | 0.2% (2) |
| Blood and lymphatic system disorders | 0 | 0.4% (5) |
| Anemia NOS | 0 | 0.3% (4) |
| Immune system disorders | 0.2% (1) | 0.4% (5) |
| Hypersensitivity NOS | 0 | 0.3% (3) |
| Nervous system disorders | 0.2% (1) | 0.5% (6) |
| Cardiac disorders | 0 | 0.4% (5) |
| Respiratory, thoracic, and mediastinal disorders | 0.2% (1) | 0.3% (3) |
| Pulmonary embolism | 0 | 0.2% (2) |
| Gastrointestinal disorders | | |
| Intestinal obstruction NOS | 0.6% (3) | 0.8% (9) |
| Small intestinal obstruction NOS | 0.4% (2) | 0.8% (9) |
| Intestinal stenosis NOS | 0 | 0.5% (6) |
| Vomiting NOS | 0 | 0.3% (4) |
| Abdominal adhesions | 0 | 0.3% (3) |
| Intestinal fistula | 0 | 0.3% (3) |
| Gastrointestinal haemorrhage | 0 | 0.2% (2) |
| Nausea | 0 | 0.2% (2) |
| Peritonitis | 0 | 0.2% (2) |
| Small intestinal perforation NOS | 0 | 0.2% (2) |
| Hepatobiliary disorders | 0 | 0.4% (5) |
| Cholelithiasis | 0 | 0.3% (4) |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia | 0 | 0.3% (3) |
| Renal and urinary disorders | 0.2% (1) | 0.3% (4) |
| Reproductive system and breast disorders | 0 | 0.3% (4) |
| Investigations | 0.2% (1) | 0.3% (3) |
| Surgical and medical procedures | 0 | 0.2% (2) |

[Values in the table above taken from pages 82-89 of the Summary of Clinical Safety]
[Design of table taken from BLA Review 125104/15 by Drs. Alice Hughes, and Susan S. McDermott (5/18/06) ]

# Section 2

# FDA

# Office of Surveillance &

# Epidemiology

# Review of Tysabri Risk

# Minimization Plan

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

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| Date: | July 2, 2007 |
| To: | FDA Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Members |
| Thru: | Gerald Dal Pan, M.D., M.H.S., Director<br>Office of Surveillance and Epidemiology (OSE) |
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| Subject: | Tysabri Risk Minimization Action Plan |
| Drug Name(s): | TYSABRI (Natalizumab) |
| Application Type/Number: | BLA 125104/33 |
| Applicant/sponsor: | Biogen Idec |
| OSE RCM #: | 2007-431 |

# CONTENTS

## EXECUTIVE SUMMARY

This is a review of the Sponsor's RiskMAP for Tysabri, a recombinant humanized monoclonal antibody currently approved for relapsing Multiple Sclerosis (MS), with a Risk Minimization Action Plan (RiskMAP). The RiskMAP was proposed to minimize the risk of Progressive Multifocal Leukoencephalopathy (PML) identified in the MS clinical trials. The Sponsor has proposed a program for patients with Crohn's Disease (CD) that is the same as the program already in place for MS. The RiskMAP consists of mandatory enrollment of prescribers, patients, infusion sites, and central pharmacies affiliated with authorized infusion centers, controlled distribution, mandatory monitoring and follow-up of patients by prescribers and infusion site staff, and education directed at healthcare providers and patients.

At this time the Tysabri RiskMAP appears to be satisfactorily working in the MS population. There has been good compliance with RiskMAP processes by prescribers and infusion site staff. The surveys of prescribers and nurses indicate a high level of understanding of the risks and requirements of the RiskMAP. To date, there have been no reports of PML or other serious opportunistic infections (OI) reported to the Agency since the reintroduction of Tysabri into the marketplace (clinical trials and in the postmarketing setting).

We recommend the Advisory Committee members discuss the RiskMAP and its implementation in the CD population with regard to the following critical issues:

- The best way to monitor the CD population for PML and other OIs
- Identification of the appropriate patient for Tysabri and how in clinical practice these patients would be identified
- Whether concomitant immunosuppressive and immunomodulatory therapy will be permitted and how flares of CD will be dealt with

The details of this discussion will be considered in the final design of the CD-TOUCH RiskMAP program.

# 1 BACKGROUND

## 1.1 INTRODUCTION

Natalizumab (Tysabri®) is a recombinant humanized monoclonal antibody that was originally approved in the United States on November 23, 2004 for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations. Its mechanism of action is inhibition of the alpha-4 mediated transvascular migration of leukocytes. The recommended dose of Tysabri is 300mg IV infusion administered every 4 weeks.

## 1.2 REGULATORY HISTORY

Tysabri was originally approved in the United States on November 23, 2004 for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations. Marketing and clinical trials were voluntarily suspended on February 28, 2005 after two patients enrolled in a long-term clinical trial developed PML. Both patients had been treated with natalizumab for MS for more than two years. A third case of fatal PML, originally diagnosed as astrocytoma, was discovered in a patient with CD who had also been in a clinical trial of Tysabri. The patients had received 8 to 37 monthly infusions. Thus, there have been a total of three confirmed cases identified from clinical trials involving approximately 3000 patients.[1]

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[1] Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. NEJM 354; 9: 924-33.

In February 2006, FDA removed the hold in clinical trial dosing of Tysabri in MS patients in the US. On March 7-8, 2006 the Peripheral and Central Nervous System Drugs Advisory Committee convened to discuss the risks associated with Tysabri administration, the efficacy of Tysabri in the treatment of MS, the possible return of Tysabri to the marketplace, and proposed Risk Minimization Action Plan (RiskMAP) for Tysabri. Given the highly efficacious nature of this product in MS, the AC recommended that the FDA approve Tysabri for return to the U.S. market for MS provided that it is approved with a RiskMAP that should include mandatory patient registration of all patients and their physicians, periodic follow-up to identify, as early as possible, any cases of PML that may occur, dosing of the drug at authorized infusion centers only and screening for symptoms suggestive of PML prior to each dose, as well as warnings in the prescribing information. On June 5, 2006 Tysabri was approved for resumed marketing under 21 CFR 601.42 Subpart E with a boxed warning for PML, a Medication Guide, a revised indication for use,[2] and a performance-linked access systems (PLAS)[3] RiskMAP that is consistent with the AC's recommendations. Tysabri's indication statement was revised to include the risk of PML, to denote it for use as monotherapy, and to relegate it to a second-line therapy for relapsing-remitting MS.

The European Commission granted European Union-wide marketing authorization for Tysabri for the treatment of MS on 27 June 2006. Tysabri is also approved in Australia, Canada, Israel and Switzerland for treatment of MS. The marketing of this drug outside of the U.S. does not require restricted access.

## 2 METHODS AND MATERIALS

The following documents were reviewed:

- Tysabri (Natalizumab) Risk Management Plan, dated December 1, 2006 and submitted on December 15, 2006 (for both the MS and CD indications)
- Tysabri RiskMAP Submissions, dated and submitted on September 22, 2006, December 21, 2006, and April 9, 2007
- Tysabri Periodic Safety Update Report, 24 November 2006 to 23 May 2007, dated June 22, 2007
- Tysabri approved labeling 6/5/07, available at http://www.tysabri.com/tysbProject/tysb.portal
- Tysabri draft labeling, submitted to the BLA 12/18/2006, available in the EDR.

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[2] The indication was revised from:

> TYSABRI® is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. (truncated)

To:

> TYSABRI is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. Because TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies. (truncated)

[3] Performance-linked access systems include systems or tools that link product access to laboratory testing results or other documentation of safe use. Guidance for Industry: Development and Use of Risk Minimization Action Plans, March 2005.

- Tysabri RiskMAP Educational and Enrollment materials, submitted to the BLA 1/12/2007 and 5/30/2007, available in EDR
- Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. NEJM 354; 9: 924-33.

# 3 RESULTS OF REVIEW

## 3.1 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

PML is a serious and often fatal disease of the brain white matter, characterized by dementia and progressive motor deterioration. The disease is thought to be caused by reactivation of latent JC virus infection in immunodeficient individuals such as those with AIDS and organ transplant recipients, or cancer patients who have received immunosuppressive medications. JC virus is carried in a latent form by 70-75% of the general population, but generally does not cause symptoms.

Consideration for the diagnosis of PML should be triggered by the clinical circumstance of a patient with immune suppression and neurologic symptomatology progressing over days to weeks. Although PML is rare, when it occurs, it frequently results in irreversible neurologic deterioration and death. Although several therapies have been used to treat PML in AIDS patients, at this time there is no known effective treatment for the disease.

The risk of acquiring PML in patients treated with natalizumab is currently estimated at 1 per 1000 patients (based on the 3 confirmed cases of PML cases in approximately 3000 patients treated with natalizumab). The risk with longer treatment and concomitant immunosuppressive or immunomodulatory agents is unknown. There have been no additional cases of PML in patients enrolled in clinical trials or reported to the Adverse Event Reporting System at FDA.

The total exposure to Tysabri in the clinical trial setting is 4,303 patients (2,433 in MS trials, 1,639 in CD trials, and 231 in Rheumatoid Arthritis trials). Worldwide postmarketing exposure to Tysabri is estimated to be 16,900 patients from initial marketing (23 November 2004) to 23 May 2007. Of the worldwide numbers of exposed patients 13,745 are US patients (~7500 exposed during the initial marketing phase from 23 November 2004 to 28 February 2005).[4]

## 3.2 TYSABRI RISKMAP

### 3.2.1 OVERVIEW

The Tysabri RiskMAP is entitled the TOUCH (Tysabri Outreach: Unified Commitment to Health) Prescribing Program. The Sponsor proposes two versions of the RiskMAP, the MS-TOUCH program for the approved MS indication, and CD-TOUCH for the proposed Crohn's Disease indication. The goals and key features of the two versions are the same; the differences that exist are primarily limited to customization of educational materials and forms to the respective Crohn's patients, their prescribers, and infusion site staff.

The risk minimization and risk assessment goals of TOUCH are:

- To promote informed risk benefit decisions regarding Tysabri use in MS and CD patients.
- To minimize the risk of PML
- To minimize death and disability due to PML

[4] Tysabri PSUR: 24 November 2006 to 23 May 2007, dated June 22, 2007, Section 5, pgs 16-19.

- To determine the incidence and risk factors for PML and other serious opportunistic infections (OI) with Tysabri treatment
- To assess further the overall safety profile of Tysabri

The key features of the Tysabri RiskMAP include mandatory enrollment of prescribers, patients, infusion sites, and central pharmacies affiliated with authorized infusion centers, controlled distribution, mandatory monitoring and follow-up of patients by prescribers and infusion site staff, and education directed at healthcare providers and patients. Each of these features is described is greater detail below.

### 3.2.2 RISKMAP TOOLS

#### 3.2.2.1 PERFORMANCE LINKED ACCESS TOOLS

- **Mandatory enrollment of Prescribers and Patients**—The RiskMAP requires enrollment of all patients and prescribers. MS patients will enroll into the MS-TOUCH program and Crohn's disease patients will enroll in CD-TOUCH. The process for enrollment in both versions of TOUCH is the same.
- **Mandatory enrollment of Infusion Sites**—The RiskMAP requires that all infusion sites that will administer Tysabri enroll and undergo mandatory training by Biogen Idec.
- **Mandatory enrollment of Central Pharmacies**—Central pharmacies that are affiliated with authorized infusion sites must be enrolled in the TOUCH program. Central pharmacies are located within a hospital, group practice, or infusion site and are affiliated with the infusion site.
- **Controlled distribution system--**Tysabri is only distributed by Specialty Pharmacy Providers (SPPs) to authorized and trained infusion sites or their affiliated central pharmacies.
- **Mandatory completion of a preinfusion checklist** by infusion site staff and real-time submission of complete preinfusion checklist to Biogen Idec. This puts into place a mechanism that ensures that all patients are monitored and evaluated monthly before each infusion. It also allows for monitoring for infusion site compliance and Tysabri dosing on a patient-specific basis.

#### 3.2.2.2 REMINDER TOOLS

- **Prescriber, Patient, Infusion Site, and Central Pharmacy Acknowledgement**—Each of the enrolled entities (prescriber, patient, infusion site, and central pharmacy) is required to acknowledge their responsibilities under the TOUCH Program. The Physician and Patient Acknowledgement are included on the Patient/Physician Enrollment Form. Likewise, the enrollment forms for the Infusion Sites and Central Pharmacies also include an acknowledgement section. The acknowledgment statements for each of the enrolled entities are included in Appendices 1-4.
- **Mandatory prescriber reauthorization** of Tysabri dosing for each patient every 6 months. This puts into place a mechanism to facilitate close clinical follow-up of the patient by their prescribing physician.

#### 3.2.2.3 EDUCATION AND OUTREACH TOOLS

The Sponsor has developed materials to educate healthcare providers and their patients about the potential risks for and consequences of PML. These materials have been previously reviewed by FDA prior to approval of the Tysabri RiskMAP, and implemented when the product was reintroduced to the market for MS patients. The Sponsor proposes to update relevant materials or

include both MS and CD versions of these materials if appropriate and if Tysabri is approved for use in CD.

- **Patient Materials**
  - **Medication Guide**—this is distributed to the patient by infusion site staff prior to each Tysabri infusion. The use of the Patient Infusion Checklist facilitates this distribution. The Medication Guide will be updated to include information regarding Tysabri use in CD.
  - **Getting Started Brochure**—this is designed to assist the patient who is considering starting treatment with Tysabri. It contains information on the risks and the TOUCH program. A CD-TOUCH version will be developed. The current approved version will be renamed MS-TOUCH.
  - **Prescriber/Patient Enrollment Form**—The form will be used to 1) convey risk information to the patient and prescriber and 2) to collect demographic information, diagnosis, and most recent MS or CD therapy. It also includes a Tysabri prescription and a Patient-Prescriber Acknowledgement section. The form also includes a Patient Authorization to Use/Disclose Health Information section, a Patient Acknowledgement section, Administration Site Information section, a Physician Acknowledgement section, and the prescription for Tysabri, which allows for up to 12 refills.
  - **Dear Patient Letter**— a letter that provides communication regarding important safety information to patients who expressed an interest in receiving updates regarding Tysabri. A letter will be sent to CD patients if Tysabri is approved for use in CD.

- **Prescriber Materials**
  - **TOUCH Enrollment Kit**—provided to potential prescribers and outlines specific responsibilities of each of the participants in the program. There will be separate CD-TOUCH and MS-TOUCH versions.
  - **Prescriber/Patient Enrollment Form**—see details above.
  - **Patient Discontinuation Notification Form**—completed by prescriber to inform Biogen Idec that patient has been permanently discontinued from Tysabri therapy. There will be MS and CD specific forms.
  - **Patient Discontinuation Questionnaire**—this questionnaire will be provided to prescribers when a patient discontinues Tysabri and 6 months after discontinuation. There will be MS and CD specific questionnaires.
  - **Status Report and Reauthorization Questionnaire**—The purpose of this questionnaire is to ascertain the vital status of the patient and the occurrence of PML or other serious OIs and for the prescriber to reauthorize the patient to continue to receive Tysabri for the next 6 months. There will be MS and CD-specific versions of the questionnaire but the process will be the same. The following questions are included in the questionnaire:

| **Patient Status Report and Reauthorization Questions** | |
|---|---|
| Is this patient still under your care? | |
| Is the patient alive? | |
| Does the patient have a diagnosis of PML that you have not already reported to Biogen Idec? | |
| Has the patient been hospitalized for an opportunistic infection that you have not already reported to Biogen Idec? | |
| (MS Version) Is the patient currently receiving or has the patient received intermittent courses of steroids for the treatment of MS relapse in the previous 6 months? If YES, please indicate the number of courses received. | (proposed CD Version) Is the patient currently receiving or has the patient received intermittent courses of steroids for the treatment of CD flare in the previous 6 months? If YES, please indicate the number of courses received. |

| | |
|---|---|
| (MS Version) Is the patient currently or has the patient received any immunomodulatory or immunosuppressant therapies in the previous 6 months? If YES, please indicate the type of therapy (AVONEX, Betaseron, Capaxone, Rebif, Novantrone, Azathioprine, Methotrexate, Mycophenolate, Cyclophosphamide, Chronic Systemic Steroids or Other immunomodulatory or immunosuppressive therapy) and number of months of use. | (proposed CD Version) Is the patient currently or has the patient received any immunomodulatory or immunosuppressant therapies in the previous 6 months? If YES, please indicate the type of therapy (Remicade, Humira Azathioprine, Methotrexate, Mercaptopurine, Thioguanine, Orencia, Systemic Steroids or Other immunomodulatory or immunosuppressive therapy) and number of months of use. |

- **Dear Doctor Letter**— a letter that provides communication regarding important safety information for use in CD patients will be sent to potential prescribers for CD.

- **Infusion Site Materials**
  - **Infusion Site Enrollment Form**—to be completed and signed by infusion site for enrollment into the TOUCH Program.
  - **Healthcare Professional Infusion Guide**—provides step-by-step considerations for appropriate infusion and reinforcement of TOUCH requirements. Currently approved materials will be used.
  - **Pre-infusion Patient Checklist**—this checklist must be completed by the infusion site staff prior to each Tysabri infusion. The purpose of the form is to minimize inappropriate use of Tysabri and facilitate early detection or worsening of neurological symptoms that may be indicative of PML. There will be MS and CD-specific versions of the checklist but the process will be the same. The following questions are included in the Pre-infusion Patient Checklist:

| **Pre-Infusion Checklist Questions** | |
|---|---|
| Over the past month, have you had new or worsening medical problems (such as a new or sudden change in your thinking, eyesight, balance, strength, or other problems) that have persisted over several days? | |
| Do you have a medical condition that can weaken your immune system, such as HIV infections or AIDS, leukemia or lymphoma, or organ transplant, that may suggest that your body is not able to fight infections well? | |
| (MS Version) In the past month, have your taken medicines to treat cancer or MS or any other medicines that weaken your immune system? | (proposed CD Version) In the past month, have your taken medicines to treat cancer or CD or any other medicines that weaken your immune system? |
| (MS Version) In the past month, other than for the treatment of a recent relapse, have you taken any of the following medicines: Solu-Medrol, methylprednisolone, Decadron, dexamethasone, Depro-Medrol, prednisone, or other steroid medicines? | (proposed CD Version) In the past month, other than for the treatment of a recent flare, have you taken any of the following medicines: betamethasone, budesonide (Entocort ECTM), dexamethasone (Decadron), methylprednisolone, prednisone, or other steroid medicines? |

- **Central Pharmacy Materials**
  - **Central Pharmacy Enrollment Form--** form to be completed and signed by central pharmacy for enrollment into the TOUCH Program.
  - **Tysabri Inventory Tracking Log**—required by central pharmacies to document dispensing of Tysabri to authorized infusion sites. Currently approved form will be used.

- **General Materials (HCPs and/or Patients)**
  - **TOUCH Prescribing Program Education Slide Set**—Powerpoint presentation to educate about the TOUCH Program. It will be updated to include CD program elements.
  - **TOUCH Prescribing Program Overview**—general description of TOUCH outlining responsibilities of all participants.
  - **Tysabri.com**—a website designed to disseminate approved labeling information and an overview of the TOUCH Program.
  - **Guidance for Evaluation of New Neurologic Symptoms in Patients Receiving Tysabri**—this document provides guidance to HCPs when undertaking the assessment and management of new or worsening neurologic symptoms in MS and CD patients treated with Tysabri.

### 3.2.3 SPONSOR'S RISKMAP OPERATIONAL COMPONENTS

The RiskMAP submission includes a description of the RiskMAP processes for the prescribers, patients, infusion sites, central pharmacies, and the Sponsor in operationalizing the RiskMAP.

**TOUCH Prescriber and Patient Enrollment/De-enrollment/Reauthorization Process**

1. Initial Enrollment
   a. Prescribers and patients complete and return to Biogen Idec the Physician-Patient Enrollment Form prior to the patient initiating therapy with Tysabri. There will be MS and CD-specific enrollment forms. Information from this form will be entered into the TOUCH database
   b. Biogen will assign a unique identification number. This number will remain the same for that patient even if they de-enroll and are subsequently re-enrolled into the program.
   c. Biogen Idec will match the patient to an enrolled infusion site or confirm that the infusion site that the physician has referred the patient to is enrolled in the TOUCH Prescribing Program. Biogen Idec will then fax a *Notice of Patient Authorization* to the infusion site and the prescriber. This form includes an authorization period which is 6 months from the first confirmed infusion.
   d. A new Physician-Patient Enrollment Form will need to be completed if the patient changes physicians.
2. Reauthorization of Patients—Prescribers are required to reauthorize all patients every six months. The purpose of reauthorization is to determine the vital status of the patient, the occurrence of PML or other opportunistic infections, and to determine if the patient is still a candidate for Tysabri treatment.
   a. At approximately 4 ½ to 5 ½ months after the initial Tysabri dose and every 24 weeks thereafter, Biogen Idec will send the enrolled prescribing physician a *Patient Status Report and Reauthorization Questionnaire*.
   b. Once Biogen receives this form from the prescriber, they will link the data to the patient, infusion site and prescriber in the TOUCH database and then send a Notice of Patient Authorization to the assigned infusion center. This notice is to be placed in the patient's file. This authorization is valid for six months.
   c. The infusion center will be authorized to allow one infusion past the authorization date in the event the prescriber forgot to send in the reauthorization form.
3. De-enrollment
   a. Deenrollment of physicians from the TOUCH Prescribing Program can occur if prescribing physicians exhibit a significant pattern of non-compliance with the

requirements of the RiskMAP. Affected patients will be redirected to other enrolled physicians in the area or may be de-enrolled.

b. De-enrollment of patients from the TOUCH Prescribing Program will occur if the patient discontinues treatment with Tysabri as indicated on the *Patient Status and Reauthorization Questionnaire* or if the physician fails to complete the *Patient Status Reauthorization Questionnaire*. Infusion sites and prescribers will receive a *Notice of Discontinuation* from Biogen for patients that have been de-enrolled from the program. If a patient discontinues Tysabri treatment Biogen will additionally call the infusion site to confirm that the patient is not scheduled for future Tysabri infusions.

**Infusion Site Processes**

1. Training and Enrollment
    a. Biogen will visit the prospective infusion site and provide training on the known risks, potential benefits, and appropriate use of Tysabri, and the requirements of the program. Sites that have previously been trained will be reeducated regarding the CD-TOUCH version of the program.
    b. The infusion site will complete and sign the *Infusion Site Enrollment Form*. The form will be signed by a person with appropriate authority at the infusion site.
    c. The form is sent to Biogen. Information from the form is entered into the TOUCH database and a unique Site Authorization Number is assigned. This number is required to order Tysabri.
2. Prior to Each Infusion
    a. Prior to each Tysabri infusion, the authorized infusion site must verify the patient is currently authorized to receive Tysabri treatment.
        i. Confirm that there is a current Notice of Patient Authorization on file and that the infusion is with the current authorization period
        ii. Confirm there is not Notice of Discontinuation on file
    b. Provide the Tysabri medication guide to patients authorized to receive Tysabri
    c. Complete a Pre-infusion Patient Checklist
3. Pre-Infusion Patient Checklist
    a. The infusion site staff must complete the Pre-infusion Patient Checklist for every patient authorized to receive Tysabri. The checklist includes 4 questions
        i. If the patient answers NO to all 4 questions, the patient may be infused
        ii. If the patient answers YES to any of the 4 questions, the prescriber needs to be contacted for further instructions. The nurse discusses the findings and the prescriber either instructs the nurse to proceed with the infusion or instructs the nurse not to infuse the patient and to refer the patient to the prescriber for further evaluation. The nurse must document if authorization was given.
    b. The infusion site enters the next scheduled infusion date. Entering the date allows Biogen to follow-up for future missing checklists.
    c. The infusion site faxes the Pre-infusion Checklist to Biogen within 1 business day of the patient's visit. A Pre-infusion Checklist must be completed and faxed to Biogen for all patients scheduled to receive Tysabri, regardless of whether the patient was infused or not.
    d. Data from the checklist is entered into the TOUCH database. This allows Biogen to monitor infusion site compliance with completion of the checklist as well as tracking the infusions on a per patient basis.

**Central Pharmacy Processes**

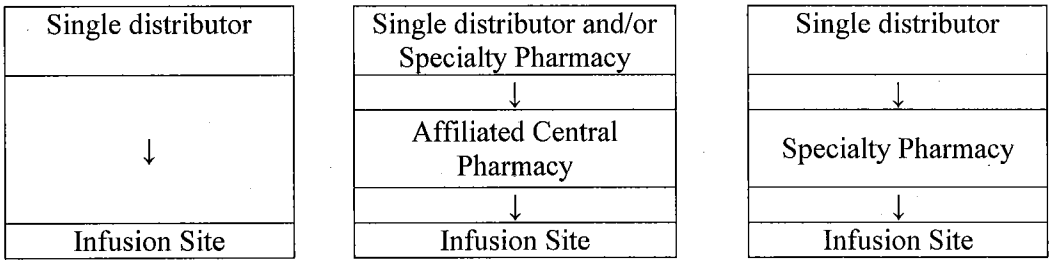
1. Training and Enrollment

a. Biogen will provide educational materials to the Central Pharmacy on TOUCH Prescribing Program and requirements of the program. Training will be updated to incorporate the addition of CD-TOUCH
b. The central pharmacy will complete and sign the *Central Pharmacy Enrollment Form*. The form will be signed by a person with appropriate authority at the central pharmacy.
c. The form is sent to Biogen. Information from the form is entered into the TOUCH database and a unique Site Authorization Number is assigned. This number is required to order Tysabri.

2. Distribution to Infusion Sites
   a. These central pharmacies may only dispense product to these authorized infusion sites and must keep a TOUCH Central Pharmacy Inventory Tracking Log which is meant to document each instance Tysabri is released by the central pharmacy including the number of vials released and the infusion site (including its unique Site Authorization Number). The central pharmacies are required to retain these logs for 5 years.

**Central Distribution Process**

1. The distribution or product flow of Tysabri will occur in one of the following manners.




2. The infusion site will obtain product either:
   a. directly from the single distributor,
   b. from a central pharmacy who obtains the product from the single distributor, or
   c. from a specialty pharmacy who obtains the product from the single distributor
3. The specialty pharmacy and single distributor will be required to obtain a shipment authorization number from Biogen prior to shipping Tysabri to either the central pharmacy or the authorized infusion site.
4. Only central pharmacies that are affiliated with an authorized infusion site(s) will be eligible to dispense Tysabri.
5. An acceptable order quantity for infusion sites and central pharmacies will be established on a site-by-site basis taking into account the amount of drug previously shipped to the site relative to the confirmed and expected demand from enrolled patients at the site. An acceptable order quantity will not be established for specialty pharmacies because they only dispense on a per patient basis.

## 3.3 PHARMACOVIGILANCE ACTIVITIES

### 3.3.1 SPECIAL ASSESSMENTS FOR PML, OTHER SERIOUS OI, AND DEATH

The Sponsor will rapidly follow-up on all cases of reported PML, OI, and death, both those reported spontaneously and through the regular follow-up questionnaires (described above). These reports will be submitted to the Agency within 15 days of receipt by the Sponsor.

- **PML**—The Sponsor will attempt to obtain source documentation such as clinical findings, MRI, and CSF JC viral DNA results. A case will be considered confirmed based on pre-defined criteria developed in collaboration with an external panel of experts. Indeterminate cases will be submitted to an external expert for opinion on the final diagnosis. The Sponsor will attempt to identify any potential risk factors based upon the data collected.
- **Serious OI**—similar diligence will be exercised for reported OI cases. Serious OI is defined as an infection due to an organism that generally does not cause disease, or causes only mild or self-limited disease, in people with normally functioning immune systems, but causes more significant disease in people with impaired immunity.
- **Deaths**—similar diligience will be exercised for all reported death cases. Death certificates will be obtained on all patients that have died. The National Death Index will be queried to ascertain the vital status of any patient lost to follow-up.

### 3.3.2 TYGRIS

The Sponsor will conduct two voluntary observational studies, one in MS patients the other in CD patients. The TYGRIS (TYSABRI Global Observational Program in Safety) protocol in MS patients has already been reviewed by OSE. Briefly, it is a prospective, observational cohort study of approximately 3000 MS patients to be treated with Tysabri in the United States and Canada. Additionally, approximately 2000 MS patients in the rest of the world will be enrolled in a separate cohort. The enrolled patients will be systematically followed for up to five years. The primary objective of the study is to determine the incidence and pattern of serious infections, malignancies, and other SAEs with longer-term use of Tysabri in MS.

The Sponsor proposes that the CD Observational Study will enroll approximately 4000 CD patients worldwide, of which approximately 2000 patients will be authorized in the US, and these patients will also be followed for up to five years. A smaller sample size is being proposed in the CD study because the Sponsor states that there is a higher rate of serious OI observed in the placebo-controlled and open-label studies of Tysabri in CD.

### 3.3.3 OTHER PHARMOCOVIGILANCE ACTIVITIES/STUDIES

The Sponsor plans the following additional clinical activities:

- National Death Index (NDI) Search – the NDI will be queried to ascertain the vital status of any patient lost to follow-up.
- Pregnancy Registry - A pregnancy registry will be established in the US to determine the safety of natalizumab in pregnant patients. The primary objective of the study will be to evaluate any pattern or increase in birth defects in children of women with MS who were exposed to natalizumab. CD patients will also be enrolled.
- Safety of Re-exposure to Tysabri - The Sponsor is planning two worldwide, multi-center, open-label, single arm re-dosing studies. Approximately 1500 MS patients who were previously exposed to Tysabri in clinical trials will participate in these studies. The primary objective will be to further evaluate the safety of Tysabri re-exposure after an interval without treatment.
- Immune function/vaccine study – The Sponsor will conduct a study of 40 MS patients to determine the effect of Tysabri on humoral and cellular immunity.

## 3.4 RISKMAP EVALUATION PLAN

The Sponsor is monitoring and analyzing health outcomes data (e.g. PML rate, overall safety), systems/process data and compliance with the RiskMAP, and healthcare providers' knowledge of the risks of Tysabri and the requirements of the RiskMAP. Summaries of these data have been provided to the Agency on a quarterly basis since Tysabri's reintroduction. These are listed in the table below as well as the period covered and date of the document.

| | **Period Covered** | **Document Date** |
|---|---|---|
| **First Report** | 5/23/06 – 8/23/06 | September 22, 2006 |
| **Second Report** | 8/24/06 – 11/23/06 | December 21, 2006 |
| **Third Report** | 11/24/06 – 2/23/07 | April 9, 2007 |

The fourth RiskMAP report is due to the Agency in July 2007 and will cover the three month period following the third report. Biogen Idec, Inc. has also established a multi-disciplinary TYSABRI® Risk Management Review Committee to evaluate the effectiveness of the RiskMAP and TYSABRI® Compliance Review Committee to facilitate RiskMAP compliance. The information below is summary data from TOUCH only.

### 3.4.1 HEALTH OUTCOMES DATA

**Tysabri Postmarketing Exposure and Patients Enrolled in TOUCH Program**

As of May 23, 2007, 13,745 US patients were exposed to Tysabri. Of these, approximately 7500 patients were exposed during the initial marketing phase from 23 November 2004 to 28 February 2005).[5] Of the total postmarketing exposure in the US patients, approximately 2,100 have received Tysabri continuously for at least 6 months to less than 12 months. No patients have received Tysabri for more than 12 months continuously. The median duration of patient exposure from resumed marketing to May 23, 2007 is 3.8 months.

The remaining data provided below is based upon postmarketing data up to February 23, 2007.

The third RiskMAP report, states that a total of 5716 patients received 19,517 infusions of Tysabri as of the end of the 3rd reporting period. Tysabri was discontinued in 297 patients. The reasons for discontinuation are not included in the RiskMAP report.

Overall, more women have been treated with Tysabri than men. The ratio of use among women to men is about 2.4:1 which is higher than the reported gender difference of 1.6:1 in patients with MS. The highest proportion of use is occurring in individuals 35 to 54 years of age. About 3% of Tysabri use is among patients aged 65 and older. The table below shows patients by gender and age bands.

| Age Group (yrs) | Males | Females | Unspecified | Total (% total patients) |
|---|---|---|---|---|
| <18 | 2 | 9 | 0 | 11 (0%) |
| 18-24 | 37 | 76 | 0 | 113 (2%) |
| 25-34 | 214 | 526 | 0 | 740 (13%) |

[5] Tysabri PSUR: 24 November 2006 to 23 May 2007, dated June 22, 2007, Section 5, pgs 16-19.

| Age Group (yrs) | Males | Females | Unspecified | Total (% total patients) |
|---|---|---|---|---|
| 35-44 | 469 | 1207 | 2 | 1678 (29%) |
| 45-54 | 560 | 1361 | 2 | 1923 (34%) |
| 55-64 | 310 | 734 | 0 | 1044 (18%) |
| 65-74 | 62 | 128 | 0 | 190 (3%) |
| 75+ | 4 | 13 | 0 | 17 (0%) |
| Total Patients | 1658 | 4054 | 4 | 5716 |
| Percent by gender | 29% | 71% | 0% | 100% |

**Recent and Concurrent Therapies**

Information about recent therapies in patients starting Tysabri is captured on enrollment into the TOUCH program. Overall, about 2.6% of all patients starting therapy with Tysabri under the TOUCH program indicate that they were naïve to any MS therapy. About 25% indicate that they had previously received Tysabri. About 16% of patients had received some form of combination therapy prior to treatment with Tysabri.

Information on concurrent therapies is indicated both on the patient checklist and on the *Patient Status and Reauthorization Form* completed by physicians every six months. The patient checklist indicates that overall 2.1% of patients are on concomitant immunosuppressants or immunomodulatory medications in the month prior to their infusion. This form does not capture the type of medication received during their Tysabri dosing. There have only been 226 patients eligible for re-authorization during the reporting periods, of these 10 had received concurrent therapies during the prior six month period. Chronic systemic steroids had the largest responses (2.2%). This information is consistent with information collected on the Pre-infusion Questionnaire (see table below).

**Monitoring for PML (Responses to Preinfusion Questions)**

Infusion site staff administers the Pre-infusion Checklist which includes four questions that are intended to screen patients for symptoms suggestive of PML as well as determine whether they have any conditions or medications (other than Tysabri) that may put them in an immuno-compromised state. Below are the four questions which are asked of all Tysabri patients prior to each dose.

| **"Yes" responses to questions on Pre-infusion checklist** | | | | |
|---|---|---|---|---|
| | 1st Report (n=236) | 2nd Report (n=5914) | 3rd Report | Cumulative (n=6150) |
| Question 1 (PML Symptoms) | 12 (5.1%) | 362 (6.1%) | 724 (5.4%) | 1098 (5.6%) |
| Question 2 (medical condition that affect the immune system) | 0 | 3 (.05%) | 4 (<0.1%) | 7 (<0.1%) |
| Question 3 (concomitant drugs that affect the immune system) | 23 (9.7%) | 198 (3.3%) | 190 (1.4%) | 411 (2.1%) |
| Question 4 (concomitant steroid medications) | 12 (5.1%) | 155 (2.6%) | 287 (2.1%) | 454 (2.3%) |
| Total checklists with at least one "yes" response | 38 (16.1%) | 619 (10.5%) | 1061 (7.8%) | 1718 (8.7%) |

Overall 8.7% (1718/19,677) of Pre-infusion Checklists had at least one "yes" response. Overall, the question with the highest proportion of "yes" responses is question 1, which is designed to

identify symptoms that might be indicative of PML. This is not surprising given that many of the symptoms of PML are subtle and may be mistaken for symptoms of MS.

**Adverse Events of Interest**

There have been no reports of PML or serious opportunistic infections reported in the first three reporting periods. There have been seven spontaneous postmarketing reports of death in patients who have received Tysabri since its reintroduction in the U.S. up to February 23, 2007. Six were in US patients and one in a patient from Austria. The table below provides a brief summary of these deaths.

| Country | Age/gender | Cause of death | Infusion | Relevant medical history or course of events |
|---|---|---|---|---|
| Austria | 68/F | Complications of a paralytic ileus | 1 to 2 | chronic constipation, MS, and HTN |
| US | 54/M | Unknown cause | 2 | Reporter learned of death in local newspaper |
| US | 44/F | Car accident | Unk | No information provided |
| US | 44/F | Bacterial sepsis related to pneumonia and pancreatitis | 2-3 | Admitted with CAP<br>PMH remitting progressive MS, restrictive lung disease |
| US | 38/F | Possible suicide or accidental overdose of methadone | 1 | "history of abusing medication"; increasing c/o pain and muscle spasms |
| US | 37/F | Unknown, reported as "possibly related to too much pain medication" | 1 | PMH: MS, migraine, depression, stress urinary incontinence |
| US | 53/F | Cardiac-related | 1-2 | Patient was hospitalized with MRSA UTI and died 3-5 days later.<br>PMH cardiac risk factors, MS, dysfunctional bladder with suprapubic urinary catheter, h/o MRSA infections. |

### 3.4.2 SYSTEMS/PROCESS DATA

**Enrolled Prescribers, Infusion Centers, and Central Pharmacies**

Since TOUCH was implemented to the end of the 3rd reporting period, 1,405 prescribers have registered with the program of which 1,124 have prescribed Tysabri to at least one patient. One thousand five hundred and four (1504) infusion sites have been trained and authorized, of which 808 have administered Tysabri to at least one patient, and 584 central pharmacies have been trained and authorized to dispense Tysabri to authorized infusion sites.

**Infusion Site Compliance with RiskMAP Process**

- **Completion of Pre-infusion Checklists**

The pre-infusion patient checklists must be completed by infusion site staff for every patient prior to each Tysabri infusion. In order to monitor infusion site compliance, the pre-infusion checklist is to be faxed to Biogen within 1 day after the infusion appointment whether the patient received the infusion or not. There have been a total of 19,677 pre-infusion checklists received for all three reporting periods. A total of 19,517 infusions have been administered.

- **Prescriber Authorization to Infuse Tysabri**

  A "yes" response to any of the four questions on the Pre-infusion Checklist requires the infusion site staff to contact the prescriber for authorization to administer Tysabri. As summarized in the section above, 1,718 of 19,677 total checklists received have had at least one "yes" response to one of the four screening questions.

  The following is a summary of the actions taken by the infusion site staff and the prescriber:

  - Prescriber was contacted and authorized infusion 1605
    - Patient infused 1600
    - Patient not infused 5
  - Prescriber was contacted and did not authorize infusion 99
    - Patient infused 0
    - Patient not infused 99
  - Unable to contact prescriber 10
    - Patient infused 0
    - Patient not infused 10
  - Unspecified (not completed on checklist) 4
    - Patient infused 1
    - Patient not infused 3

  These data indicate good compliance with infusion sites in contacting prescribers to receive authorization when there was a "yes" response indicated on the checklist. In the majority of cases, prescribers provided authorization to administer Tysabri. No patients who were <u>not</u> authorized by the prescribing physician to receive Tysabri were administered Tysabri. There were 10 instances where the infusion site was unable to contact the prescriber. None of the 10 patients were actually infused Tysabri. There is only one instance where it was not documented by infusion site staff whether the prescriber authorized the infusion, but the infusion was subsequently administered.

**Prescriber Compliance with RiskMAP Process**

Prescribers are required to reauthorize all patients every six months by completing and returning to Biogen the Patient Status and Reauthorization Form. The purpose of the form is to determine the vital status of the patient, the occurrence of PML or other opportunistic infections, and to determine if the patient is still a candidate for Tysabri treatment.

All 226 re-authorization forms expected by the company during the reporting periods were completed and received by the company. Of these, 218 patients were authorized to continue to receive Tysabri for an additional six months.

**Vials Shipped to Authorized Infusion Sites and Central Pharmacies**

Distribution by the Specialty Pharmacy Providers (SPPs) of Tysabri is only allowed to authorized and trained infusion sites or their affiliated central pharmacies. The table below provides a summary of shipment data from resumption of marketing to February 23, 2007.

| Distribution of Tysabri | |
|---|---|
| | Cumulative |
| Number of Shipments | 5630 |
| Shipments to unauthorized sites | 7 |
| Number of vials shipped | 23,033* |
| Total infusions | 19,517 |

Of the seven unauthorized shipments, six were sent directly to the patients' homes and the seventh shipment was sent directly to the prescriber. All of the patients were authorized to receive Tysabri and the prescriber was enrolled and authorized to prescribe Tysabri. The unauthorized shipments involved four SPPs. Three of the four were retrained and the 4th was de-authorized to distribute Tysabri until the SPP can demonstrate appropriate controls and procedures to prevent recurrence.

### 3.4.3 KNOWLEDGE AND BEHAVIOR SURVEYS

As part of the overall evaluation of the Tysabri RiskMAP, the Sponsor is conducting a survey of prescribers and infusion site nurses to assess their understanding and knowledge of the key risk management messages of the TOUCH Program and their actions to minimize the risk of PML. The first surveys were conducted in February 2007. Respondents were recruited from their database. Of their list of 1,275 neurologists, 135 agreed to participate. One hundred eighty-four (184) nurses from 1,409 infusion sites also agreed to participate.

Overall, both prescribers and nurses provided high percentages of correct responses to questions relating to their knowledge of the key risk management messages and to questions relating to their actions taken to minimize the risk of PML.

Of note, the survey methodology and questionnaire were not reviewed by the Agency so we cannot comment on the overall results or on the ability of the survey as designed to assess prescribers' and nurses' knowledge and behavior of the risks.

## 4 DISCUSSION

The TOUCH Prescribing Program is designed to address several goals. The first is to inform and educate patients and HCPs about the risk of PML associated with Tysabri use. The Sponsor has employed several educational tools to address this goal. Patients and prescribers are required to sign an acknowledgement form that describes the risk of PML. Patients are given a Medication Guide prior to each infusion of Tysabri, and prescribers and infusion site staff are given educational tools to aid in the clinical assessment of patients.

The second goal is to minimize the risk of PML. To address this goal the Sponsor is requiring that all patients, prescribers, infusion sites, and central pharmacies enroll in the TOUCH Prescribing Program. Under this program, the appropriate use of Tysabri is emphasized. Prescribers sign and acknowledge that they are prescribing Tysabri to patients for which the product is indicated. In MS patients it is those with relapsing MS. The proposed indication for CD patients is in the treatment of moderately to severely active CD. The Sponsor also requires that prescribers follow-up with their patients every six months to determine whether Tysabri is still appropriate therapy for that patient.

The third goal is to minimize the health consequences of PML such as death and disability. To that end, the Sponsor is requiring that the infusion site staff administer the pre-infusion checklist prior to dosing each patient. This checklist is designed to screen patients for symptoms suggestive of PML as well as determine whether they have any conditions or are taking medications (other than Tysabri) that may put them in an immunocompromised state. Although there is no known effective cure for PML and it is unclear whether this checklist will effectively screen patients for PML, early recognition and treatment may improve outcome.[6]

At this time the TOUCH program appears to be working satisfactorily in the MS population. There has been good compliance with RiskMAP processes by prescribers and infusion site staff. The surveys of prescribers and nurses indicate a high level of understanding of the risks and requirements of the RiskMAP, although the participation in the surveys has been very low. To date, there have been no reports of PML reported to the Agency since the reintroduction of Tysabri into the marketplace (clinical trials and in the postmarketing setting).

Although the Sponsor proposes a RiskMAP that is the same for both MS and CD patients, the indications cover disparate patient populations, and there are several issues in CD that merit careful consideration. Whereas the patient with CD is unlikely to have the issue of overlapping symptoms between PML and the disease for which they are being treated (as is the case in MS patients), as the CD-TOUCH program is currently designed, CD patients would be evaluated by their prescribing physician for symptoms of PML. These physicians, primarily gastro-enterologists, are unaccustomed to recognizing the signs and symptoms of PML. This is in contrast to MS, where recognition of PML may be confounded by the underlying disease, but treatment is typically directed by specialists (neurologists) who are familiar with it. Early recognition of PML may be important only if discontinuation of Tysabri and institution of specific treatment alters the course of the disease. In the absence of a salutary treatment for PML, we recognize that early detection of PML, while desirable, may have less impact.

Although it is unknown whether the risk of PML increases with concomitant immunosuppressive or immunomodulatory therapies, PML is an OI, and all three PML patients from Tysabri clinical trials were receiving concomitant immunomodulatory therapies. The indication for Tysabri in MS is as monotherapy; accordingly, the vast majority of postmarketing use has been as monotherapy. The clinical trials for CD have been as add-on therapy, not monotherapy.[7] Patients with severe CD are often treated with systemic steroids and possibly other immunosuppressive drugs sometimes used as steroid sparing agents or biologic agents in addition to Tysabri. In the management of CD, there are two possible therapeutic scenarios that have been advocated by clinical experts, 'step up' therapy where one starts with 5-amino salicylates and then steps to steroids for flares and to immunosuppressives such as 6-MP or azathioprine (steroid-sparing agents), and finally to biological agents. The other scenario is 'top-down' therapy advocated by some clinical investigators. With this approach, at the time of initial diagnosis of CD, early treatment with biological agents, in particular TNFα blockers often in combination with other agents is undertaken in order to modify the subsequent course of the disease.[8,9] Thus, it is

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[6] Crowder CD, et al. Successful Outcome of Progressive Mulitfocal Leukoencephalopathy in a Renal Transplant Patient. Am J Transplant 2005; 5:1151-8.

[7] The pivotal trials were not prospectively monotherapy trials but about 1/3 were treated with Tysabri monotherapy.

[8] Oldenburg B, Hommes D. Biological therapies in inflammatory bowel disease: top-down or bottom-up? Curr Opin Gastroenterol 2007; 23(4):395-9.

[9] Hanauer SB. Turning traditional treatment strategies on their heads: current evidene for "step-up" versus "top-down". Rev Gastroenterol Disord 2007; 7 Suppl 2: S17-22.

necessary to define clearly whether avoidance of certain combinations of agents that may put patients at high risk for opportunistic infections or PML is an objective of the RiskMAP. For instance, is an objective of the CD-TOUCH program to ensure monotherapy in CD treatment failures with other meds (e.g. 2nd line treatment)? Will patients currently treated with immunosuppressive drugs or biologics be permitted to receive Tysabri; given the possible increased of risk of PML and other OIs with these products? Furthermore, in the event of a CD short duration and long duration flares during Tysabri treatment, additional rescue therapies and their duration that are permissible and continuation rules for Tysabri should be provided. Many of the agents that are used to treat CD have prolonged pharmacokinetic and possibly long lasting physiologic effects. If sequential therapy is to be advocated, in CD patients who fail other treatments, specific requirements for 'washout times' should be provided.

Another issue for consideration in CD patients is the selection of the appropriate patient for treatment of Tysabri based on disease severity. The current proposed indication in CD is in patients with moderately to severely active CD who had an inadequate response or in patients who are unable to tolerate conventional therapies. The RiskMAP proposal does not specifically indicate the measures that are to be used to determine disease severity such as the use of the Crohn's Disease Activity Index (CDAI), nor do they indicate the types of therapy that the patient would have to have failed. We believe that RiskMAP should clearly indicate an approach to appropriate patient selection based on measures of disease severity and non-response to other treatments.

The final issue for consideration is the concern that CD patients when treated with Tysabri may be susceptible to OIs and certain malignancies. In addition, because patients with CD are prone to abscesses and infected enteric fistulae, monitoring for manifestations of bacterial infections and sepsis is warranted. It should be noted that in the CD clinical trial database the number of patients treated with Tysabri for longer than 6 months was relatively small making it difficult to draw firm conclusions about risk of long term exposure to this agent in CD patients. Even so, during the CD clinical trials some patients were reported to have developed lower respiratory tract opportunistic infections during treatment. Any postmarketing pharmacovigilance plan should be designed to adequately monitor for events of concern. In particular, it would be important that postmarketing studies be adequately powered, include a comparator group, collect and report pertinent diagnostic information, and that enrolled patients are followed-up for clinical outcomes.

## 5 CONCLUSION

OSE agrees that the Tysabri RiskMAP may help meet the goal of promoting informed risk-benefit decisions regarding Tysabri use in the treatment of MS and CD patients if there is a population of CD patients in whom benefit exceeds risk. We also believe that the goal of minimizing the risk of PML is achievable to the extent that the prescriber and patient heed the warnings in the prescribing information, the patient and physician acknowledgement, and the Medication Guide, in particular, with regard to limiting prescribing to patients with relapsing MS and moderate to severe CD (if such a population is easily identified), and limiting its use to monotherapy.

At this time the TOUCH program appears to be working satisfactorily in the MS population. There has been good compliance with RiskMAP processes by prescribers and infusion site staff. The surveys of prescribers and nurses indicate a high level of understanding of the risks and requirements of the RiskMAP. To date, there have been no reports of PML to the Agency since the reintroduction of Tysabri into the marketplace (in the clinical trials and the postmarketing setting).

We recommend the Advisory Committee members discuss the following critical issues:

- The best way to monitor the CD population for PML and other OIs
- Identification of the appropriate patient for Tysabri and how in clinical practice these patients would be identified
- Whether concomitant immunosuppressive and immunomodulatory therapy will be permitted and how flares of CD will be dealt with

The details of this discussion will be considered in the final design of the CD-TOUCH RiskMAP program.

## APPENDIX 1. PATIENT ACKNOWLEDGEMENT

<table>
<tr><td colspan="2">I acknowledge that:</td></tr>
<tr><td>MS Version</td><td>CD Version (proposed)</td></tr>
<tr><td>Tysabri is a medicine approved to treat patients with relapsing forms of multiple sclerosis (MS)</td><td>Tysabri is a medicine approved to treat patients with moderately to severely active Crohn's Disease (CD)</td></tr>
<tr><td>• Tysabri is generally recommended for patients who have not been helped by, or cannot tolerate other treatments for MS</td><td>• Tysabri is generally recommended for patients who have not been helped by, or cannot tolerate other treatments for CD</td></tr>
<tr><td colspan="2">• I have talked to my doctor and understand the benefits and risks of Tysabri treatment</td></tr>
<tr><td colspan="2">Tysabri increases your chance of getting a rare brain infection that usually causes death or severe disability</td></tr>
<tr><td colspan="2">• This infection is called progressive mulitfocal leuckoencephalopthay (PML). PML usually happens in people with weakened immune systems</td></tr>
<tr><td colspan="2">• No one can predict who will get PML. There is no known treatment, prevention, or cure for PML</td></tr>
<tr><td>• My chance for getting PML may be higher if I am also being treated with other medicines that can weaken my immune system, including other MS treatments</td><td>• My chance for getting PML may be higher if I am also being treated with other medicines that can weaken my immune system, including other CD treatments</td></tr>
<tr><td>• Even if I use Tysabri alone to treat MS, it is not known if my chance for getting PML will be lower. It is also not known if treatment for a long period of time with Tysabri can increase my chance for PML</td><td>• Even if I use Tysabri alone to treat CD, it is not known if my chance for getting PML will be lower. It is also not known if treatment for a long period of time with Tysabri can increase my chance for PML</td></tr>
<tr><td colspan="2">• I should call my doctor right away if I get any new or worsening symptoms that last several days, especially nervous system symptoms. Some of these symptoms include a new or sudden change in my thinking, eyesight, balance, or strength, but I should also report other new or worsening symptoms</td></tr>
<tr><td colspan="2">To receive Tysabri, all patients must be enrolled in a special program called the TOUCH Prescribing Program.</td></tr>
<tr><td colspan="2">• The TOUCH Prescribing Program is run by the company that makes Tysabri. The company will collect information about my health at regular time periods. I cannot receive Tysabri if I do not agree to follow the requirements of the TOUCH Prescribing Program</td></tr>
<tr><td colspan="2">• I must notify the TOUCH Prescribing Program if I switch doctors or infusion sites</td></tr>
<tr><td colspan="2">• I have received, read, and understand the Patient Medication Guide</td></tr>
<tr><td colspan="2">• I will bring to each Tysabri infusion a list of all medicines and treatments that I have taken during the last month</td></tr>
</table>

## APPENDIX 2. PRESCRIBER ACKNOWLEDGEMENT

| **I acknowledge that:** | |
|---|---|
| ***MS Version*** | ***CD Version (proposed)*** |
| • I have read and understand the full Prescribing Information for Tysabri | |
| • TYSABRI is indicated as monotherapy for relapsing forms of MS | • TYSABRI is indicated for the treatment of moderately to severely active CD |
| • This patient has a relapsing form of MS based on clinical and radiological evidence | • This patient has moderately to severely active CD with inflammation based on clinical and laboratory evidence |
| • Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Although the cases of PML were limited to patients with recent or concomitant exposure to other immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with TYSABRI monotherapy | |
| • I am able to diagnose and manage opportunistic infections and PML, or am prepared to refer patients to specialists with these abilities | |
| • Because Tysabri increases the risk of PML, it is generally recommended for patients who have hand an inadequate response to, or are unable to tolerate, alternate MS therapies. I have discussed other MS treatments with this patient | • Because Tysabri increases the risk of PML, it is generally recommended for patients who have hand an inadequate response to, or are unable to tolerate, alternate CD therapies. I have discussed other CD treatments with this patient |
| • Tysabri is not ordinarily recommended for patients who are receiving chronic immuno-suppressant or immunomodulatory therapy, or who are significantly immunocompromised from any other cause | |
| • This patient has no known contraindications to Tysabri treatment, including PML | |
| • I have instructed the patient to promptly report to me any continuously worsening symptoms that persist over several days | |
| • This patient should be seen and evaluated 3 months after the first infusion, 6 months after the first infusion, at least every 6 months thereafter for as long as the patient receives Tysabri, and for at least 6 months after Tysabri has been discontinued | |
| • I will determine every 6 months whether this patient should continue on Tysabri and if so, authorize treatment every 6 months | |
| • NA | • (Proposed in CD patients) Patients receiving steroid therapy at the time of Tysabri initiation should undergo a steroid taper regimen once a clinical response is achieved. Steroids should be discontinued no later than 6 months after Tysabri initiation. If this is not possible, Tysabri therapy should be discontinued. Intermittent short courses of steroids are permissible to treat acute disease flares |
| • I should report, as soon as possible, any case of PML, any hospitalization due to opportunistic infection, and any death to Biogen Idec | |
| • Data concerning this patient and me will be entered into the mandatory TOUCH Prescribing Program. Biogen Idec requires my cooperation with periodic data collection. Failure to provide the requested information or otherwise comply with the requirements of the TOUCH Prescribing Program may result in discontinuation of TYSABRI treatment for this patient and forfeiture of my authorization to prescribe Tysabri | |
| • I have received educational materials regarding the benefits and risks of Tysabri treatment | |
| • I have, or another healthcare provider under my direction has, educated this patient on the benefits and risks of treatment with Tysabri, provided him or her with the Patient Medication Guide and Enrollment Form, instructed him or her to read these materials, and encouraged him or her to ask questions when considering Tysabri | |

## APPENDIX 3. INFUSION SITE ACKNOWLEDGEMENT

| |
|---|
| • A representative of Biogen Idec or Elan Pharmaceuticals, Inc. has provided traiing and education materials on the TOUCH Prescribing Program. |
| • Tysabri will be administered only to patients that are enrolled in the TOUCH prescribing program |
| • The patient's enrollment must be verified prior to infusing Tysabri. Enrollment is confirmed by obtaining the patient authorization number from Biogen (fax or telephone) |
| • Each patient will receive a copy of the Tysabri Patient Medication Guide prior to each infusion |
| • A Preinfusion Checklist must be completed for every patient scheduled to receive Tysabri. One copy of the Checklist must be faxed to Biogen with in 1 business day of the patient visit, and one copy will be placed in the patient's medical record |
| • The infusion site is subject to audit by Biogen, FDA, or a third party designated by either. |
| • Noncompliance with the requirements of TOUCH will result in deenrollment of the infusion site and forfeiture of the authorization to infusion Tysabri |

## APPENDIX 4. CENTRAL PHARMACY ACKNOWLEDGEMENT

| |
|---|
| • A representative of Biogen Idec or Elan Pharmaceuticals, Inc. has provided training and education materials on the TOUCH Prescribing Program. |
| • Central pharmacies may dispense Tysabri only to authorized infusion sites |
| • The Tysabri Inventory Tracking Log must be completed for every dose of Tysabri dispensed to authorized infusion sites. Inventory Trackingg logs must be kept for at lest 5 years from the date of final log entry. |
| • I understand that, per the requirements of the TOUCH Prescribing Program, this central pharmacy may be audited by the Food and Drug Administration (FDA), Biogen Idec, Elan Pharmaceuticals Inc., and/or a third party designated by the FDA Biogen Idec, or Elan Pharmaceuticals Inc. |
| • Noncompliance with the requirements of the TOUCH Prescribing Program may result in de-enrollment of the central pharmacy and forfeiture of the authorization to dispense Tysabri |

# Section 3A

## Summaries from March 7-8, 2006

## Advisory Committee on Tysabri

(www.fda.gov/ohrms/dockets/ac/cder06.html#PeripheralCentralNervousSystem)

A. Clinical Review Summary

# 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.

# Section 3B

## Summaries from March 7-8, 2006,

## Advisory Committee on Tysabri

## (www.fda.gov/ohrms/dockets/ac/cder06.html#PeripheralCentralNervousSystem)

B. Summary Minutes

# Food and Drug Administration
# Center for Drug Evaluation and Research

5630 Fishers Lane, Room 1066, Rockville, Maryland 20857

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee meeting on March 7 & 8, 2006:

*The committee discussed Tysabri (Natalizumab) biologic license application 125104/15; Biogen Idec Inc. for an indication in patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The committee will discuss the risks (including progressive multifocal leukoencephalopathy (PML)) associated with Tysabri administration, the efficacy of Tysabri in the treatment of multiple sclerosis relapses and/or disability, the possible return of Tysabri to the marketplace, and proposed risk management plan(s) for Tysabri.*

These summary minutes for the March 7 & 8, 2006 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee were approved on March 14, 2006.

I certify that I attended the March 7 & 8, 2006 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____//S//_____
Lt. Sohail Mosaddegh, Pharm.D., RPh.
Acting Executive Secretary, PCNS

_____//S//_____
Karl Kieburtz, M.D., M.P.H.
Chair, PCNS

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the Sponsor. The meeting was called to order by Karl Kieburtz, M.D., M.P.H. (Committee Chair); the conflict of interest statement was read into the record by Lt. Sohail Mosaddegh, Pharm.D., R.Ph. (Acting Executive Secretary). There were approximately 300 persons in attendance. There were 36 speakers for the Open Public Hearing sessions.

**Attendance:**
**Peripheral and Central Nervous System Drugs Advisory Committee Member:**
Karl D. Kieburtz, M.D., M.P.H., Larry B. Goldstein, M.D., Steven T. DeKosky, M.D., Michael D. Hughes, Ph.D., Ralph L. Sacco, M.D., M.S., James R. Couch Jr., M.D., Ph.D., F.A.C.P., Lily K.F. Jung, M.D., M.M.M.

**Peripheral and Central Nervous System Drugs Advisory Committee Consultant (voting):**
Carol Koski, M.D., Cynthia Sitcov, James Sejvar M.D. (Federal Employee)

**Anesthetic and Life Support Drugs Advisory Committee (voting)**
Justin C. McArthur, M.D,

**Drug Safety and Risk Management Advisory Committee (Voting):**
George Ricaurte, M.D., Ph.D.

**Peripheral and Central Nervous System Drugs Advisory Committee (non-voting):**
Roger Porter, M.D.

**FDA Participants:**
Russell Katz, M.D., Marc Walton, Ph.D., M.D., Susan McDermott, M.D., Alice Hughes, M.D., Robert Temple, M.D., Gerald Dal Pan, M.D., MHS, Douglas Throckmorton, M.D., Diane Wysowski, Ph.D.

**Open Public Hearing Speakers:**

Alison Kutler, Audrey Ann Greenfeld, Barbara Sales, Barbara Crooks, Bartira Tiburtius, Carol Fuquay (Via Video), Charlie Richardson, Cheryl Bloom, Christopher Hughes, Christy Cooksey, Clive Milton, David Smith, David Miller, Doug Franklin, Emily Canavan, Frank Burroughs, Heather Smith, Jack Calfee, Jason Mark, John Richert, K.P. Lyons, Karen Miller, Larry P. Keller, Lauren Roberts (Via Video), Linda Lyons, Lisa Casanova, Alex MacDonald, Marcy Canavan, Mark Godec, Martha Rogers, Michael Kahn, Mike Barron, Pamela Sue Clark, Peter Wade, Sonda Lawson, Stan Croydon, Stephen Melvin Lore, Steven Triedman, Virginia Ladd, William Stuart.

**Issue:** The committee will discuss Tysabri (Natalizumab) biologic license application 125104/15; Biogen Idec Inc. for an indication in patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The committee will discuss the risks (including progressive multifocal leukoencephalopathy (PML)) associated with Tysabri administration, the efficacy of Tysabri in the treatment of multiple sclerosis relapses and/or disability, the possible return of Tysabri to the marketplace, and proposed risk management plan(s) for Tysabri.

The agenda was as follows:

*March 7, 2006*

| | |
|---|---|
| **Introduction** | Russell Katz, M.D.<br>Director, Division<br>Division of Anti-Infective and Ophthalmology Products<br>CDER, FDA |

**Sponsor Presentations (Biogen-Idec Inc.)**

| | |
|---|---|
| Introduction | Burt Adelman, M..D.<br>Executive Vice President, Development |

| | |
|---|---|
| | Biogen Idec Inc. |
| Efficacy Data | Alfred Sandrock, M.D., Ph..D.<br>Vice President, Neurology<br>Biogen Idec Inc. |
| Safety Data | Michael Panzara, M.D., M.P.H.<br>Vice President, Neurology<br>Biogen Idec Inc. |
| Risk-Management Plan | Carmen Bozic, M.D.<br>Vice President, Drug Safety and Risk Management<br>Biogen Idec Inc. |
| Clinical Perspective | Richard A. Rudick, M.D.<br>Director, The Mellen Center<br>Chairman, Division of Clinical Research<br>Cleveland Clinic Foundation<br>**Committee questions to the sponsor** |

**Food and Drug Administration Presentation**

| | |
|---|---|
| Background, Efficacy and PML | Susan McDermott, M.D.<br>Clinical Reviewer, DNP, FDA |
| Safety | Alice Hughes, M.D.<br>Clinical Safety Reviewer, DNP, FDA |
| Risk Minimization Action Plan | Diane Wysowski, Ph.D.<br>Reviewer, Office of Drug Safety, FDA |
| | **Committee Questions to the FDA** |
| | **Open Public Hearing** |

The committee adjourned at approximately 4:00 P.M.

**Agenda March 8, 2006**

**Committee Discussion**

**Questions to the Committee**

**Questions to the Committee:**

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?
   **After discussion the committee consensus was that Biogen has demonstrated natalizumab' s efficacy on reducing the frequency of relapses through two years and fulfilled their commitment made under the Accelerated Approval regulations.**

2. Has Biogen demonstrated efficacy on reduced accumulation of physical disability?
   **After discussion the committee consensus was that Biogen has demonstrated efficacy on reducing the 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?
   **After significant discussion the committee consensus was that hypersensitivity reactions and development of antibodies were important considerations in making a risk-benefit assessment.**

b. Non-PML infectious disease risks (e.g., opportunistic infections, herpes CNS infections)?
**After significant discussion the committee consensus was that there is some concern of serious viral 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?
**After some discussion the committee consensus was that the risk of PML is not 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).
**After some discussion the committee consensus was that they did not need additional data on determining whether natalizumab may return to the marketplace.**

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)
**After significant debate the chair polled the committee members on 4 questions. These were polls to see if the committee was at a consensus and was not an official vote.**
**Should natalizumab be permitted as first line therapy?**
**YES: 7 NO: 5**

b. Patients with MS who are above or below a specific level of disability or have some other specific disease-related criteria
**The second poll was is there an upper level of disability that would be a consideration in the use of natalizumab?**
**YES: 1 NO: 11**
**The third poll was is there a lower level of disability that would be a consideration in the use of natalizumab?**
**YES: 1 NO: 10 ABSTAIN: 1**

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
***(See transcripts for detailed discussion)***

d. Patients with MS who have tried one of the available therapies and been unable to continue treatment due to intolerability of adverse effects
***(See transcripts for detailed discussion)***

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.
**After some discussion a fourth poll was taken. Should natalizumab be taken with betaseron, Copaxone, Rebif, or Novantrone?**
**YES: 0 NO: 12**
**The committee also came to the consensus that a wash out period would be needed if switching to natalizumab from one of these medications.**

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.
**This question was voted on.**
**YES: 12 NO: 0**

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 (minimization) plan. In this discussion, consider the risk management plan proposed by the sponsor, and comment on the appropriateness of specific aspects of the proposed 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

        What information (e.g., deaths, PML, other infections, serious adverse events, concomitant immunomodulators), if any, is it essential to obtain on all patients who receive Tysabri?
        **The committee discussed the matter and the overall consensus was that the proposed information from the sponsor was necessary but some of the members wanted more information. There was no clear consensus on the extra information that would be needed.** ***(See transcripts for detailed discussion)***

    b. Patient observational study

        1. What additional information, if any, is it important to obtain in a subset of patients who receive Tysabri (i.e., an observational study that is more intensive than the registry)?
        **After much debate the general consensus of the committee was that there are some additional questions that the committee thinks are worth addressing but are more appropriate in the context of a research study rather than mandatory as part of clinical care.** ***(See transcripts for detailed discussion)***

        2. If an observational study is appropriate, how large should the observational study be?
        ***(See transcripts for detailed discussion)***

    c. Restrictions on distribution system

        1. Should each vial be distributed using a 1:1 system so that every shipped vial is designated for administration to a specific patient?
        **The general consensus of the committee was that there should be some restriction on the distribution but not on a 1:1 basis. There should also be some mandatory monthly reporting back about the use of the checklists.** ***(See transcripts for detailed discussion)***

        2. Should infusion centers be permitted to maintain a stock of natalizumab that is not designated for any specific subject?
        ***(See transcripts for detailed discussion)***

        3. Should only a single dose be shipped at any one time, with shipment of the subsequent dose dependent on receiving some information back from the infusion center? If so, what information (e.g., physical exam, immunosuppression checklist, PML symptom checklist) should be necessary to prompt distribution of the next dose?
        ***(See transcripts for detailed discussion)***

        4. Should there be a periodic reauthorization of Tysabri administration? If so, how often (e.g., prior to each infusion, every 6 months), and by whom (e.g., infusion center nurse, patient's physician)?
        ***(See transcripts for detailed discussion)***
        5. Does the patient's neurologist need to examine the patient with some frequency and re-prescribe Tysabri? If so, what frequency is appropriate?
        ***(See transcripts for detailed discussion)***

    d. Restriction to only MS patients
        **This question was discussed by the committee earlier as part of question 6 and the committee's consensus was that Tysabri be used only in MS patients.** ***(See transcripts for detailed discussion)***

e. Restriction to only MS patients for whom natalizumab was deemed appropriate in the answer to Question 7
***(See transcripts for detailed discussion)***

f. Immunosuppression checklist

1. Is an immunosuppression checklist appropriate?
***(See transcripts for detailed discussion)***

2. If a checklist is required, what are essential elements of this checklist?
***(See transcripts for detailed discussion)***

3. Who should administer the checklist, and how often? ***(See transcripts for detailed discussion)*** ***(See transcripts for detailed discussion)***

4. Is any other monitoring of immunosuppression necessary prior to each infusion? Or at some other time interval
***(See transcripts for detailed discussion)***

g. PML checklist

1. Is a PML symptom checklist appropriate?
***(See transcripts for detailed discussion)***

2. If a checklist is required, what are essential elements of this checklist?
***(See transcripts for detailed discussion)***

3. Who should administer the checklist, and how often?
***(See transcripts for detailed discussion)***

4. Is any additional monitoring for PML necessary prior to each infusion? Or at some other time interval?
***(See transcripts for detailed discussion)***

**There was a great deal of debate on these questions but the general consensus was that with regards to PML any observed or reported exacerbation would be treated as though it could be a new case of PML and evaluated as such.** ***(See transcripts for detailed discussion)***

h. Other potential requirements for ongoing monitoring while receiving natalizumab, including, but not limited to:

1. JC Virus assay in serum and/or cerebrospinal fluid
***(See transcripts for detailed discussion)***

2. MRI of brain
***(See transcripts for detailed discussion)***

3. Quantitative cognitive testing or brief cognitive screening questionnaire
***(See transcripts for detailed discussion)***

4. Periodic full neurologic exam or brief physical function questionnaire
***(See transcripts for detailed discussion)***

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?
**The committee came to the consensus that annual monitoring should be done for two to three years after natalizumab therapy is stopped.** ***(See transcripts for detailed discussion)***

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? **The committee came to the consensus that annual monitoring should be done for two to three years after natalizumab therapy is stopped.**

    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?
    **The committee agreed that there needed to be a wash out period but due to lack of evidence a firm time period could not be given. The periods discussed as recommendations were two weeks and two to three months**

    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?
    **The committee agreed that there needed to be a wash out period but due to lack of evidence a firm time period could not be given. The periods discussed as recommendations were two weeks and two to three months**

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
    **After discussion regarding choices 11a, 11b, 11c, and 11d all committee members chose option 11b.**

    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

***(See transcripts for detailed discussion)***

# Food and Drug Administration
# Center for Drug Evaluation and Research

5630 Fishers Lane, Room 1066, Rockville, Maryland 20857

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee meeting on March 7 & 8, 2006:

*The committee discussed Tysabri (Natalizumab) biologic license application 125104/15; Biogen Idec Inc. for an indication in patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The committee will discuss the risks (including progressive multifocal leukoencephalopathy (PML)) associated with Tysabri administration, the efficacy of Tysabri in the treatment of multiple sclerosis relapses and/or disability, the possible return of Tysabri to the marketplace, and proposed risk management plan(s) for Tysabri.*

These summary minutes for the March 7 & 8, 2006 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee were approved on March 14, 2006.

I certify that I attended the March 7 & 8, 2006 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Lt. Sohail Mosaddegh, Pharm.D., RPh.
Acting Executive Secretary, PCNS

_____//S//_____
Karl Kieburtz, M.D., M.P.H.
Chair, PCNS

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the Sponsor. The meeting was called to order by Karl Kieburtz, M.D., M.P.H. (Committee Chair); the conflict of interest statement was read into the record by Lt. Sohail Mosaddegh, Pharm.D., R.Ph. (Acting Executive Secretary). There were approximately 300 persons in attendance. There were 36 speakers for the Open Public Hearing sessions.

**Attendance:**
**Peripheral and Central Nervous System Drugs Advisory Committee Member:**
Karl D. Kieburtz, M.D., M.P.H., Larry B. Goldstein, M.D., Steven T. DeKosky, M.D., Michael D. Hughes, Ph.D., Ralph L. Sacco, M.D., M.S., James R. Couch Jr., M.D., Ph.D., F.A.C.P., Lily K.F. Jung, M.D., M.M.M.

**Peripheral and Central Nervous System Drugs Advisory Committee Consultant (voting):**
Carol Koski, M.D., Cynthia Sitcov, James Sejvar M.D. (Federal Employee)

**Anesthetic and Life Support Drugs Advisory Committee (voting)**
Justin C. McArthur, M.D,

**Drug Safety and Risk Management Advisory Committee (Voting):**
George Ricaurte, M.D., Ph.D.

**Peripheral and Central Nervous System Drugs Advisory Committee (non-voting):**
Roger Porter, M.D.

**FDA Participants:**
Russell Katz, M.D., Marc Walton, Ph.D., M.D., Susan McDermott, M.D., Alice Hughes, M.D., Robert Temple, M.D., Gerald Dal Pan, M.D., MHS, Douglas Throckmorton, M.D., Diane Wysowski, Ph.D.

**Open Public Hearing Speakers:**

Alison Kutler, Audrey Ann Greenfeld, Barbara Sales, Barbara Crooks, Bartira Tiburtius, Carol Fuquay (Via Video), Charlie Richardson, Cheryl Bloom, Christopher Hughes, Christy Cooksey, Clive Milton, David Smith, David Miller, Doug Franklin, Emily Canavan, Frank Burroughs, Heather Smith, Jack Calfee, Jason Mark, John Richert, K.P. Lyons, Karen Miller, Larry P. Keller, Lauren Roberts (Via Video), Linda Lyons, Lisa Casanova, Alex MacDonald, Marcy Canavan, Mark Godec, Martha Rogers, Michael Kahn, Mike Barron, Pamela Sue Clark, Peter Wade, Sonda Lawson, Stan Croydon, Stephen Melvin Lore, Steven Triedman, Virginia Ladd, William Stuart.

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The agenda was as follows:

*March 7, 2006*

| | |
|---|---|
| **Introduction** | Russell Katz, M.D.<br>Director, Division<br>Division of Anti-Infective and Ophthalmology Products<br>CDER, FDA |

**Sponsor Presentations (Biogen-Idec Inc.)**

| | |
|---|---|
| Introduction | Burt Adelman, M..D.<br>Executive Vice President, Development |

| | |
|---|---|
| | Biogen Idec Inc. |
| Efficacy Data | Alfred Sandrock, M.D., Ph..D.<br>Vice President, Neurology<br>Biogen Idec Inc. |
| Safety Data | Michael Panzara, M.D., M.P.H.<br>Vice President, Neurology<br>Biogen Idec Inc. |
| Risk-Management Plan | Carmen Bozic, M.D.<br>Vice President, Drug Safety and Risk Management<br>Biogen Idec Inc. |
| Clinical Perspective | Richard A. Rudick, M.D.<br>Director, The Mellen Center<br>Chairman, Division of Clinical Research<br>Cleveland Clinic Foundation<br>**Committee questions to the sponsor** |

**Food and Drug Administration Presentation**

| | |
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| Background, Efficacy and PML | Susan McDermott, M.D.<br>Clinical Reviewer, DNP, FDA |
| Safety | Alice Hughes, M.D.<br>Clinical Safety Reviewer, DNP, FDA |
| Risk Minimization Action Plan | Diane Wysowski, Ph.D.<br>Reviewer, Office of Drug Safety, FDA |
| | **Committee Questions to the FDA** |
| | **Open Public Hearing** |

The committee adjourned at approximately 4:00 P.M.

**Agenda March 8, 2006**

**Committee Discussion**

**Questions to the Committee**

**Questions to the Committee:**

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?
   **After discussion the committee consensus was that Biogen has demonstrated natalizumab' s efficacy on reducing the frequency of relapses through two years and fulfilled their commitment made under the Accelerated Approval regulations.**

2. Has Biogen demonstrated efficacy on reduced accumulation of physical disability?
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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?
   **After significant discussion the committee consensus was that hypersensitivity reactions and development of antibodies were important considerations in making a risk-benefit assessment.**

b. Non-PML infectious disease risks (e.g., opportunistic infections, herpes CNS infections)?
**After significant discussion the committee consensus was that there is some concern of serious viral infections.**

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**After some discussion the committee consensus was that the risk of PML is not 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).
**After some discussion the committee consensus was that they did not need additional data on determining whether natalizumab may return to the marketplace.**

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)
**After significant debate the chair polled the committee members on 4 questions. These were polls to see if the committee was at a consensus and was not an official vote.**
**Should natalizumab be permitted as first line therapy?**
**YES: 7 NO: 5**

b. Patients with MS who are above or below a specific level of disability or have some other specific disease-related criteria
**The second poll was is there an upper level of disability that would be a consideration in the use of natalizumab?**
**YES: 1 NO: 11**
**The third poll was is there a lower level of disability that would be a consideration in the use of natalizumab?**
**YES: 1 NO: 10 ABSTAIN: 1**

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
***(See transcripts for detailed discussion)***

d. Patients with MS who have tried one of the available therapies and been unable to continue treatment due to intolerability of adverse effects
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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.
**After some discussion a fourth poll was taken. Should natalizumab be taken with betaseron, Copaxone, Rebif, or Novantrone?**
**YES: 0 NO: 12**
**The committee also came to the consensus that a wash out period would be needed if switching to natalizumab from one of these medications.**

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.
**This question was voted on.**
**YES: 12 NO: 0**

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 (minimization) plan. In this discussion, consider the risk management plan proposed by the sponsor, and comment on the appropriateness of specific aspects of the proposed 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

        What information (e.g., deaths, PML, other infections, serious adverse events, concomitant immunomodulators), if any, is it essential to obtain on all patients who receive Tysabri?
        **The committee discussed the matter and the overall consensus was that the proposed information from the sponsor was necessary but some of the members wanted more information. There was no clear consensus on the extra information that would be needed.** ***(See transcripts for detailed discussion)***

    b. Patient observational study

        1. What additional information, if any, is it important to obtain in a subset of patients who receive Tysabri (i.e., an observational study that is more intensive than the registry)?
        **After much debate the general consensus of the committee was that there are some additional questions that the committee thinks are worth addressing but are more appropriate in the context of a research study rather than mandatory as part of clinical care.** ***(See transcripts for detailed discussion)***

        2. If an observational study is appropriate, how large should the observational study be?
        ***(See transcripts for detailed discussion)***

    c. Restrictions on distribution system

        1. Should each vial be distributed using a 1:1 system so that every shipped vial is designated for administration to a specific patient?
        **The general consensus of the committee was that there should be some restriction on the distribution but not on a 1:1 basis. There should also be some mandatory monthly reporting back about the use of the checklists.** ***(See transcripts for detailed discussion)***

        2. Should infusion centers be permitted to maintain a stock of natalizumab that is not designated for any specific subject?
        ***(See transcripts for detailed discussion)***

        3. Should only a single dose be shipped at any one time, with shipment of the subsequent dose dependent on receiving some information back from the infusion center? If so, what information (e.g., physical exam, immunosuppression checklist, PML symptom checklist) should be necessary to prompt distribution of the next dose?
        ***(See transcripts for detailed discussion)***

        4. Should there be a periodic reauthorization of Tysabri administration? If so, how often (e.g., prior to each infusion, every 6 months), and by whom (e.g., infusion center nurse, patient's physician)?
        ***(See transcripts for detailed discussion)***
        5. Does the patient's neurologist need to examine the patient with some frequency and re-prescribe Tysabri? If so, what frequency is appropriate?
        ***(See transcripts for detailed discussion)***

    d. Restriction to only MS patients
        **This question was discussed by the committee earlier as part of question 6 and the committee's consensus was that Tysabri be used only in MS patients.** ***(See transcripts for detailed discussion)***

e. Restriction to only MS patients for whom natalizumab was deemed appropriate in the answer to Question 7
***(See transcripts for detailed discussion)***

f. Immunosuppression checklist

1. Is an immunosuppression checklist appropriate?
***(See transcripts for detailed discussion)***

2. If a checklist is required, what are essential elements of this checklist?
***(See transcripts for detailed discussion)***

3. Who should administer the checklist, and how often? ***(See transcripts for detailed discussion)*** ***(See transcripts for detailed discussion)***

4. Is any other monitoring of immunosuppression necessary prior to each infusion? Or at some other time interval
***(See transcripts for detailed discussion)***

g. PML checklist

1. Is a PML symptom checklist appropriate?
***(See transcripts for detailed discussion)***

2. If a checklist is required, what are essential elements of this checklist?
***(See transcripts for detailed discussion)***

3. Who should administer the checklist, and how often?
***(See transcripts for detailed discussion)***

4. Is any additional monitoring for PML necessary prior to each infusion? Or at some other time interval?
***(See transcripts for detailed discussion)***

**There was a great deal of debate on these questions but the general consensus was that with regards to PML any observed or reported exacerbation would be treated as though it could be a new case of PML and evaluated as such.** ***(See transcripts for detailed discussion)***

h. Other potential requirements for ongoing monitoring while receiving natalizumab, including, but not limited to:

1. JC Virus assay in serum and/or cerebrospinal fluid
***(See transcripts for detailed discussion)***

2. MRI of brain
***(See transcripts for detailed discussion)***

3. Quantitative cognitive testing or brief cognitive screening questionnaire
***(See transcripts for detailed discussion)***

4. Periodic full neurologic exam or brief physical function questionnaire
***(See transcripts for detailed discussion)***

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?
**The committee came to the consensus that annual monitoring should be done for two to three years after natalizumab therapy is stopped.** ***(See transcripts for detailed discussion)***

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? **The committee came to the consensus that annual monitoring should be done for two to three years after natalizumab therapy is stopped.**

    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?
    **The committee agreed that there needed to be a wash out period but due to lack of evidence a firm time period could not be given. The periods discussed as recommendations were two weeks and two to three months**

    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?
    **The committee agreed that there needed to be a wash out period but due to lack of evidence a firm time period could not be given. The periods discussed as recommendations were two weeks and two to three months**

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
    **After discussion regarding choices 11a, 11b, 11c, and 11d all committee members chose option 11b.**

    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

***(See transcripts for detailed discussion)***

# Section 5

# Current Tysabri Package Insert

# (approved June 5, 2006)

**TYSABRI® (natalizumab)**

WARNING

TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with TYSABRI® monotherapy.

- Because of the risk of PML, TYSABRI® is available only through a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI® must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program **(see WARNINGS, Progressive Multifocal Leukoencephalopathy; and WARNINGS, Prescribing, Distribution, and Administration Program for TYSABRI®)**.

- Healthcare professionals should monitor patients on TYSABRI® for any new sign or symptom that may be suggestive of PML. TYSABRI® dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended **(see CONTRAINDICATIONS and WARNINGS, Progressive Multifocal Leukoencephalopathy)**.

## DESCRIPTION

TYSABRI® (natalizumab) is a recombinant humanized IgG4κ monoclonal antibody produced in murine myeloma cells. Natalizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to α4-integrin. The molecular weight of natalizumab is 149 kilodaltons. TYSABRI® is supplied as a sterile, colorless, and clear to slightly opalescent concentrate for intravenous (IV) infusion.

Each 15 mL dose contains 300 mg natalizumab; 123 mg sodium chloride, USP; 17.0 mg sodium phosphate, monobasic, monohydrate, USP; 7.24 mg sodium phosphate, dibasic, heptahydrate, USP; 3.0 mg polysorbate 80, USP/NF, in water for injection, USP at pH 6.1.

## CLINICAL PHARMACOLOGY

### General

TYSABRI® binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s). The receptors for the α4 family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium, and mucosal addressin cell adhesion molecule-1 (MadCAM-1) present on vascular endothelial cells of the gastrointestinal tract. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. *In vitro*, anti-α4-integrin antibodies also block α4-mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). *In vivo*, TYSABRI® may further act to inhibit the interaction of α4-expressing leukocytes with their ligand(s) in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells.

The specific mechanism(s) by which TYSABRI® exerts its effects in multiple sclerosis have not been fully defined. In multiple sclerosis, lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and their counter-receptors present on endothelial cells of the vessel wall. The clinical effect of natalizumab in multiple sclerosis may be secondary to blockade of the molecular interaction of α4β1-integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain. Data from an experimental autoimmune encephalitis animal model of multiple sclerosis demonstrate reduction of leukocyte migration into brain parenchyma and reduction of plaque formation detected by magnetic resonance imaging (MRI) following repeated administration of natalizumab. The clinical significance of these animal data is unknown.

### Pharmacokinetics

Following the repeat intravenous administration of a 300 mg dose of natalizumab to patients with multiple sclerosis, the mean maximum observed serum concentration was 110 ± 52 mcg/mL. Mean average steady-state trough concentrations ranged from 23 mcg/mL to 29 mcg/mL. The observed time to steady-state was approximately 24 weeks after every 4 weeks of dosing. The mean half-life, volume of distribution, and clearance of natalizumab were 11 ± 4 days, 5.7 ± 1.9 L, and 16 ± 5 mL/hour, respectively.

The effects of covariates such as body weight, age, gender, and presence of anti-natalizumab antibodies on natalizumab pharmacokinetics were investigated in a population pharmacokinetic study. Natalizumab clearance increased with body weight in a less than proportional manner such that a 43% increase in body weight resulted in a 32% increase in clearance. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 3-fold **(see ADVERSE REACTIONS, Immunogenicity)**. Age (18 to 62 years) and gender did not influence natalizumab pharmacokinetics.

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

**Pharmacodynamics**

TYSABRI® administration increases the number of circulating leukocytes (including lymphocytes, monocytes, basophils, and eosinophils) due to inhibition of transmigration out of the vascular space. TYSABRI® does not affect the number of circulating neutrophils **(see PRECAUTIONS, Laboratory Tests)**.

## CLINICAL STUDIES

TYSABRI® was evaluated in two randomized, double-blind, placebo-controlled trials in patients with multiple sclerosis. Both studies enrolled patients who experienced at least one clinical relapse during the prior year and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.0.

In both studies, neurological evaluations were performed every 12 weeks and at times of suspected relapse. Magnetic resonance imaging evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study 1 enrolled patients who had not received any interferon-beta or glatiramer acetate for at least the previous 6 months; approximately 94% had never been treated with these agents. Median age was 37, with a median disease duration of 5 years. Patients were randomized in a 2:1 ratio to receive TYSABRI® 300 mg IV infusion (n=627) or placebo (n=315) every 4 weeks for up to 28 months (30 infusions).

Study 2 enrolled patients who had experienced one or more relapses while on treatment with AVONEX® (Interferon beta-1a) 30 mcg intramuscularly (IM) once weekly during the year prior to study entry. Median age was 39, with a median disease duration of 7 years. Patients were evenly randomized to receive TYSABRI® 300 mg (n=589) or placebo (n=582) every 4 weeks for up to 28 months (30 infusions). All patients continued to receive AVONEX® 30 mcg IM once weekly.

The efficacy of TYSABRI® alone was not compared with the efficacy of TYSABRI® plus AVONEX®.

Results for each study are shown in Tables 1 and 2. Median time on study drug was 120 weeks in each study. Safety and efficacy of treatment with TYSABRI® beyond two years are not known.

The primary endpoint at 2 years was time to onset of sustained increase in disability, defined as an increase of at least 1 point on the EDSS from baseline EDSS $\geq$ 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS=0 that was sustained for 12 weeks. Time to onset of sustained increase in disability was longer in TYSABRI®-treated patients than in placebo-treated patients in Studies 1 (Figure 1) and 2. The proportion of patients

with increased disability and the annualized relapse rate were also lower in TYSABRI®-treated patients than in placebo-treated patients in Studies 1 and 2 (Tables 1 and 2).

Changes in MRI findings often do not correlate with changes in the clinical status of patients (e.g., disability progression). The prognostic significance of the MRI findings in these studies has not been evaluated.

**Table 1. Clinical and MRI Endpoints in Study 1 (Monotherapy Study) at 2 Years**

| | **TYSABRI®** n=627 | **Placebo** n=315 |
|---|---|---|
| **Clinical Endpoints** | | |
| Percentage with sustained increase in disability | 17% | 29% |
| Relative Risk Reduction | 42% (95% CI 23%, 57%) | |
| Annualized relapse rate | 0.22 | 0.67 |
| Relative reduction (percentage) | 67% | |
| Percentage of patients remaining relapse-free | 67% | 41% |
| **MRI Endpoints** | | |
| New or newly enlarging T2-hyperintense lesions | | |
| Median | 0.0 | 5.0 |
| Percentage of patients with*: | | |
| 0 lesions | 57% | 15% |
| 1 lesion | 17% | 10% |
| 2 lesions | 8% | 8% |
| 3 or more lesions | 18% | 68% |
| Gd-enhancing lesions | | |
| Median | 0.0 | 0.0 |
| Percentage of patients with: | | |
| 0 lesions | 97% | 72% |
| 1 lesion | 2% | 12% |
| 2 or more lesions | 1% | 16% |

All analyses were intent-to-treat. For each endpoint, $p<0.001$. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS and age; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

*Values do not total 100% due to rounding.

**Table 2. Clinical and MRI Endpoints in Study 2 (Add-On Study) at 2 Years**

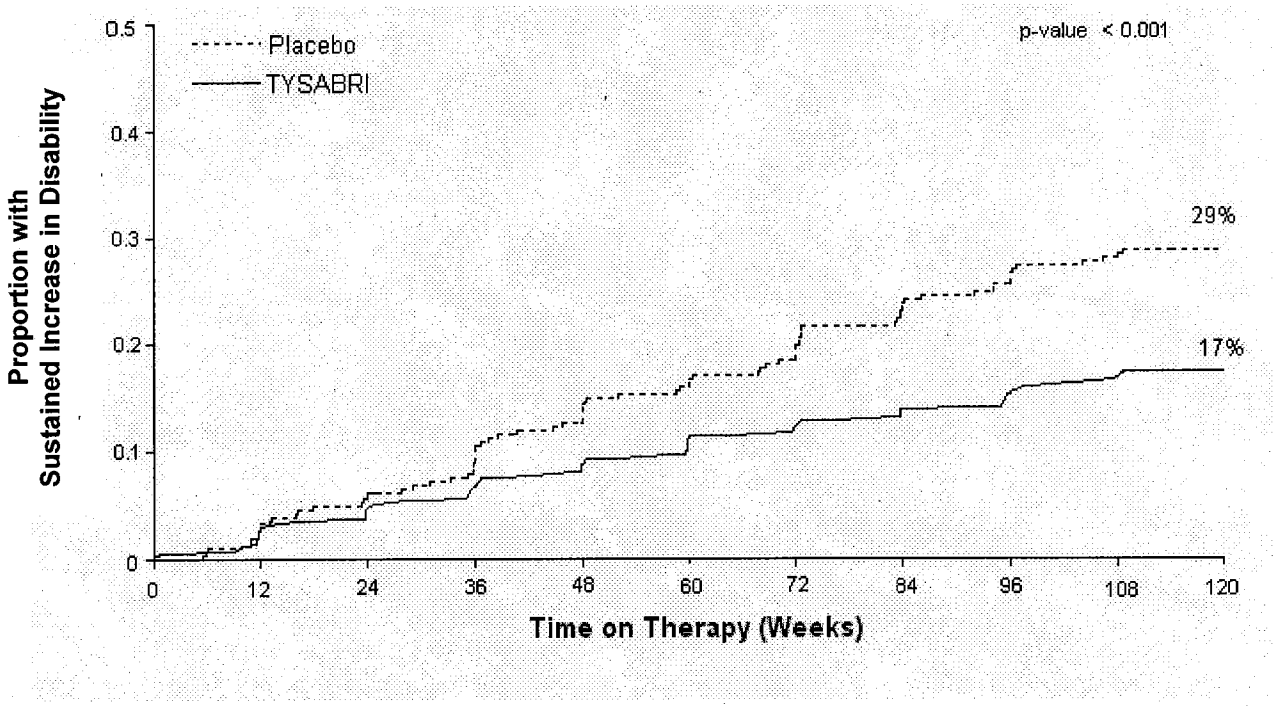
| | TYSABRI® plus AVONEX® n=589 | Placebo plus AVONEX® n=582 |
|---|---|---|
| **Clinical Endpoints** | | |
| Percentage with sustained increase in disability | 23% | 29% |
| Relative Risk Reduction | 24% (95% CI 4%, 39%) | |
| Annualized relapse rate | 0.33 | 0.75 |
| Relative reduction (percentage) | 56% | |
| Percentage of patients remaining relapse-free | 54% | 32% |
| **MRI Endpoints** | | |
| New or newly enlarging T2-hyperintense lesions | | |
| Median | 0.0 | 3.0 |
| Percentage of patients with*: | | |
| 0 lesions | 67% | 30% |
| 1 lesion | 13% | 9% |
| 2 lesions | 7% | 10% |
| 3 or more lesions | 14% | 50% |
| Gd-enhancing lesions | | |
| Median | 0.0 | 0.0 |
| Percentage of patients with*: | | |
| 0 lesions | 96% | 75% |
| 1 lesion | 2% | 12% |
| 2 or more lesions | 1% | 14% |

All analyses were intent-to-treat. For disability accumulation p=0.024, for all other endpoints, p<0.001. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

*Values do not total 100% due to rounding.

**Figure 1. Time to Increase in Disability Sustained for 12 Weeks in Study 1**




## INDICATIONS AND USAGE

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

Because TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (**see BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**), TYSABRI® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies.

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

## CONTRAINDICATIONS

TYSABRI® should not be administered to patients with known hypersensitivity to TYSABRI® or any of its components.

TYSABRI® is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) **(see BOXED WARNING and WARNINGS).**

## WARNINGS

**Progressive Multifocal Leukoencephalopathy (PML)**

**Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus that typically occurs in patients that are immunocompromised, has occurred in 3 patients who received TYSABRI® in clinical trials (see BOXED WARNING). Two cases of PML were observed in 1869 patients with multiple sclerosis treated for a median of 120 weeks. The third case occurred among 1043 patients with Crohn's disease after the patient received 8 doses. The absolute risk for PML in patients treated with TYSABRI® cannot be precisely estimated, and factors that might increase an individual patient's risk for PML have not been identified. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI® will mitigate the disease. There is limited experience beyond 2 years of treatment. The relationship between the risk of PML and the duration of treatment is unknown.**

**All three cases of PML occurred in patients who were concomitantly exposed to immunomodulators (interferon beta in the patients with multiple sclerosis) or were immunocompromised due to recent treatment with immunosuppressants (e.g., azathioprine in the patient with Crohn's disease). Ordinarily, therefore, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI®. However, the number of cases is too few and the number of patients treated too small to reliably conclude that the risk of PML is lower in patients treated with TYSABRI® alone than in patients who are receiving other drugs that decrease immune function or who are otherwise immunocompromised.**

**Because of the risk of PML, TYSABRI® is available only under a special restricted distribution program, the TOUCH™ Prescribing Program.**

**An MRI scan should be obtained prior to initiating therapy with TYSABRI®. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML. Healthcare professionals should monitor patients on TYSABRI® for any new sign or symptom suggestive of PML. TYSABRI® dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.**

**Prescribing, Distribution, and Administration Program for TYSABRI®**

TYSABRI® is available only under a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI® must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program (**see BOXED WARNING** and/or contact the TOUCH™ Prescribing Program at 1-800-456-2255).

To enroll in the TOUCH™ Prescribing Program, prescribers and patients are required to understand the risks of treatment with TYSABRI®, including PML and other opportunistic infections. Prescribers are required to understand the information in the Prescribing Information and to be able to:

- Diagnose and manage opportunistic infections and PML, or be prepared to refer patients to specialists with these abilities.
- Educate patients on the benefits and risks of treatment with TYSABRI®, provide them with the Medication Guide, instruct them to read it, and encourage them to ask questions when considering TYSABRI®. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction.
- Review the TOUCH™ Prescriber/Patient Enrollment form for TYSABRI® with the patient and answer all questions.
- As part of the initial prescription process for TYSABRI®, obtain the patient's signature and initials on the TOUCH™ program enrollment form, sign it, place the original signed form in the patient's medical record, send a copy to Biogen Idec, and give a copy to the patient.
- Report serious opportunistic and atypical infections with TYSABRI® to Biogen Idec at 1-800-456-2255 and to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.
- Evaluate the patient 3 months after the first infusion, 6 months after the first infusion, and every 6 months thereafter.
- Determine every 6 months whether patients should continue on treatment and if so reauthorize treatment every 6 months.
- Submit to Biogen Idec the TYSABRI® Patient Status Report and Reauthorization Questionnaire 6 months after initiating treatment and every 6 months thereafter.

**Information for Patients**

Patients should be fully counseled on and understand the risks and benefits of TYSABRI® before an initial prescription is written. The patient may be educated by either the enrolled prescriber or a healthcare provider under that prescriber's direction.

PATIENTS WHO ARE PRESCRIBED TYSABRI® SHOULD BE INSTRUCTED TO:

- Read the Medication Guide before starting TYSABRI® and before each TYSABRI® infusion.
- Promptly report any continuously worsening symptoms that persist over several days to their prescriber **(see BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy)**.
- Inform all of their physicians that they are receiving TYSABRI®.
- Plan to see their prescriber 3 months after the first infusion, 6 months after the first infusion, and at least as frequently as every 6 months thereafter.

If patients experience symptoms consistent with a hypersensitivity reaction (e.g., urticaria with or without associated symptoms) during or following an infusion of TYSABRI®, they should report these symptoms to their prescriber immediately **(see WARNINGS, Hypersensitivity)**.

**Hypersensitivity**

TYSABRI® has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. These reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to TYSABRI®.

If a hypersensitivity reaction occurs, discontinue administration of TYSABRI® and initiate appropriate therapy **(see ADVERSE REACTIONS, Infusion-related Reactions)**. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI®. The possibility of antibodies to TYSABRI® should be considered in patients who have hypersensitivity reactions **(see ADVERSE REACTIONS, Immunogenicity)**.

**Immunosuppression**

The immune system effects of TYSABRI® may increase the risk for infections. In Study 1, certain types of infections, including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections, occurred more often in TYSABRI®-treated patients than in placebo-treated patients **(see WARNINGS, Progressive Multifocal Leukoencephalopathy (PML); and ADVERSE REACTIONS, General and Infections)**. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI® in Study 1.

Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of TYSABRI® alone **(see BOXED WARNING; WARNINGS, Progressive Multifocal Leukoencephalopathy; and ADVERSE REACTIONS, Infections)**. The safety and efficacy of TYSABRI® in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established.

Concurrent use of short courses of corticosteroids was associated with an increase in infections in Studies 1 and 2. However, the increase in infections in TYSABRI®-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids.

**PRECAUTIONS**

**Information for Patients**

**See WARNINGS, Information for Patients**

**Laboratory Tests**

TYSABRI® induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persist during TYSABRI® exposure, but are

reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils are not observed. TYSABRI® induces mild decreases in hemoglobin levels that are frequently transient.

**Drug Interactions**

See **BOXED WARNING** and **WARNINGS, Immunosuppression.**

**Carcinogenesis, Mutagenesis, and Impairment of Fertility**

No clastogenic or mutagenic effects of natalizumab were observed in the Ames test or *in vitro* chromosomal aberration assay in human lymphocytes. Natalizumab showed no effects in *in vitro* assays of α4-integrin positive human tumor line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude mice with two α4-integrin positive human tumor lines (leukemia, melanoma) demonstrated no increase in tumor growth rates or metastasis resulting from natalizumab treatment.

Reductions in female guinea pig fertility were observed in one study at dose levels of 30 mg/kg, but not at the 10 mg/kg dose level (2.3-fold the clinical dose). A 47% reduction in pregnancy rate was observed in guinea pigs receiving 30 mg/kg relative to control. Implantations were seen in only 36% of animals having corpora lutea in the 30 mg/kg group versus 66-72% in the other groups. Natalizumab did not affect male fertility at doses up to 7-fold the clinical dose.

**Pregnancy (Category C)**

There are no adequate and well-controlled studies of TYSABRI® therapy in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking TYSABRI®, discontinuation of TYSABRI® should be considered.

If a woman becomes pregnant while taking TYSABRI®, consider enrolling her in the TYSABRI® Pregnancy Exposure Registry by calling 1-800-456-2255.

In reproductive studies in monkeys and guinea pigs, there was no evidence of teratogenic effects at doses up to 30 mg/kg (7 times the human clinical dose based on a body weight comparison). In one study where female guinea pigs were exposed to natalizumab during the second half of pregnancy, a small reduction in pup survival was noted at post-natal day 14 with respect to control (3 pups/litter for the group treated with 30 mg/kg natalizumab and 4.3 pups/litter for the control group). In one of five studies that exposed monkeys or guinea pigs during pregnancy, the number of abortions in treated (30 mg/kg) monkeys was 33% versus 17% in controls. No effects on abortion rates were noted in any other study. TYSABRI® underwent trans-placental transfer and produced *in utero* exposure in developing guinea pigs and cynomolgus monkeys. When pregnant dams were exposed to natalizumab at approximately 7-fold the clinical dose, serum levels in fetal animals at delivery were approximately 35% of maternal serum natalizumab levels. A study in pregnant cynomolgus monkeys treated at 2.3-fold the clinical dose demonstrated natalizumab-related changes in the fetus. These changes included mild anemia, reduced platelet

count, increased spleen weights, and reduced liver and thymus weights associated with increased splenic extramedullary hematopoiesis, thymic atrophy, and decreased hepatic hematopoiesis. In offspring born to mothers treated with natalizumab at 7-fold the clinical dose, platelet counts were also reduced. This effect was reversed upon clearance of natalizumab. There was no evidence of anemia in these offspring. Offspring exposed *in utero* and via breast milk had no natalizumab-related changes in the lymphoid organs and had normal immune response to challenge with a T-cell dependent antigen.

### Nursing Mothers

It is not known whether TYSABRI® is excreted in human milk. Because many drugs and immunoglobulins are excreted in human milk, and because the potential for serious adverse reactions is unknown, discontinuation of TYSABRI® or alternatives to nursing should be considered.

### Geriatric Use

Clinical studies of TYSABRI® did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients.

### Pediatric Use

Safety and effectiveness of TYSABRI® in pediatric patients with multiple sclerosis below the age of 18 have not been studied. TYSABRI® is not indicated for use in pediatric patients.

### Immunizations

No data are available on the effects of vaccination in patients receiving TYSABRI®. No data are available on the secondary transmission of infection by live vaccines in patients receiving TYSABRI®.

## ADVERSE REACTIONS

### General

The most frequently reported serious adverse events in Study 1 **(see CLINICAL STUDIES)** with TYSABRI® were infections (3.2% versus 2.6% in placebo, including urinary tract infection [0.8% versus 0.3%] and pneumonia [0.6% versus 0%]), acute hypersensitivity reactions (1.1% versus 0.3%, including anaphylaxis/anaphylactoid reaction [0.8% versus 0%]), depression (1.0% versus 1.0%, including suicidal ideation or attempt [0.6% versus 0.3%]), and cholelithiasis (1.0% versus 0.3%). In Study 2, serious adverse events of appendicitis were also more common in patients who received TYSABRI® (0.8% versus 0.2% in placebo) **(see WARNINGS, Hypersensitivity and ADVERSE REACTIONS, Infections)**.

The most frequently reported adverse reactions resulting in clinical intervention (i.e., discontinuation of TYSABRI®), were urticaria (1%) and other hypersensitivity reactions (1%) **(see WARNINGS, Hypersensitivity)**.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of TYSABRI® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

A total of 1617 multiple sclerosis patients in controlled studies received TYSABRI®, with a median duration of exposure of 28 months.

Table 3 enumerates adverse events and selected laboratory abnormalities that occurred in Study 1 at an incidence of at least 1 percentage point higher in TYSABRI®-treated patients than was observed in placebo-treated patients.

**Table 3. Adverse Reactions in Study 1 (Monotherapy Study)**

| **Adverse Events (Preferred Term)** | **TYSABRI® n=627 Percentage** | **Placebo n=312 Percentage** |
|---|---|---|
| General | | |
| Headache | 38% | 33% |
| Fatigue | 27% | 21% |
| Arthralgia | 19% | 14% |
| Chest discomfort | 5% | 3% |
| Acute hypersensitivity reactions** | 4% | <1% |
| Other hypersensitivity reactions** | 5% | 2% |
| Seasonal allergy | 3% | 2% |
| Rigors | 3% | <1% |
| Weight increased | 2% | <1% |
| Weight decreased | 2% | <1% |
| Infection | | |
| Urinary tract infection | 21% | 17% |
| Lower respiratory tract infection | 17% | 16% |
| Gastroenteritis | 11% | 9% |
| Vaginitis* | 10% | 6% |
| Tooth infections | 9% | 7% |
| Herpes | 8% | 7% |
| Tonsillitis | 7% | 5% |
| Psychiatric | | |
| Depression | 19% | 16% |

| Adverse Events (Preferred Term) | TYSABRI® n=627 Percentage | Placebo n=312 Percentage |
|---|---|---|
| Musculoskeletal/Connective Tissue Disorders | | |
| Pain in extremity | 16% | 14% |
| Muscle cramp | 5% | 3% |
| Joint swelling | 2% | 1% |
| Gastrointestinal | | |
| Abdominal discomfort | 11% | 10% |
| Diarrhea NOS | 10% | 9% |
| Abnormal liver function test | 5% | 4% |
| Skin | | |
| Rash | 12% | 9% |
| Dermatitis | 7% | 4% |
| Pruritus | 4% | 2% |
| Night sweats | 1% | 0% |
| Menstrual Disorders* | | |
| Irregular menstruation | 5% | 4% |
| Dysmenorrhea | 3% | <1% |
| Amenorrhea | 2% | 1% |
| Ovarian cyst | 2% | <1% |
| Neurologic Disorders | | |
| Somnolence | 2% | <1% |
| Vertigo | 6% | 5% |
| Renal and Urinary Disorders | | |
| Urinary incontinence | 4% | 3% |
| Urinary urgency/frequency | 9% | 7% |
| Injury | | |
| Limb injury NOS | 3% | 2% |
| Skin laceration | 2% | <1% |
| Thermal burn | 1% | <1% |

*Percentage based on female patients only.
** Acute versus other hypersensitivity reactions are defined as occurring within 2 hours post-infusion versus more than 2 hours.

In Study 2, peripheral edema was more common in patients who received TYSABRI® (5% versus 1% in placebo).

**Infections**

Progressive Multifocal Leukoencephalopathy (PML) has occurred in 3 patients who received TYSABRI® in clinical trials **(see BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy).** Two cases of PML were observed in the 1869 patients with multiple sclerosis who were treated for a median of 120 weeks. These 2 patients had received TYSABRI in addition to interferon beta-1a **(see BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy)**. The third case occurred after 8 doses in one of the 1043 patients with Crohn's disease who were evaluated for PML.

In Studies 1 and 2, the rate of any type of infection was approximately 1.5 per patient-year in both TYSABRI®-treated patients and placebo-treated patients. The infections were predominately upper respiratory tract infections, influenza, and urinary tract infections.

In Study 1, the incidence of serious infection was approximately 3% in TYSABRI®-treated patients and placebo-treated patients. Most patients did not interrupt treatment with TYSABRI® during infections.

The only opportunistic infection in the multiple sclerosis clinical trials was a case of cryptosporidial gastroenteritis with a prolonged course.

In clinical studies for indications other than multiple sclerosis, opportunistic infections (e.g., pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been uncommonly observed in TYSABRI®-treated patients; some of these patients were receiving concurrent immunosuppressants **(see WARNINGS, Immunosuppression)**. Two serious non-bacterial meningitides occurred in TYSABRI®-treated patients compared to none in placebo-treated patients.

In post-marketing experience, one patient who received TYSABRI® developed herpes encephalitis and died; a second patient developed herpes meningitis and recovered with appropriate treatment.

**Infusion-related Reactions (see WARNINGS, Hypersensitivity)**

An infusion-related reaction was defined in clinical trials as any adverse event occurring within 2 hours of the start of an infusion. Approximately 24% of TYSABRI®-treated multiple sclerosis patients experienced an infusion-related reaction, compared to 18% of placebo-treated patients. Events more common in the TYSABRI®-treated patients included headache, dizziness, fatigue, urticaria, pruritus, and rigors. Acute urticaria was observed in approximately 2% of patients. Other hypersensitivity reactions were observed in 1% of patients receiving TYSABRI®. Serious systemic hypersensitivity infusion reactions occurred in <1% of patients. All patients recovered with treatment and/or discontinuation of the infusion.

Patients who became persistently positive for antibodies to TYSABRI® were more likely to have an infusion-related reaction than those who were antibody-negative **(see ADVERSE REACTIONS, Immunogenicity)**.

**Immunogenicity**

Patients in Study 1 were tested for antibodies to natalizumab every 12 weeks. The assays used were unable to detect low to moderate levels of antibodies to natalizumab. Approximately 9% of patients receiving TYSABRI® developed detectable antibodies at least once during treatment. Approximately 6% of patients had positive antibodies on more than one occasion. Approximately 82% of patients who became persistently antibody-positive developed detectable antibodies by 12 weeks. Anti-natalizumab antibodies were neutralizing *in vitro*.

The presence of anti-natalizumab antibodies was correlated with a reduction in serum natalizumab levels. In Study 1, the Week 12 pre-infusion mean natalizumab serum concentration in antibody-negative patients was 14.9 mcg/mL compared to 1.3 mcg/mL in antibody-positive patients. Persistent antibody-positivity was associated with a substantial decrease in the effectiveness of TYSABRI®. The risk of increased disability and the annualized relapse rate were similar in persistently antibody-positive TYSABRI®-treated patients and patients who received placebo. A similar phenomenon was also observed in Study 2.

Infusion-related reactions most often associated with persistent antibody-positivity included urticaria, rigors, nausea, vomiting, headache, flushing, dizziness, pruritus, tremor, feeling cold, and pyrexia. Additional adverse events more common in persistently antibody-positive patients included myalgia, hypertension, dyspnea, anxiety, and tachycardia.

If the presence of persistent antibodies is suspected, antibody testing should be performed. Antibodies may be detected and confirmed with sequential serum antibody tests. Antibodies detected early in the treatment course (e.g., within the first 6 months) may be transient and disappear with continued dosing. Repeat testing at 3 months after the initial positive result is recommended in patients in whom antibodies are detected to confirm that antibodies are persistent. Prescribers should consider the overall benefits and risks of TYSABRI® in a patient with persistent antibodies.

The long-term immunogenicity of TYSABRI® and the effects of low to moderate levels of antibody to natalizumab are unknown. Experience with other monoclonal antibodies suggests that patients who receive therapeutic antibodies after an extended period without treatment may be at higher risk of hypersensitivity reactions than patients who received regularly scheduled treatment. It is not known if this will occur with TYSABRI® **(see WARNINGS, Hypersensitivity and ADVERSE REACTIONS, Infusion-related Reactions)**.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody-positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to TYSABRI® with the incidence of antibodies to other products may be misleading.

## OVERDOSAGE

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of TYSABRI® that can be safely administered has not been determined.

## DOSAGE AND ADMINISTRATION

Only prescribers registered in the TOUCH™ Prescribing Program may prescribe TYSABRI® **(see BOXED WARNING)**.

The recommended dose of TYSABRI® is 300 mg IV infusion every four weeks. Dilute TYSABRI® concentrate 300 mg/15 mL in 100 mL 0.9% Sodium Chloride Injection, USP, and infuse over approximately one hour. Do not administer TYSABRI® as an IV push or bolus injection **(see Preparation Instructions)**.

Observe patients during the infusion and for 1 hour after the infusion is complete. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction **(see WARNINGS, Hypersensitivity)**.

### Preparation Instructions

Use aseptic technique when preparing TYSABRI® solution for IV infusion. Each vial is intended for single use only.

TYSABRI® is a colorless, clear to slightly opalescent concentrate. Inspect the TYSABRI® vial for particulate material prior to dilution and administration. If visible particulates are observed and/or the liquid in the vial is discolored, the vial must not be used. Do not use TYSABRI® beyond the expiration date stamped on the carton or vial.

To prepare the solution, withdraw 15 mL of TYSABRI® concentrate from the vial using a sterile needle and syringe. Inject the concentrate into 100 mL 0.9% Sodium Chloride Injection, USP. No other IV diluents may be used to prepare the TYSABRI® solution.

Gently invert the TYSABRI® solution to mix completely. Do not shake. Inspect the solution visually for particulate material prior to administration.

Following dilution, infuse TYSABRI® solution immediately, or refrigerate solution at 2-8°C, and use within 8 hours. If stored at 2-8°C, allow the solution to warm to room temperature prior to infusion. DO NOT FREEZE.

### Administration Instructions

Infuse TYSABRI® 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP over approximately one hour. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.

Use of filtration devices during administration has not been evaluated. Other medications should not be injected into infusion set side ports or mixed with TYSABRI®.

## HOW SUPPLIED

TYSABRI® concentrate is supplied as 300 mg natalizumab in a sterile, single-use vial free of preservatives. Each package contains a single-use vial. NDC 59075-730-15

TYSABRI® is available only through registered infusion centers participating in the TOUCH™ Prescribing Program. To locate these infusion centers, contact Biogen Idec at 1-800-456-2255.

### Storage

TYSABRI® single-use vials must be refrigerated between 2-8°C (36°-46°F). Do not use beyond the expiration date stamped on the carton and vial label. DO NOT SHAKE OR FREEZE. Protect from light.

If not used immediately, store the TYSABRI® solution for infusion at 2-8°C (36°-46°F). TYSABRI® solution for infusion must be administered within 8 hours of preparation.

I61061-2 Issue date [XXXX]

TYSABRI® (natalizumab)

Manufactured by:
Biogen Idec Inc.
14 Cambridge Center
Cambridge, MA 02142 USA
1-800-456-2255

Distributed by:
Elan Pharmaceuticals, Inc.
San Diego, CA 92121



U.S. Patent Numbers: 5,840,299, 6,033,665, 6,602,503, 5,168,062, 5,385,839, 5,730,978

# MEDICATION GUIDE

## TYSABRI® (tie–SA–bree)
## (natalizumab)

Read the Medication Guide given to you before you start TYSABRI® and before each infusion. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Ask your doctor or nurse if you have any questions.

### What is the most important information I should know about TYSABRI®?

- **TYSABRI® increases your chance of getting a rare brain infection that usually causes death or severe disability. This infection is called progressive multifocal leukoencephalopathy (PML).** PML usually happens in people with weakened immune systems.
- No one can predict who will get PML.
- There is no known treatment, prevention, or cure for PML.
- Your chance of getting PML may be higher if you are also being treated with other medicines that can weaken your immune system, including other MS treatments.
- Even if you use TYSABRI® alone to treat your MS, it is not known if your chance of getting PML will be lower. It is also not known if treatment for a long period of time with TYSABRI® can increase your chance of getting PML.
- TYSABRI® is available only through a restricted distribution program called the TOUCH™ Prescribing Program. In order to receive TYSABRI®, you must talk to your doctor and understand the benefits and risks of TYSABRI® and agree to all of the instructions in the TOUCH™ Prescribing Program.

- If you take TYSABRI®, it is important that you call your doctor right away if you get any new or worsening medical problems (such as a new or sudden change in your thinking, eyesight, balance, or strength or other problems) that have lasted over several days. Tell all of your doctors that you are getting treatment with TYSABRI®.

Also, see **"What are the possible side effects with TYSABRI®?"** for other serious side effects with TYSABRI®.

## What is TYSABRI®?

TYSABRI® is a prescription medicine approved for patients with relapsing forms of MS to:

- slow the worsening of disability that is common in patients with MS and,
- decrease the number of flare-ups (relapses)

- Because of the chance of getting PML, TYSABRI® is generally recommended for patients that have not been helped enough by, or cannot tolerate other treatments for MS.

- TYSABRI® does not cure MS.

- TYSABRI® has not been studied for use longer than 2 years. Also, TYSABRI® has not been studied in patients with chronic progressive MS, or in children. It is not known if patients older than 65 years have a different response to TYSABRI®.

## TYSABRI® is only:

- prescribed by doctors who are enrolled in the TOUCH™ Prescribing Program

- infused at an infusion center that is enrolled in the TOUCH™ Prescribing Program

- given to patients who are enrolled in the TOUCH™ Prescribing Program

## Who should not receive TYSABRI®?

Do **not receive** TYSABRI® if you:

- have PML
- are allergic to TYSABRI®

**TYSABRI is not recommended if you:**

- have a medical condition that can weaken your immune system such as HIV infection or AIDS, leukemia or lymphoma, or an organ transplant, and others.
- are taking medicines that can weaken your immune system. Talk with your doctor about all of the medicines you take or have taken.

If you have questions about any of the above, talk to your doctor.

**What should I tell my doctor and nurse before receiving each infusion of TYSABRI®?**

Tell your doctor and nurse about all of your medical conditions. Tell them if you:

- have any new or worsening medical problems (such as a new or sudden change in your thinking, eyesight, balance, or strength or other problems) that have lasted several days
- have had hives, itching or trouble breathing during or after an infusion of TYSABRI®
- have a fever or infection (including shingles or any unusually long lasting infection)
- are pregnant or plan to become pregnant
- are breastfeeding

Tell your doctor and nurse about all of the medicines you are taking, including prescription and non-prescription medicines, vitamins and herbal supplements.

- Know the medicines you take. Keep a list of them with you to show your doctor and nurse. The nurse may ask to see this list before every TYSABRI® infusion.

**How do I receive TYSABRI®?**

- TYSABRI® is given once every four weeks through a needle placed in a vein (IV infusion).
- You must follow all the instructions of the TOUCH™ Prescribing Program. Before you can begin to receive TYSABRI®, your doctor or nurse will:
    - explain the TOUCH™ Prescribing Program to you
    - have you sign the TOUCH™ Prescriber/Patient Enrollment Form
- Before every TYSABRI® infusion you will be asked a series of questions to confirm that TYSABRI® is still right for you.
- Call your doctor who prescribes TYSABRI® right away to report any medical problems that keep getting worse and last several days.

**What are the possible side effects of TYSABRI®?**

**TYSABRI® increases your chance of getting a rare brain infection that usually causes death or severe disability. This infection is called progressive multifocal leukoencephalopathy (PML).** PML usually happens in people with weakened immune systems. (see **"What is the most important information I should know about TYSABRI®?")**

Other serious side effects with TYSABRI® include:

- Allergic reactions including serious allergic reactions. Symptoms can include:
    - hives
    - itching
    - trouble breathing
    - chest pain
    - dizziness
    - chills
    - rash
    - nausea
    - flushing of skin
    - low blood pressure

- Serious allergic reactions usually happen within 2 hours of the start of the infusion, but they can happen at any time after receiving TYSABRI®.
- Tell your doctor or nurse right away if you have any symptom of an allergic reaction, even if it happens after you leave the infusion center. You may need treatment if you are having an allergic reaction.

- **Infections.** TYSABRI® may increase your chance of getting an unusual or serious infection because TYSABRI® can affect your immune system.

**Other side effects with TYSABRI® include:**

- headache
- urinary tract infection
- lung infection
- pain in your arm and legs
- vaginitis
- feeling tired
- joint pain
- depression
- diarrhea
- rash
- stomach area pain

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with TYSABRI®. Ask your doctor for more information.

**General information about the safe and effective use of TYSABRI®**

This Medication Guide provides a summary of the most important information about TYSABRI®. If you would like more information or have any questions, talk with your doctor or nurse. You can ask your doctor or nurse for information about TYSABRI that is written for healthcare professionals. You can also call 1-800-456-2255 or visit www.TYSABRI.com.

**What are the ingredients in TYSABRI®?**

Each dose of TYSABRI® contains natalizumab; sodium chloride; sodium phosphate, monobasic, monohydrate; sodium phosphate, dibasic, heptahydrate; polysorbate 80; and water for injection.

Manufactured by Biogen Idec Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

I61061-X
XX/06

Manufactured by: Biogen Idec Inc., 14 Cambridge Center, Cambridge, MA 02142 USA
Distributed by: Elan Pharmaceuticals, Inc., San Diego, CA 92121

Final

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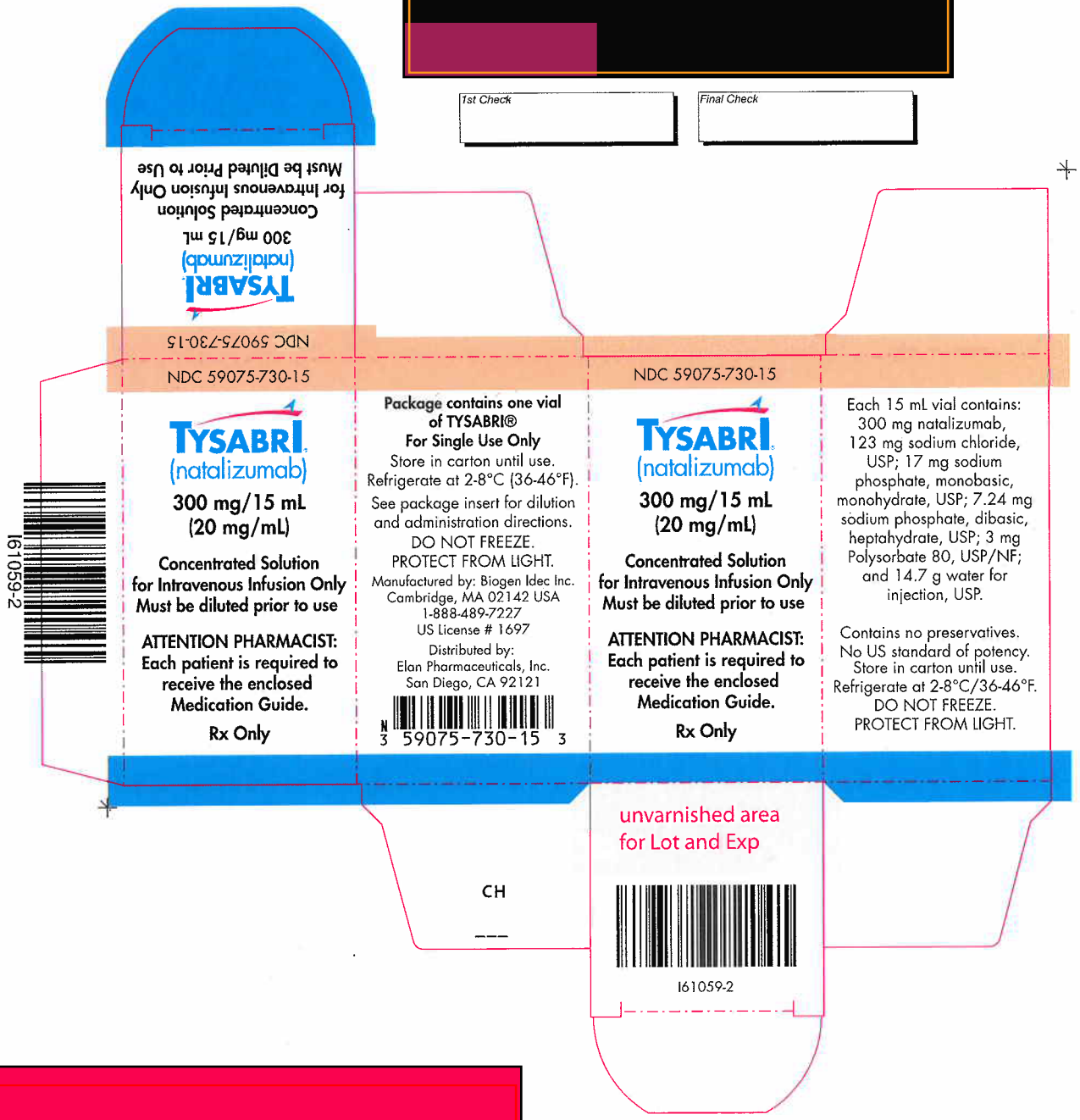
1st Check

Final Check

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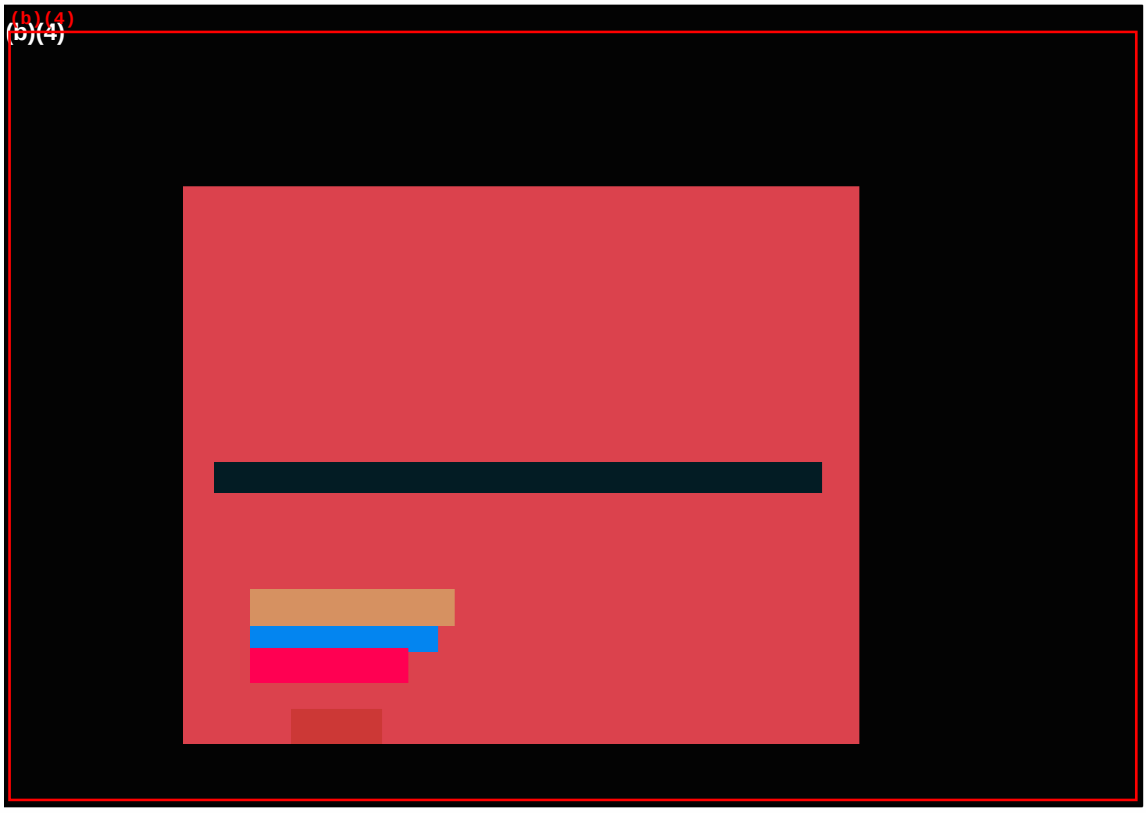


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# TYSABRI® RISK MINIMIZATION ACTION PLAN: SUMMARY OF TOUCH™

TOUCH™ is a distribution program designed to assess the risk of progressive multifocal leukoencephalopathy (PML) associated with TYSABRI®, minimize the risk of PML, minimize death and disability due to PML, and promote informed risk-benefit decisions regarding TYSABRI® use. The risks of TYSABRI® treatment are addressed through the distribution program, along with education of prescribers, pharmacists, infusion center staff, and patients about potential PML infection associated with TYSABRI® treatment.

## 1. Prescribing Program

### 1.1 General Requirements

Biogen Idec, Inc. will ensure that the following requirements are addressed by its Risk Minimization Action Plan, TOUCH™:

- TYSABRI® will only be available under a special restricted distribution program called TOUCH™.
- Only prescribers registered with TOUCH™ and who agree to comply with the TOUCH™ program will be able to prescribe TYSABRI®.
- Only infusion centers registered and authorized under TOUCH™ will be able to administer TYSABRI®.
- Only pharmacies registered with TOUCH™ will be able to dispense TYSABRI® to affiliated authorized infusion centers.
- Only patients enrolled in TOUCH™ and who agree to comply with the TOUCH™ program will be able to receive TYSABRI®.
- All TOUCH™ prescribers, pharmacies, infusion centers, and patients will be educated about the TOUCH™ program and the risks of TYSABRI® treatment.
- Safety surveillance, including monitoring and reporting of PML infections, other serious opportunistic infections, and deaths and systematic tracking of patients and drug disposition will be conducted.

## 1.2 Pharmacy and Infusion Center Requirements

Biogen Idec, Inc. will limit the distribution of TYSABRI® through specialty and central pharmacies to authorized infusion centers. The agreements between Biogen Idec and the specialty and central pharmacies and infusion centers require the following:

- All pharmacies and infusion sites will be registered with the TOUCH™ program, and agree to comply with the TOUCH™ program.
- Infusion sites and central pharmacies will obtain TYSABRI® directly from a single contract distributor or specialty pharmacy.
- All appropriate pharmacy and infusion center staff will be trained by Biogen Idec and/or Elan Pharmaceuticals about the TOUCH™ program and about the known risks, potential benefits, and appropriate use of TYSABRI®.
- All appropriate pharmacy and infusion center staff will be trained by Biogen Idec and/or Elan Pharmaceuticals in adverse experience reporting procedures, including 15 day reporting of PML infection, other serious opportunistic infections, and deaths.
- Infusion center staff are to follow the infusion guidelines outlined below:
    - Accept only prescriptions from prescribers in the TOUCH™ program.
    - Only infuse patients who are enrolled in the TOUCH™ program.
    - Prior to infusing a patient, the infusion site will verify in the patient's medical record that the patient is authorized to receive TYSABRI®.
    - Prior to infusing a patient, the infusion site will, confirm that there is a current Notice of Patient Authorization on file, and confirm that there is not a Notice of Discontinuation on file.
    - Prior to infusing a patient, the infusion site will provide the patient the Medication Guide and give the patient time to read it.
    - Prior to infusing a patient, the infusion site will complete the Pre-Infusion Patient Checklist and confirm prescriber clearance if needed.
    - Within one day of completing the Pre-Infusion Patient Checklist, the infusion site will fax the form to Biogen Idec.
    - The infusion site will not dispense TYSABRI® if it is determined that the patient (or their prescriber) is not in conformance with the TOUCH™ program.
    - Keep a record of the TYSABRI® prescription, Notice of Patient Authorization, and the Pre-infusion Patient Checklist, with each TYSABRI® prescription for each corresponding patient.
- Central pharmacies are to follow the dispensing guidelines outlined below:
    - Fill valid prescriptions for TYSABRI® in accordance with all applicable laws and regulations
    - Dispense TYSABRI® only to affiliated authorized infusion sites.

- Complete the TYSABRI® Inventory Tracking Log for every dose/vial of TYSABRI® dispensed to authorized infusion sites. The Inventory Tracking Log will be kept for at least 5 years from the date of the final log entry.

### 1.3 Prescriber Requirements

Biogen Idec will accept registration of prescribers who agree to the following:

- To comply with the TOUCH™ program.
- To determine that a patient has a relapsing form of MS based on clinical and radiological evidence before prescribing TYSABRI®.
- That he/she is capable of diagnosing and managing opportunistic infections and PML, or prepared to refer to specialists with those abilities.
- To counsel all patients on the benefits and risks of TYSABRI® therapy, including the risks of PML, and to provide each patient with the TYSABRI® Medication Guide.
- To not prescribe TYSABRI® to any patient who is inappropriate for receiving the drug under the TOUCH™ program.
- To sign and complete the Prescriber/Patient Enrollment form for each patient, and to fax it to Biogen Idec before the patient can begin to receive infusions.
- To report to Biogen Idec, as soon as possible, any case of PML, any hospitalization due to opportunistic infection, and any death.
- To evaluate the patient 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter as long as the patient receives TYSABRI®, and 6 months after TYSABRI® has been discontinued.
- To determine every 6 months whether each patient should continue on TYSABRI® therapy and fill out the Patient Status Report and Reauthorization Questionnaire.

### 1.4 Patient Requirements

Biogen Idec will accept registration for patients who meet the following conditions:

- Must be registered in the TOUCH™ program.
- Must understand the risks and benefits of TYSABRI® treatment, including that taking the drug increases the risk of getting PML.
- Must complete and sign the Prescriber/Patient Enrollment Form indicating the patient's understanding of the potential risks associated with TYSABRI® treatment.
- Must agree to contact their prescriber if new or worsening symptoms, especially nervous system symptoms develop.
- Must read the TYSABRI® Medication Guide.
- Must agree to notify the TOUCH™ program if they switch infusion sites and/or prescribers
- Must provide information about other medicines and treatments at each TYSABRI® infusion.

## 2. Educational Program

Biogen Idec, Inc. will provide prescribers, infusion site staff, pharmacists and patients with educational materials on the benefits and risks associated with TYSABRI® therapy, the increased risk of PML, and the requirements of the TOUCH™ program.

### 2.1 Healthcare Provider and Patient Educational Materials

Educational information about the drug will be distributed to prescribers, pharmacies, infusion sites, and patients.

**The TOUCH™ Educational Materials and forms include:**

- The Patient Medication Guide and Package Insert (for patients and prescribers)
- TOUCH™ Prescribing Education Slide Set
- TYSABRI® and TOUCH™ Prescribing Program Slide Set (for prescribers and patients)
- TOUCH™ Prescribing Program Overview (general description)
- Prescriber/Patient Enrollment Form (signed by patients and prescribers)
- Infusion Site Enrollment Form (for infusion site enrollment)
- Central Pharmacy Enrollment Form (for central pharmacy enrollment into TOUCH™)
- TYSABRI® Inventory Tracking Log (central pharmacies use to document dispensing of TYSABRI® to affiliated authorized infusion sites)
- Patient Status Report and Reauthorization Questionnaire (filled out ever 6 months by prescribers)
- TYSABRI® Patient Discontinuation Notification Form (for prescribers to de-enroll a patient from the program)
- TYSABRI® Patient Discontinuation Questionnaire (for prescribers to complete at discontinuation and 6 months after the patient discontinues TYSABRI®)
- TOUCH™ Enrollment Kit (for prospective prescribers -- contains above information and describes program)
- Dear Doctor and Dear Patient Letters
- Patient Getting Started Brochure (information for patients about TOUCH™ and TYSABRI®)
- Healthcare Professional Infusion Guide (for infusion sites)
- Guidance for Evaluation of New Neurologic Symptoms in Patients Receiving TYSABRI® (for healthcare professionals)

### 2.2 Additional Information Sources

- www.TYSABRI.com
- Biogen Idec's Call Center: a call center designed to respond to healthcare provider, pharmacist, infusion center, and patient questions and requests for information.

**3. Reporting: Biogen Idec, Inc. will implement a reporting and collection system for safety information as follows:**

- All spontaneous and solicited adverse event reports from any post-marketing source will be reported as per 21 CFR 600.80.
- Within 15 calendar days a report for all confirmed cases of PML will be sent to FDA. Summary numbers for possible cases as flagged by the pre-infusion checklist will be reported in the periodic report.
- Within 15 calendar days a report of any other serious opportunistic infections or deaths of any cause will be reported to FDA.

Biogen Idec, Inc. will also establish a Pregnancy Registry in the US to determine the safety of TYSABRI® in pregnant patients. The primary objective will be to evaluate any pattern or increase in birth defects in children of women with MS who were exposed to TYSABRI® at any time within 3 months prior to conception, or at any time during pregnancy, where the outcome of the pregnancy is unknown at the time of enrollment.

**4. TOUCH™ Safety Surveillance**

Biogen Idec, through the TOUCH™ prescribing program will systematically follow and actively solicit information regarding the occurrence of PML and other serious opportunistic infections through a variety of mechanisms on every TYSABRI®-treated patient in the U.S. The various mechanisms include: through collection and assessment of Pre-Infusion Patient Checklists and the Prescriber/Patient Enrollment form; through serious adverse event reporting; and through contact with prescribers every 6 months in the form of a Patient Status Report and Reauthorization Questionnaire. In addition, attempts will be made to find and follow for 6 months patients who discontinue TYSABRI® treatment. Biogen Idec and Elan Pharmaceuticals are also creating a joint TYSABRI® Safety Review Committee to review safety data and determine any appropriate corrective actions, if needed.

**5. TOUCH™ Program Evaluation**

Biogen Idec, Inc. will evaluate the effectiveness of the TYSABRI® RiskMAP and will report the results quarterly for the first year, then every 6 months for 2 years, and annually thereafter to FDA. Each submission to FDA will include analyses of two major datasets:

- Health Outcomes Data (e.g. PML rate, overall safety)
- Systems/Process Data, Quality and Compliance Metrics

Biogen Idec, Inc. is also establishing a multi-disciplinary TYSABRI® Risk Management Review Committee to evaluate the effectiveness of the risk management plan. The decisions and outcomes of the Committee will be included in the TYSABRI® RiskMAP reports to FDA. In addition, Biogen Idec, Inc. and Elan Pharmaceuticals will create a joint TYSABRI® Compliance Review Committee to facilitate RiskMAP compliance.