CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125104/33

Trade Name: Tysabri

Generic Name: natalizumab

Sponsor: Biogen Idec, Inc.

Approval Date: January 14, 2008

Indications: 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. TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies. It is also used for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of TNF-α.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPLICATION NUMBER:

BLA 125104/33

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

Biogen Idec, Inc.
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your supplement to your biologics license application for TYSABRI® (Natalizumab), to update the Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, and Clinical Studies sections of the package insert with safety and efficacy data, submitted under section 351 of the Public Health Service Act.

This supplement, considered for approval under 21 CFR 601.42 (Subpart E), at your request, provides for the use of TYSABRI® for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α, submitted under section 351 of the Public Health Service Act.

We have completed our review of your supplement dated December 14, 2006, including all amendments to this supplement received through January 14, 2008. This supplement is approved under the provisions of 21 CFR 601.42 (Subpart E), effective on the date of this letter, for use as recommended in the agreed upon labeling text, required patient labeling, and the components of the TOUCH ™ Prescribing Program Risk Minimization Action Plan (RiskMAP) for Crohn's disease (CD) patients referred to as the CD TOUCH ™ Prescribing Program.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted January 14, 2008, the Medication Guide submitted January 14, 2008, and carton and container labels submitted December 14, 2006). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Under 21 CFR 601.42, distribution of TYSABRI® is limited as described below and in the attached detailed TOUCH ™ Prescribing Program. The primary goals of the TOUCH ™ Prescribing Program are 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.

TYSABRI® RiskMAP:

We remind you that your TYSABRI® RiskMAP for Crohn's disease patients is an important part of the postmarketing risk management for TYSABRI®, and must include each of the following components:

1. Enrollment in the TOUCH ™ Prescribing Program of prescribers, infusion centers, and pharmacies associated with infusion centers, and patients who agree to specific responsibilities in order to prescribe, dispense, infuse, and use TYSABRI®.

2. Implementation of a program and distribution of materials to educate prescribers, pharmacies, nurses, and patients about the risks and benefits of TYSABRI®, including materials that describe the roles of the TOUCH ™ Prescribing Program participants.

3. Implementation of a reporting and data collection system for safety surveillance.

4. Implementation of a plan to monitor, evaluate, and determine the incidence and risk factors for PML, other serious opportunistic infections, malignancies and compliance with restrictions for safe use under the TOUCH ™ Prescribing Program.

The TYSABRI® Risk Minimization Action Plan, submitted on January 7, 2008, and as described in the attached document, adequately addresses each of these requirements. This plan includes ongoing assessment and periodic reporting to FDA of the operation of the program and needed revisions, if any. Any change to the program must be discussed with FDA prior to its institution and is subject to FDA's determination that the required components are still present. We expect your continued cooperation to resolve any problems regarding the TOUCH ™ Prescribing Program that may be identified following approval of this application.

Pediatric Studies:

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages 0 to 5 years because the necessary studies are impossible or highly impracticable because the number of pediatric Crohn's disease patients in this age group is so small. We are deferring submission of your pediatric studies for ages 6 to 17 years for this application because pediatric studies should be delayed until additional safety data have been collected.

Your deferred pediatric studies required by section 505B(a) of the Food, Drug, and Cosmetic Act are required postmarketing study commitments. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Food, Drug, and Cosmetic Act. These commitment(s) are listed below.

1. Assess data anticipated from adults in protocol "TYSABRI Observational Study in Safety in CD (Crohn's disease)" (Postmarketing Commitment Number 4, below) and establish a pediatric study plan that incorporates these new data. These data must be analyzed, to include an assessment of safety, before the required pediatric studies are initiated. The due date for submitting this assessment and pediatric study plan is June 30, 2012.

2. Unless FDA agrees, based on your completion of Postmarketing Commitment Number 1 above, that it is not appropriate to conduct a pediatric study in pediatric patients age 12 to 17 years, conduct a pediatric study in pediatric patients age 12 to 17 years for the treatment of Crohn's disease.

   This pediatric study will enroll pediatric patients age 12 to 17 years into four study arms (placebo, 3 mg/kg, 4.5 mg/kg, and 6 mg/kg of TYSABRI administered intravenously every 4 weeks), and evaluate safety, efficacy, and pharmacokinetics of natalizumab.

   Study Start Date: December 31, 2012
   Study Completion Date: April 30, 2014
   Final Report Submission: September 30, 2014

3. Unless FDA agrees, based on your completion of Postmarketing Commitment Number 1 above, that it is not appropriate to conduct a pediatric study in pediatric patients age 6 to 11 years, after completing the study described in Postmarketing Commitment Number 2, conduct a pediatric study in pediatric patients age 6 to 11 years for the treatment of Crohn's disease.

   This second pediatric study will enroll pediatric patients age 6 to 11 years in a single, open-label arm (dose of TYSABRI will be selected based on results in older pediatric patients), and evaluate safety, pharmacokinetics, and response/remission rates.

   Study Start Date: January 31, 2015
   Study Completion Date: December 31, 2016
   Final Report Submission: June 30, 2017

Submit final study reports to this BLA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

We acknowledge your written commitment, as described in your letter of January 9, 2008, and as agreed upon during our teleconference of January 8, 2008, to conduct the postmarketing commitment outlined below:

Postmarketing Observational Study subject to reporting requirements of 21 CFR 601.70.

4. To conduct a prospective, observational study in at least 2000 subjects with Crohn's disease who are receiving TYSABRI, with each subject followed for at least five years, by completing protocol, "TYSABRI Observational Study in Safety in CD (Crohn's disease)." You will ensure having at least 1000 patients with two years of TYSABRI treatment, and will increase the total number of patients enrolled beyond 2000 if necessary to achieve this. The final protocol will be submitted by March 31, 2008.

Study Start Date: June 30, 2008
Study Patient Accrual Completion Date: June 30, 2012
Study Completion Date: June 30, 2017
Final Report Submission: March 31, 2018

In addition, postmarketing commitments numbers 3 through 16 agreed to in the approval of STN BL 125104/0 and described in the November 23, 2004 approval letter that are not yet fulfilled are still in effect. Postmarketing commitment number 1 agreed to in the approval of STN BL 125104/15 and described in the June 5, 2006, approval letter is also still in effect.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125104. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

Under 21 CFR Part 208, we previously determined that this product posed a serious and significant public health concern requiring the distribution of a Medication Guide. Natalizumab is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. Therefore, a Medication Guide continues to be necessary for safe and effective use of this product and FDA hereby approves the revised Medication Guide you submitted January 14, 2008. Please note your continued requirement to adhere to *General Requirements for a Medication Guide* specified in 21 CFR 208 Subpart B.

As part of the approval and as required by 21 CFR 601.45, you must submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological

product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

This information will be included in your biologics license application file.

Sincerely,

MD WPT 1/14/08

Joyce A. Korvick, M.D., M.P.H.
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachments:

Tysabri BLA STN 125104/33 Final Label
Tysabri® Risk Minimization Action Plan: SUMMARY OF TOUCH

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125104/33

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYSABRI safely and effectively. See full prescribing information for TYSABRI.

TYSABRI (natalizumab) injection for intravenous use
Initial U.S. Approval: 2004

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

See full prescribing information for complete boxed 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 (5.1)**
- **Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)**
- **TYSABRI is available only through a special restricted distribution program called the TOUCH™ Prescribing Program and must be administered only to patients enrolled in this program (5.1, 5.2)**

RECENT MAJOR CHANGES

Indications and Usage

Crohn's Disease (1.2)	1/2008

Dosage and Administration

Crohn's Disease (2.2)	1/2008

Warnings and Precautions

Progressive Multifocal Leukoencephalopathy (5.1)	1/2008
Distribution Program for TYSABRI (5.2)	1/2008
Immunosuppression/Infections (5.4)	1/2008
Hepatotoxicity (5.5)	1/2008

INDICATIONS AND USAGE

TYSABRI is an integrin receptor antagonist indicated for treatment of:

Multiple Sclerosis (MS) (1.1)

- 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. TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies.

Crohn's Disease (CD) (1.2)

- Inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of TNF-α.

Important Limitations:

- In CD, TYSABRI should not be used in combination with immunosuppressants or inhibitors of TNF-α.

DOSAGE AND ADMINISTRATION

- 300 mg infused intravenously over approximately one hour, every four weeks. Do not give as an intravenous push or bolus (2.1, 2.2).
- TYSABRI solution must be administered within 8 hours of preparation (2.3).
- Observe patients during the infusion and for one hour after the infusion is complete (2.4).
- In CD, discontinue in patients that have not experienced therapeutic benefit by 12 weeks of induction therapy, and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy (2.2).

DOSAGE FORMS AND STRENGTHS

- Solution [300 mg per 15 mL vial] for dilution prior to infusion (2.2, 3).

CONTRAINDICATIONS

- Patients who have or have had PML (4).
- Patients who have had a hypersensitivity reaction to TYSABRI (4).

WARNINGS AND PRECAUTIONS

- Progressive Multifocal Leukoencephalopathy (PML): Has occurred in 3 patients who received TYSABRI. Patients who have significantly compromised immune system function should not ordinarily be treated with TYSABRI. Obtain an MRI scan in MS patients prior to initiating TYSABRI. Monitor MS and CD patients and withhold TYSABRI at the first sign or symptom suggestive of PML (5.1).
- Hypersensitivity reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have occurred. Permanently discontinue TYSABRI if such a reaction occurs (5.3).
- Immunosuppression/Infections: TYSABRI may increase the risk for certain infections. Monitor patients for development of infections due to increased risk with use of TYSABRI (5.4).
- Hepatotoxicity: Clinically significant liver injury has occurred. Discontinue TYSABRI in patients with jaundice or evidence of liver injury (5.5).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 10%) in MS were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea NOS, and rash; and in CD were headache, upper respiratory tract infections, nausea, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec or Elan at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy: Physicians are encouraged to enroll pregnant patients in the TYSABRI Pregnancy Exposure Registry by calling 1-800-456-2255 (8.1)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 1/2008

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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 [see *Warnings and Precautions (5.1)*].

- **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 and Precautions (5.1, 5.2)*].**
- **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 (4), Warnings and Precautions (5.1)*].**

1 INDICATIONS AND USAGE

1.1 Multiple Sclerosis (MS)

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, TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies [see *Boxed Warning, Warnings and Precautions (5.1)*].

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

1.2 Crohn's Disease (CD)

TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α [see *Boxed Warning, Warnings and Precautions (5.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Multiple Sclerosis (MS)

Only prescribers registered in the MS TOUCH™ Prescribing Program may prescribe TYSABRI for multiple sclerosis [see *Boxed Warning, Warnings and Precautions (5.2)*]. The recommended dose of TYSABRI for multiple sclerosis is 300 mg intravenous infusion over one hour every four weeks.

2.2 Crohn's Disease (CD)

Only prescribers registered in the CD TOUCH™ Prescribing Program may prescribe TYSABRI for Crohn's disease [see *Boxed Warning, Warnings and Precautions (5.1)*].

The recommended dose of TYSABRI for Crohn's disease is 300 mg intravenous infusion over one hour every four weeks. TYSABRI should not be used with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or concomitant inhibitors of TNF-α. Aminosalicylates may be continued during treatment with TYSABRI.

If the patient with Crohn's disease has not experienced therapeutic benefit by 12 weeks of induction therapy, discontinue TYSABRI. For patients with Crohn's disease that start TYSABRI while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of TYSABRI has occurred; if the patient with Crohn's disease cannot be tapered off of oral corticosteroids within six months of starting TYSABRI, discontinue TYSABRI. Other than the initial six-month taper, prescribers should consider discontinuing TYSABRI for patients who require additional steroid use that exceeds three months in a calendar year to control their Crohn's disease.

2.3 Dilution Instructions

1. Use aseptic technique when preparing TYSABRI solution for intravenous infusion. Each vial is intended for single use only.

2. TYSABRI is a colorless, clear to slightly opalescent concentrate. Inspect the TYSABRI vial for particulate material and discoloration 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.

3. 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.

4. Gently invert the TYSABRI solution to mix completely. Do not shake. Inspect the solution visually for particulate material prior to administration.

5. The final dosage solution has a concentration of 2.6 mg/mL.

6. Following dilution, infuse TYSABRI solution immediately, or refrigerate solution at 2 to 8°C, and use within 8 hours. If stored at 2 to 8°C, allow the solution to warm to room temperature prior to infusion. DO NOT FREEZE.

2.4 Administration Instructions

- Infuse TYSABRI 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP, over approximately one hour (infusion rate approximately 5 mg per minute). Do not administer TYSABRI as an intravenous push or bolus injection. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.

- Observe patients during the infusion and for one 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 and Precautions (5.3)*].

- 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.

3 DOSAGE FORMS AND STRENGTHS

TYSABRI is a concentrated solution that must be diluted prior to intravenous infusion. TYSABRI injection is supplied as 300 mg natalizumab in 15 mL (20 mg/mL) in a sterile, single-use vial free of preservatives.

4 CONTRAINDICATIONS

- TYSABRI is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) [see *Boxed Warning, Warnings and Precautions (5.1)*].

- TYSABRI should not be administered to a patient who has had a hypersensitivity reaction to TYSABRI. Observed reactions range from urticaria to anaphylaxis [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus, and which typically only occurs in patients that are immunocompromised, has occurred in three 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 eight 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 two 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.

In multiple sclerosis patients, 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.

In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on TYSABRI therapy are uncommon.

Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. Withhold TYSABRI dosing 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.

5.2 Distribution 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. For prescribers and patients, the TOUCH™ Prescribing Program has two components: MS TOUCH™ (for patients with multiple sclerosis) and CD TOUCH™ (for patients with Crohn's disease). TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the MS or CD TOUCH™ Prescribing Program. Contact the TOUCH™ Prescribing Program at 1-800-456-2255 [see *Boxed Warning*].

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:

- Educate patients on the benefits and risks of treatment with TYSABRI, ensure that the patient receives 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 or Elan at 1-800-456-2255 and to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.
- Evaluate the patient three months after the first infusion, six months after the first infusion, and every six months thereafter.
- Determine every six months whether patients should continue on treatment and if so reauthorize treatment every six months.
- Submit to Biogen Idec the TYSABRI Patient Status Report and Reauthorization Questionnaire six months after initiating treatment and every six months thereafter.

5.3 Hypersensitivity/Antibody Formation

Hypersensitivity reactions have occurred in patients receiving TYSABRI, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. These reactions usually occur within two 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. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI. Hypersensitivity reactions were more frequent in patients with antibodies to TYSABRI compared to patients who did not develop antibodies to TYSABRI in both MS and CD studies. Therefore, the possibility of antibodies to TYSABRI should be considered in patients who have hypersensitivity reactions [see *Adverse Reactions (6.2)*].

Antibody testing: 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 six months) may be transient and disappear with continued dosing. Repeat testing at three 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.

Experience with monoclonal antibodies, including TYSABRI, suggests that patients who receive therapeutic monoclonal antibodies after an extended period without treatment may be at higher risk of hypersensitivity reactions than patients who received regularly scheduled treatment. Given that patients with persistent antibodies to TYSABRI experience reduced efficacy, and that hypersensitivity reactions are more common in such patients, consideration should be given to testing for the presence of antibodies in patients who wish to recommence therapy following a dose interruption. Following a period of dose interruption, patients testing negative for antibodies prior to re-dosing have a risk of antibody development with re-treatment that is similar to TYSABRI naïve patients [see *Adverse Reactions (6.2)*].

5.4 Immunosuppression/Infections

The immune system effects of TYSABRI may increase the risk for infections. In Study MS1 [see *Clinical Studies (14.1)*], 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 and Precautions (5.1), Adverse Reactions (6.1)*]. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI in Study MS1.

In Studies MS1 and MS2, an increase in infections was seen in patients concurrently receiving short courses of corticosteroids. However, the increase in infections in TYSABRI-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids.

In CD clinical studies, opportunistic infections (pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been observed in <1% of TYSABRI-treated patients; some of these patients were receiving concurrent immunosuppressants [see *Boxed Warning, Warnings and Precautions (5.1, 5.4), Adverse Reactions (6.1)*].

In Studies CD1 and CD2, an increase in infections was seen in patients concurrently receiving corticosteroids. However, the increase in infections was similar in placebo-treated and TYSABRI-treated patients who received steroids.

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 and Precautions (5.1), Adverse Reactions (6.1)*]. The safety and efficacy of TYSABRI in combination with antineoplastic,

immunosuppressant, or immunomodulating agents have not been established. Patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not ordinarily be treated with TYSABRI.

For patients with Crohn's disease who start TYSABRI while on chronic corticosteroids, commence steroid withdrawal as soon as a therapeutic benefit has occurred. If the patient cannot discontinue systemic corticosteroids within six months, discontinue TYSABRI.

5.5 Hepatotoxicity
Clinically significant liver injury has been reported in patients treated with TYSABRI in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses. In some patients, liver injury recurred upon rechallenge, providing evidence that TYSABRI caused the injury. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients.

TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

5.6 Laboratory Test Abnormalities
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.

5.7 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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
The most serious adverse reactions were [see *Warnings and Precautions (5)*]:

- Progressive Multifocal Leukoencephalopathy (PML)
- Hypersensitivity
- Immunosuppression/Infections

The most common adverse reactions (incidence ≥ 10%) were headache and fatigue in both the multiple sclerosis (MS) and Crohn's disease (CD) studies. Other common adverse reactions (incidence ≥ 10%) in the MS population were arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea NOS, and rash. Other common adverse reactions (incidence ≥ 10%) in the CD population were upper respiratory tract infections and nausea.

The most frequently reported adverse reactions resulting in clinical intervention (i.e., discontinuation of TYSABRI), in the MS studies were urticaria (1%) and other hypersensitivity reactions (1%), and in the CD studies (Studies CD1 and CD2) were the exacerbation of Crohn's disease (4.2%) and acute hypersensitivity reactions (1.5%) [see *Warnings and Precautions (5.3)*].

A total of 1617 multiple sclerosis patients in controlled studies received TYSABRI, with a median duration of exposure of 28 months. A total of 1563 patients received TYSABRI in all CD studies for a median exposure of 5 months; of these patients, 33% (n=518) received at least one year of treatment and 19% (n=297) received at least two years of treatment.

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.

Multiple Sclerosis Clinical Studies

The most frequently reported serious adverse reactions in Study MS1 [see *Clinical Studies (14.1)*] 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 MS2, serious

adverse reactions of appendicitis were also more common in patients who received TYSABRI (0.8% versus 0.2% in placebo) [see *Warnings and Precautions (5.4), Adverse Reactions - Infections*].

Table 1 enumerates adverse reactions and selected laboratory abnormalities that occurred in Study MS1 at an incidence of at least 1 percentage point higher in TYSABRI-treated patients than was observed in placebo-treated patients.

Table 1. Adverse Reactions in Study MS1 (Monotherapy Study)

Adverse Reactions (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%
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 MS2, peripheral edema was more common in patients who received TYSABRI (5% versus 1% in placebo).

Crohn's Disease Clinical Studies

The following serious adverse events in the induction Studies CD1 and CD2 [see *Clinical Studies (14.2)*] were reported more commonly with TYSABRI than placebo and occurred at an incidence of at least 0.3%: intestinal obstruction or stenosis (2% vs. 1% in placebo), acute hypersensitivity reactions (0.5% vs. 0%), abdominal adhesions (0.3% vs. 0%), and cholelithiasis (0.3% vs. 0%). Similar serious adverse events were seen in the maintenance Study CD3. Table 2 enumerates adverse drug reactions that occurred in Studies CD1 and CD2 (median exposure of 2.8 months). Table 3 enumerates adverse drug reactions that occurred in Study CD3 (median exposure of 11.0 months).

Table 2. Adverse Reactions in Studies CD1 and CD2 (Induction Studies)

Adverse Reactions*	**TYSABRI n=983 Percentage**	**Placebo n=431 Percentage**
General		
Headache	32%	23%
Fatigue	10%	8%
Arthralgia	8%	6%
Influenza-like illness	5%	4%
Acute hypersensitivity reactions	2%	<1%
Tremor	1%	<1%
Infection		
Upper respiratory tract infection	22%	16%
Vaginal infections**	4%	2%
Viral infection	3%	2%
Urinary tract infection	3%	1%
Respiratory		
Pharyngolaryngeal pain	6%	4%
Cough	3%	<1%

Gastrointestinal		
Nausea	17%	15%
Dyspepsia	5%	3%
Constipation	4%	2%
Flatulence	3%	2%
Aphthous stomatitis	2%	<1%
Skin		
Rash	6%	4%
Dry skin	1%	0%
Menstrual Disorder		
Dysmenorrhea**	2%	<1%

*Occurred at an incidence of at least 1% higher in TYSABRI-treated patients than placebo-treated patients.

**Percentage based on female patients only.

Table 3. Adverse Reactions in Study CD3 (Maintenance Study)

Adverse Reactions*	TYSABRI n=214 Percentage	Placebo n=214 Percentage
General		
Headache	37%	31%
Influenza-like illness	11%	6%
Toothache	4%	<1%
Peripheral edema	6%	3%
Infection		
Influenza	12%	5%
Sinusitis	8%	4%
Viral infection	7%	3%
Vaginal infections**	8%	<1%
Respiratory		
Cough	7%	5%
Gastrointestinal		
Lower abdominal pain	4%	2%
Musculoskeletal and Connective Tissue		
Back pain	12%	8%
Menstrual disorder		
Dysmenorrhea**	6%	3%

*Occurred at an incidence of at least 2% higher in TYSABRI-treated patients than placebo-treated patients.

**Percentage based on female patients only.

Infections

Progressive Multifocal Leukoencephalopathy (PML) has occurred in three patients who received TYSABRI in clinical trials [see *Boxed Warning, Warnings and Precautions (5.1)*]. Two cases of PML were observed in the 1869 patients with multiple sclerosis who were treated for a median of 120 weeks. These two patients had received TYSABRI in addition to interferon beta-1a [see *Boxed*

Warning, Warnings and Precautions (5.1)]. The third case occurred after eight doses in one of the 1043 patients with Crohn's disease who were evaluated for PML.

In Studies MS1 and MS2 [see *Clinical Studies (14.1)*], 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 MS1, 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 Studies CD1 and CD2 [see *Clinical Studies (14.2)*], the rate of any type of infection was 1.7 per patient-year in TYSABRI-treated patients and 1.4 per patient-year in placebo-treated patients. In Study CD3, the incidence of any type of infection was 1.7 per patient-year in TYSABRI-treated patients and was similar in placebo-treated patients. The most common infections were nasopharyngitis, upper respiratory tract infection, and influenza. The majority of patients did not interrupt TYSABRI therapy during infections and recovery occurred with appropriate treatment. Concurrent use of TYSABRI in CD clinical trials with chronic steroids and/or methotrexate, 6-MP, and azathioprine did not result in an increase in overall infections compared to TYSABRI alone; however, the concomitant use of such agents could lead to an increased risk of serious infections.

In Studies CD1 and CD2, the incidence of serious infection was approximately 2.1% in both TYSABRI-treated patients and placebo-treated patients. In Study CD3, the incidence of serious infection was approximately 3.3% in TYSABRI-treated patients and approximately 2.8% in placebo-treated patients.

In clinical studies for CD, opportunistic infections (pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been observed in <1% of TYSABRI-treated patients; some of these patients were receiving concurrent immunosuppressants [see *Warnings and Precautions (5.4)*]. Two serious non-bacterial meningitides occurred in TYSABRI-treated patients compared to none in placebo-treated patients.

Infusion-related Reactions

An infusion-related reaction was defined in clinical trials as any adverse event occurring within two hours of the start of an infusion. In MS clinical trials, approximately 24% of TYSABRI-treated multiple sclerosis patients experienced an infusion-related reaction, compared to 18% of placebo-treated patients. In the controlled CD clinical trials, infusion-related reactions occurred in approximately 11% of patients treated with TYSABRI compared to 7% of placebo-treated patients. Reactions more common in the TYSABRI-treated MS patients compared to the placebo-treated MS 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 [see *Warnings and Precautions (5.3)*]. All patients recovered with treatment and/or discontinuation of the infusion.

Infusion-related reactions more common in CD patients receiving TYSABRI than those receiving placebo included headache, nausea, urticaria, pruritus, and flushing. Serious infusion reactions occurred in Studies CD1, CD2, and CD3 at an incidence of <1% in TYSABRI-treated patients.

MS and CD patients who became persistently positive for antibodies to TYSABRI were more likely to have an infusion-related reaction than those who were antibody-negative.

6.2 Immunogenicity

Patients in Study MS1 [see *Clinical Studies (14.1)*] 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 MS1, the Week 12 pre-infusion mean natalizumab serum concentration in antibody-negative patients was 15 mcg/mL compared to 1.3 mcg/mL in antibody-positive patients. Persistent antibody-positivity resulted in 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 MS2.

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 reactions more common in persistently antibody-positive patients included myalgia, hypertension, dyspnea, anxiety, and tachycardia.

Patients in CD studies [see *Clinical Studies (14.2)*] were first tested for antibodies at Week 12, and in a substantial proportion of patients, this was the only test performed given the 12-week duration of placebo-controlled studies. Approximately 10% of patients were found to have anti-natalizumab antibodies on at least one occasion. Five percent (5%) of patients had positive antibodies on more than one occasion. Persistent antibodies resulted in reduced efficacy and an increase in infusion-related reactions with symptoms that include urticaria, pruritus, nausea, flushing, and dyspnea.

The long-term immunogenicity of TYSABRI and the effects of low to moderate levels of antibody to natalizumab are unknown [see *Warnings and Precautions (5.3), Adverse Reactions (6.1)*].

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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TYSABRI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In post-marketing experience, one MS patient who received TYSABRI developed herpes encephalitis and died; a second MS patient developed herpes meningitis and recovered with appropriate treatment.

7 DRUG INTERACTIONS

Because of the potential for increased risk of PML and other infections, Crohn's disease patients receiving TYSABRI should not be treated with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α, and corticosteroids should be tapered in those patients with Crohn's disease who are on chronic corticosteroids when they start TYSABRI therapy [see *Boxed Warning, Indications and Usage (1.2), Warnings and Precautions (5.1, 5.4)*]. Ordinarily, MS patients receiving chronic immunosuppressant or immunomodulatory therapy should not be treated with TYSABRI [see *Boxed Warning, Indications and Usage (1.1), Warnings and Precautions (5.1, 5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. TYSABRI has been shown to reduce pup survival in guinea pigs when given in doses 7 times the human dose, and has been shown to have hematologic effects on the fetus in monkeys when given in doses 2.3 times the human dose [see *Nonclinical Toxicology (13.2)*]. There are no adequate and well-controlled studies in pregnant women. TYSABRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman becomes pregnant while taking TYSABRI, consider enrolling her in the TYSABRI Pregnancy Exposure Registry by calling 1-800-456-2255.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TYSABRI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of TYSABRI in pediatric patients with multiple sclerosis or Crohn's disease below the age of 18 years have not been established. TYSABRI is not indicated for use in pediatric patients.

8.5 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. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 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.

11 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 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Natalizumab 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*, natalizumab 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 and Crohn's disease 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.

In Crohn's disease, the interaction of the α4β7 integrin with the endothelial receptor MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to gut lymph tissue found in Peyer's patches. MAdCAM-1 expression has been found to be increased at active sites of inflammation in patients with CD, which suggests it may play a role in the recruitment of leukocytes to the mucosa and contribute to the inflammatory response characteristic of CD. The clinical effect of natalizumab in CD may therefore be secondary to blockade of the molecular interaction of the α4ß7-integrin receptor with MAdCAM-1 expressed on the venular endothelium at inflammatory foci. VCAM-1 expression has been found to be upregulated on colonic endothelial cells in a mouse model of IBD and appears to play a role in leukocyte recruitment to sites of inflammation. The role of VCAM-1 in CD, however, is not clear.

12.2 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 absolute count of circulating neutrophils [see *Warnings and Precautions (5.6)*].

12.3 Pharmacokinetics

Multiple Sclerosis (MS) Patients:

In patients with MS, following the repeat intravenous administration of a 300 mg dose of TYSABRI, the mean ± SD 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 four weeks of dosing. The mean ± SD 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 (n=2195). 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 (6.2)]*.

Crohn's Disease (CD) Patients:

In patients with CD, following the repeat intravenous administration of a 300 mg dose of TYSABRI, the mean ± SD maximum observed serum concentration was 101 ± 34 mcg/mL. The mean ± SD average steady-state trough concentration was 10 ± 9 mcg/

mL. The estimated time to steady-state was approximately 16 to 24 weeks after every four weeks of dosing. The mean ± SD half-life, volume of distribution, and clearance of natalizumab were 10 ± 7 days, 5.2 ± 2.8 L, and 22 ± 22 mL/hour, respectively.

The effects of total body weight, age, gender, race, selected hematology and serum chemistry measures, co-administered medications (infliximab, immunosuppressants, or steroids), and the presence of anti-natalizumab antibodies were investigated in a population pharmacokinetic analysis (n=1156). The presence of anti-natalizumab antibodies was observed to increase natalizumab clearance [see *Adverse Reactions (6.2)*].

Pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 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 to 72% in the other groups. Natalizumab did not affect male fertility at doses up to 7-fold the clinical dose.

13.2 Animal Toxicology and/or Pharmacology

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.

14 CLINICAL STUDIES

14.1 Multiple Sclerosis

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. Results for each study are shown in Tables 4 and 5. Median time on study drug was 120 weeks in each study. 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 MS1 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 intravenous infusion (n=627) or placebo (n=315) every 4 weeks for up to 28 months (30 infusions).

Study MS2 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.

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 ≥ 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 MS1 (Figure 1) and MS2. 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 MS1 and MS2 (Tables 4 and 5).

Table 4. Clinical and MRI Endpoints in Study MS1 (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 mo 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 5. Clinical and MRI Endpoints in Study MS2 (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 MS1

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.

Safety and efficacy of treatment with TYSABRI beyond two years are not known.

14.2 Crohn's Disease

The safety and efficacy of TYSABRI were evaluated in three randomized, double-blind, placebo-controlled clinical trials in 1414 adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥220 and ≤450) [see *Reference (15)*]. Concomitant inhibitors of TNF-α were not permitted. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunosuppressants (e.g., 6-mercaptopurine, azathioprine, or methotrexate) were permitted, and 89% of patients continued to receive at least one of these medications. Although permitted in the clinical trials, combination therapy with immunosuppressants is not recommended [see *Indications and Usage (1.2)*]. Overall, approximately two-thirds of patients were not taking concomitant immunosuppressants, and approximately one-third of patients were taking neither concomitant immunosuppressants nor concomitant corticosteroids.

Induction of clinical response (defined as ≥70-point decrease in CDAI from baseline) was evaluated in two studies. In Study CD1, 896 patients were randomized 4:1 to receive three monthly infusions of either 300 mg TYSABRI or placebo. Clinical results were assessed at Week 10, and patients with incomplete information were considered as not having a clinical response. At Week 10, 56% of the 717 patients receiving TYSABRI were in response compared to 49% of the 179 patients receiving placebo (treatment effect: 7%; 95% confidence interval (CI): [-1%, 16%]; p=0.067). In a *post hoc* analysis of the subset of 653 patients with elevated baseline C-reactive protein (CRP), indicative of active inflammation, 57% of TYSABRI patients were in response compared to 45% of those receiving placebo (treatment effect: 12%; 95% CI: [3%, 22%]; nominal p=0.01).

In the second induction trial, Study CD2, only patients with elevated serum C-reactive Protein (CRP) were studied. A total of 509 patients were randomized 1:1 to receive three monthly infusions of either 300 mg TYSABRI or placebo. In Study CD2, in contrast to Study CD1, clinical response and clinical remission (defined as CDAI score <150) were required to be met at both Weeks 8 and 12, rather than at a single time-point; patients with incomplete information were considered as not having a response (Table 6).

Table 6. Induction of Clinical Response and Remission in Study CD2

	TYSABRI	**Placebo**	**Treatment Difference (95% CI)**
	n=259	**n=250**	
Clinical Response at:			
Week 8	56%	40%	16% (8%, 26%)
Week 12	60%	44%	16% (7%, 25%)
Both Weeks 8 & 12*	48%	32%	16% (7%, 24%)

Clinical Remission at:			
Week 8	32%	21%	11% (3%, 19%)
Week 12	37%	25%	12% (4%, 21%)
Both Weeks 8 & 12*	26%	16%	10% (3%, 18%)

*p<0.005

Response is defined as a ≥70-point reduction in CDAI score from baseline.

Remission is defined as CDAI <150.

In studies CD1 and CD2, for subgroups defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF-α), the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither concomitant immunosuppressants nor concomitant corticosteroids, the treatment effect was generally similar to that seen in the whole study population. Patients with inadequate response to inhibitors of TNF-α appeared to have lower clinical response and lower clinical remission in both the treatment and placebo groups. For patients in Study CD2 with an inadequate response to prior treatment with inhibitors of TNF-α, clinical response at both Weeks 8 and 12 was seen in 38% of those randomized to TYSABRI, and clinical remission at both Weeks 8 and 12 was seen in 17%.

Maintenance therapy was evaluated in Study CD3. In this study, 331 patients from Study CD1 that had had a clinical response to TYSABRI at both Weeks 10 and 12 were re-randomized 1:1 to treatment with continuing monthly infusions of either 300 mg TYSABRI or placebo.

Maintenance of response was assessed by the proportion of patients who did not lose clinical response at any study visit for an additional 6 and 12 months of treatment (i.e., Month 9 and Month 15 after initial treatment with TYSABRI). The study also assessed the proportion of patients who did not lose clinical remission at any study visit within the subset of those who were in remission at study entry. Requiring maintenance of response or remission at each visit, as opposed to just at Month 9 or Month 15, may result in lower proportions meeting endpoint criteria, and may make a comparison of these results with those of other products used to treat Crohn's disease misleading (Table 7).

Table 7. Maintenance of Clinical Response and Remission in Study CD3

	TYSABRI	**Placebo**	**Treatment Difference (95% CI)**
	n=164	**n=167**	
Clinical Response through:			
Month 9*	61%	29%	32% (21%, 43%)
Month 15	54%	20%	34% (23%, 44%)
	n=128†	**n=118†**	
Clinical Remission through:			
Month 9*	45%	26%	19% (6%, 31%)
Month 15	40%	15%	25% (13%, 36%)

*p<0.005

†Number of patients included for analysis of "through" Month 9 and Month 15 includes only those in remission upon entry into Study CD3.

Response is defined as CDAI <220 and a ≥70-point reduction in CDAI score compared to Baseline from Study CD1.

Remission is defined as CDAI <150.

For subgroups in study CD3 defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF-α), the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither concomitant immunosuppressants nor concomitant corticosteroids, the treatment effect was generally similar to that seen in the whole study population. Patients with inadequate response to inhibitors of TNF-α appeared to have lower maintenance of clinical response and lower maintenance of clinical remission in both the treatment and placebo groups. For patients in study CD3 with an inadequate response to prior treatment with inhibitors of TNF-α, maintenance of clinical response through Month 9 was seen in 52% of those randomized to TYSABRI, and maintenance of clinical remission through Month 9 was seen in 30%.

Given the requirement to discontinue chronic steroids it is important to note that in the subgroup of patients (n=65) who were receiving corticosteroid medication at baseline, responded to TYSABRI in Study CD1, and were re-randomized to TYSABRI in Study CD3, approximately two-thirds were able to discontinue steroids within 10 weeks of initiating a steroid taper.

15 REFERENCES

- Best WR, Becktel JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70(3): 439-444.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 59075-730-15, TYSABRI injection is supplied as 300 mg natalizumab in 15 mL in a sterile, single-use vial free of preservatives. Each package contains a single-use vial. TYSABRI is a colorless and clear to slightly opalescent solution for dilution prior to intravenous infusion.

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.

TYSABRI single-use vials must be refrigerated between 2 to 8°C (36° to 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 diluted TYSABRI solution for infusion at 2 to 8°C (36° to 46°F). TYSABRI solution for infusion must be administered within 8 hours of preparation.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6)

17.1 General Counseling Information

Counsel patients to 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. INSTRUCT PATIENTS USING TYSABRI TO:

- Read the Medication Guide before starting TYSABRI and before each TYSABRI infusion.
- Promptly report any new or continuously worsening symptoms that persist over several days to their prescriber [see *Boxed Warning, Warnings and Precautions (5.1)*].
- Inform all of their physicians that they are receiving TYSABRI.
- Plan to see their prescriber three months after the first infusion, six months after the first infusion, and at least as frequently as every six months thereafter.

17.2 Progressive Multifocal Leukoencephalopathy

Inform patients that Progressive Multifocal Leukoencephalopathy (PML) has occurred in three patients who received TYSABRI. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Instruct the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. Instruct the patient that the progression of deficits usually leads to death or severe disability over weeks or months [see *Warnings and Precautions (5.1)*].

17.3 Hypersensitivity Reactions

Instruct patients to report immediately if they experience symptoms consistent with a hypersensitivity reaction (e.g., urticaria with or without associated symptoms) during or following an infusion of TYSABRI [see *Warnings and Precautions (5.3)*].

17.4 Immunosuppression/Infections

Inform patients that TYSABRI may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection [see *Warnings and Precautions (5.4)*].

17.5 Hepatotoxicity

Inform patients that TYSABRI may cause liver injury. Instruct the patient to contact their doctor if they develop symptoms of hepatoxicity [see *Warnings and Precautions (5.5)*].

I61061-4

TYSABRI (natalizumab)

Manufactured by:
Biogen Idec Inc.

14 Cambridge Center
Cambridge, MA 02142 USA
1-800-456-2255

Distributed by:
Elan Pharmaceuticals, Inc.
South San Francisco, CA 94080

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TYSABRI® is a registered trademark of Elan Pharmaceuticals, Inc.
AVONEX® is a registered trademark of Biogen Idec
TOUCH™ is a trademark of Elan Pharmaceuticals, Inc.

U.S. Patent Numbers: 5,840,299, 6,033,665, 6,602,503, 5,168,062, 5,385,839, 5,730,978

17.6 Medication Guide
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).** If PML happens, it 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 treatments for Multiple Sclerosis (MS) and Crohn's disease (CD).
- Even if you use TYSABRI alone to treat your MS or CD, 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:

1. **adult patients with relapsing forms of Multiple Sclerosis (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 treatments for MS.

2. **adult patients with moderate to severe Crohn's disease:**

- To reduce signs and symptoms of Crohn's disease
- In patients who have not been helped enough by, or cannot tolerate usual Crohn's disease medicines and medicines called tumor necrosis factor (TNF) inhibitors.
- Patients should not be taking certain medicines that weaken the immune system at the same time they are taking TYSABRI. Ask your doctor if you have questions.

- TYSABRI does not cure MS or Crohn's disease.

- TYSABRI has not been studied for use longer than 2 years. Also, TYSABRI has not been studied in patients with chronic progressive MS. It is not known if patients older than 65 years have a different response to TYSABRI.

- TYSABRI is not approved for use in patients under age 18.

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). If PML happens, it 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	• chills
• itching	• rash
• trouble breathing	• nausea
• chest pain	• flushing of skin
• dizziness	• low blood pressure
• wheezing	

- 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.

- **Liver damage.** TYSABRI may cause liver damage. Symptoms can include:

• yellowing of the skin and eyes (jaundice)	• unusual darkening of the urine
• nausea	• feeling tired or weak
• vomiting	

Blood tests can be done to check for liver damage. Call your doctor right away if you have symptoms of liver damage.

Other side effects with TYSABRI include:

• headache	• feeling tired
• urinary tract infection	• joint pain
• lung infection	• depression

• pain in your arm and legs	• diarrhea
• vaginitis	• rash
• nose and throat infections	• 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**.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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.

I61061-4
01/08

Manufactured by: Biogen Idec Inc., 14 Cambridge Center, Cambridge, MA 02142 USA
Distributed by: Elan Pharmaceuticals, Inc., South San Francisco, CA 94080

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TOUCH™ is a trademark of Elan Pharmaceuticals, Inc.

Revised: 1/2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125104/33

SUMMARY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Division of Gastroenterology Products
HFD-180

Date: **January 14, 2008**

From: **John Hyde, Ph.D., M.D., Clinical Team Leader, DGP**

John E Hyde 1-14-08

Through: **Joyce Korvick, M.D., Ph.D., Deputy Division Director, DGP**

Subject: **Clinical Team Leader Summary Review of BLA/STN 125104/33 TYSABRI for Crohn's Disease**

To: **sBLA 125104/33 File**

Identifying information

BLA/STN#:	125104/33
Applicant:	Biogen Idec, Inc. (in collaboration with Elan Pharmaceuticals)
Biologic name:	natalizumab
Trade name:	TYSABRI
Submission date:	December 14, 2006
Stamp date:	December 15, 2006
PDUFA goal date:	January 14, 2008
Formulation:	300 mg natalizumab in 15 mL solution in sterile glass vial, for dilution in saline prior to infusion.
Proposed indication:	Induction and maintenance of clinical response and remission in moderately to severely active Crohn's disease.
Proposed regimen:	300 mg intravenous infusion every four weeks.
Recommended regulatory action:	Approval under 21 CFR 601, Subpart E (restricted distribution).

Introduction and Regulatory Background

This supplemental BLA is to expand the indication for Tysabri to include the treatment of Crohn's disease (CD). Tysabri is currently approved for use in multiple sclerosis (MS). Because Tysabri has a risk of progressive multifocal leukoencephalopathy (PML), it is only allowed to be marketed under a restricted distribution program to control the risk by ensuring it is used in the

appropriate patients and with adequate monitoring for the development of PML. This supplement would be the second indication for Tysabri.

Tysabri is a formulation of natalizumab, a recombinant humanized IgGκ monoclonal antibody that binds to the α4-subunit of α4β1 and α4β7 integrins, which are expressed on the surface of non-neutrophil leukocytes. The integrin receptors are VCAM-1 and MadCAM-1, expressed by vascular endothelium, the latter receptor being present on GI tract endothelium. Binding of natalizumab to integrins blocks their interaction with receptors and interferes with leukocyte migration into tissue.

Tysabri was originally approved for relapsing forms of MS on November 23, 2004, as an accelerated approval due its striking effectiveness after only one year. Within a few months of approval, two cases of PML occurred in MS patients taking Tysabri, and marketing was voluntarily suspended on February 28, 2005. An extensive investigation was undertaken of all patients who had taken Tysabri in clinical studies, and one additional case of PML was found in a Crohn's disease patient. Following a review of the safety data by FDA and an Advisory Committee in March 2006, Tysabri was reintroduced to the market under Subpart E in June 5, 2006, as monotherapy for relapsing forms of MS.

Under the currently approved labeling, Tysabri is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction to Tysabri. There is a boxed warning for the risk of PML. There are also warnings and precautions providing information about hypersensitivity, immunosuppression and infections, changes in laboratory tests (reversible increases in leukocytes and nucleated RBC's), immunizations (relating the lack of data on the effects of vaccination while receiving Tysabri), and the restricted distribution program. The pregnancy category is C. The most common adverse reactions in MS are headache, fatigue, arthralgia, UTI, extremity pain, abdominal discomfort, diarrhea, and rash. The safety and efficacy have not been established for pediatric patients with MS.

The recommended dosing for MS is 300 mg via intravenous infusion over about one hour, given every four weeks. The proposed dosing for CD is the same.

The Applicant had 12 reportable postmarketing commitments (PMC's) from the 2004 approval. The first two, including the commitment related to accelerated approval have been fulfilled. With the 2006 approval for reintroduction, the Applicant made a postmarketing commitment to conduct a registry study in MS (TYGRIS study), which is ongoing.

The Applicant of record is Biogen Idec, Inc., but the application represents collaboration between Biogen Idec and Elan Pharmaceuticals. Clinical studies of Tysabri in inflammatory bowel disease were conducted under Elan's IND 9,981, which was opened with a submission received 8/20/01. A pre-sBLA meeting was held on 7/26/06 with Elan Pharmaceuticals. At the meeting FDA indicated that the general submission plan appeared reasonable, but that filabilty and wording of the indication were issues that would be determined after the application was received. In response to questions about use of patient-reported outcomes, such as IBDQ and SF-36, in the labeling, FDA noted that the SEALD group would participate in the review, and the endpoints would be considered in accordance with the recently published draft guidance.

Elan was advised that the proposed labeling in the application would need to be in the new PLR format. FDA said the Elan's proposal to adapt the Tysabri RiskMAP to include Crohn's disease appeared reasonable, but that the Division would work with OSE to determine what elements might need further modification.

The sBLA submission was received on December 15, 2006. The application was granted standard review status because the Division did not feel adequate evidence has been presented to show that Tysabri filled an unmet need or to demonstrate superiority over existing therapy. The due date was therefore October 15, 2007. The supplement was presented to an Advisory Committee on July 31, 2007, to seek recommendations on approvability, patient selection, and the risk management plans. Late in September 2007 it was realized that clinical site inspections had not been initiated and would not be completed by the due date. Additional information about the risk management plan was received in October 2007; this was considered as a major amendment, moving the due date to January 14, 2008.

Tysabri was approved by the EMEA for MS on June 29, 2006, but Tysabri has not been approved for Crohn's disease in any foreign country.

The relevant primary review disciplines have all written review documents, which should be consulted for more specific details of the application. This memorandum summarizes selected information from these documents. The primary documents relied upon are the following:

Clinical Efficacy and Safety Review by A, Rajpal, dated 1/8/08
Statistical Review and Evaluation by L. Kammerman, dated 1/8/08
Clinical Pharmacology Review by A. Adebowale and C. Tornoe, dated 10/11/07.
DSI Clinical Inspection Summary by S. Samuels, dated 12/21/07.
OBP/DMA CMC review by B. Rellahan, dated 9/14/07.
SEALD Study Endpoint Review by A. Trentacosti, dated 6/6/07.
SEALD Labeling memo by I. Masucci, dated 12/13/07.
DDMAC labeling review by M. Brony, dated 1/14/08.
OSE/DMETS Labeling Review by J. Park, dated 4/4/07.
OSE/DDRE Serious liver injury memo by C. Flowers, dated 10/4/07.
OSE RiskMAP review by OSE Tysabri RiskMAP Review Team, dated 1/8/08
OB/DB VI consult on postmarketing study sample size by M. Levenson, dated 11/1/07
Transcript of joint meeting of the GI Drug Advisory Committee (GIDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) on July 31, 2007.

Clinical Background

Crohn's disease, also known as regional enteritis, terminal ileitis, or granulomatous colitis, is an inflammatory bowel disease of unknown etiology. The disease is manifest as discontinuous transmural inflammatory changes that can occur anywhere in the GI tract but it primarily involves small bowel or colon. Involved areas classically show noncaseating granulomas and fissuring. Complications include strictures, obstruction, malabsorption, malnutrition, and fistula formation. Growth retardation is a complication of concern in pediatric patients. There is an increased risk of malignancy with longstanding disease. Crohn's disease is more common in

whites vs. non-whites and in Jews vs. non-Jews. Peak ages of diagnosis are the teens to twenties, but it can occur at any age. Presentation much before the age of five or six years is uncommon. Pediatric Crohn's disease is infrequent enough to be eligible for an Orphan Drug Designation.

Approved therapies for Crohn's disease include formulations of oral and IV steroids. Commonly used, but unapproved, therapies are aminosalicylates, azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX). Use of any of the preceding has come to be considered part of "conventional therapy" for the disease. For the proposed indication of moderately to severely active Crohn's disease with inadequate response to conventional therapy, the only approved treatments in adults are Remicade (infliximab) and Humira (adalimumab); Remicade is also approved for Crohn's disease in children.

Chemistry, manufacturing, and controls issues

The reader is referred to the CMC review by B. Rellahan.

Tysabri is currently approved and marketed for the MS indication. This supplemental application did not involve any change in formulation or manufacturing, so there was no new CMC information.

The CMC reviewer did comment on the wording for the section of labeling dealing with the mechanism of action in Crohn's disease. In her review of the literature that was provided by the Applicant regarding the role of VCAM-1 in CD, she found the information contradictory and inconclusive. The Applicant's original proposed wording (b) (4) . The CMC reviewer recommended that the labeling could describe findings in animal studies, but that the labeling should state the role of VCAM-1 in CD is unclear.

Conclusions and Recommendations

The CMC reviewer recommended revision to the labeling in the section describing the mechanism of action in CD, as noted above.

Pre-clinical pharmacology and toxicology issues

Tysabri is currently approved and marketed for the MS indication. There were no new pharmacology and toxicology data in the application, and no new pre-clinical issues were raised during the review.

Clinical Pharmacology Issues

The reader is referred to the Clinical Pharmacology review by A. Adebowale and C. Tornoe.

Noncompartmental analyses in CD patients found steady-state values of 101 μg/mL for C_{max}, 10 μg/mL for trough concentration, mean $t_{1/2}$ of 10 days, mean V_d of 5.2 L and Mean CL of 22 mL/hr, which were fairly similar to values found in MS patients.

A population PK analysis in CD patients found a fall in CL by about 25% with repeated administration, antibodies occurred in about 10% of CD patients and increased CL by about 40%, which the reviewer felt could be an underestimate. The effects of weight, age, race, liver enzymes, bilirubin, and creatinine clearance were examined. Despite the finding of some statistically significant effects, the reviewers noted that the effects were minor. They concluded that the covariates had no clinically relevant effect on PK, suggesting that fixed dosing was appropriate.

Exposure-response analyses found an inverted U dose- and exposure-response relationship for clinical effect as measured by CDAI. No reason for this was identified. A trend toward higher incidence of herpes simplex infection with higher exposed was observed with the probability appearing to increase for natalizumab AUC_{ss} over 20 mg*hr/mL, but no correlation with natalizumab exposure was found for serious infections, UTI's, or serious AE's.

Conclusions and Recommendations

The Clinical Pharmacology reviewer recommended that the supplement was approvable from the Clinical Pharmacology standpoint, provided certain clarifying changes were made to the labeling as described in the Clinical Pharmacology Review. No Phase 4 commitment was recommended.

Clinical/Statistical Issues

The reader is referred to the Clinical Review by A. Rajpal and to the Statistical Review and Evaluation by L. Kammerman.

This supplement included reports of three Phase 3 controlled studies in CD, two for induction therapy and one for maintenance therapy. These three studies are discussed further below. The CD development program also included several Phase 2 clinical studies and pharmacokinetics studies. Those other studies are not covered in this review; see the Clinical Review and Clinical Pharmacology Review for additional information.

The CD development program was undertaken before the safety issue with PML was identified. Consequently, no special consideration was given to patient selection, concomitant medications, specialized monitoring, or other features of design that might be incorporated to manage the risk of developing PML. The joint GIDAC/DSaRM Advisory Committee made several recommendations regarding the appropriate population of CD patients for whom Tysabri should be indicated and the use on concomitant medications. One of the challenges in reviewing the clinical data was determining the applicability of the clinical data to support an indication that deviated from the indication for which the studies had been designed. The Clinical and Statistical Reviewers undertook several post hoc subset and secondary analyses to try to assess the sensitivity of results to eligibility criteria and concurrent medication use.

In the study descriptions below, "clinical response," which was the primary endpoint in all three studies, is defined as obtaining a reduction in Crohn's Disease Activity Index (CDAI) of ≥ 70 points compared to baseline. The secondary clinical endpoints included "clinical remission," defined as CDAI score < 150 points. Moderately to severely active disease was defined as CDAI ≥ 220 and ≤ 450 for purposes of eligibility criteria. "Conventional therapy" is used to mean treatment with 5-ASA drugs, antibiotics, oral steroids, azathioprine, 6-mercaptopurine, or methotrexate.

Induction Study 301 (ENACT-1)

This was a randomized, double-blind, placebo-controlled, multi-center, ten-week induction study in 905 adult Crohn's disease patients at 142 sites in 19 countries, mostly in North America and Europe. The objective was to evaluate the efficacy and safety of Tysabri as induction therapy.

To be eligible, patients had to be at least age 18 years of age and have moderately to severely active Crohn's disease. Reasons for exclusion included current TNF-α blocking therapy, active fistulae, short bowel syndrome, and unstable concomitant medications. See Clinical Review for details of eligibility criteria.

Patients were randomly assigned in a ratio of 4:1 to receive Tysabri 300 mg IV or placebo; randomization was stratified on baseline CDAI score and use of oral steroids. Treatment was administered as intravenous infusion at Weeks 0, 4 and 8. Concomitant medication could include conventional therapy (as described above) but was to remain stable during the study. TNF-α blocking agents were not allowed. Patients who completed the study could enroll in a placebo-controlled maintenance study (Study CD303, described below) providing they met that study's eligibility criteria. Otherwise they could participate in a safety follow-up to Week 32 or enter and open-label extension study identified as Study 351.

Patients were evaluated at Weeks 2, 4, 6, 8, 10, and 12 following the initial infusion. The primary endpoint was clinical response at Week 10, and the primary analysis was a comparison of Tysabri vs. placebo. Patients who received rescue medication or who had a missing CDAI score were considered not in response. Secondary endpoints included clinical remission, changes in inflammatory bowel disease questionnaire (IBDQ), and SF-36 questionnaire.

Of the 905 patients enrolled, the average age was 38 years, with 3% over 65. They were 58% female, and 94% were white. The mean duration of disease was 9.6 years. At baseline the mean CDAI score was 302, and 73% had elevated CRP (> 2.87 mg/L). At baseline 39% were taking steroids and 33% were taking immunosuppressants; 40% reported previous TNF-α blocker use.

The results found clinical response rates at Week 10 of 56.4% for Tysabri vs. 48.6% for placebo, for a difference in rates of 7.8% and yielding a p-value of 0.051. An exploratory subgroup analysis found that for those subjects with elevated baseline CRP the response rates were 57.6 for Tysabri vs. 44.8% for placebo, for a difference of 12.8% and a (nominal) p-value of 0.007. Principal results are shown in the table below:

Induction of Clinical Response in Study 301 (Original Results)

	TYSABRI % (n)	Placebo % (n)	Treatment Difference (95% CI)
All Subjects[1]	**56.4%** (721)	**48.6%** (181)	**8.0% (-0.6%, 17%)**
CRP Subgroups:			
CRP ≥ 2.87[2]	58% (526)	45% (134)	13% (3%, 23%)
CRP < 2.87	52% (169)	62% (39)	-9% (-29%, 11%)

[1] primary endpoint, p = 0.051
[2] post hoc analysis, p = 0.007

The Statistical Reviewer concluded that the study was suggestive of a treatment effect (p = 0.051), but that in the absence of a second study, the results could not stand on their own. The Statistical Reviewer noted that the analyses of secondary endpoints were not adjusted for multiplicity, and concluded they should be viewed as exploratory only. Additional subset analyses were performed by the reviewers and requested from the Application as discussed below under Supplemental Efficacy Analyses.

Because the DSI inspections let to the recommendation not to use data from the Manchester, CT site (see Clinical Site Inspections, below), the Statistical Reviewer did supplementary analysis with that site removed. She found that the Week 10 response rates were 56.2% for Tysabri vs. 48.6% for placebo, for a difference of 7.6% with a p-value using an CMH test of 0.0695; for the subgroup with elevated CRP at baseline, the rates were Tysabri 57.3% vs. 42.7% for placebo; for at difference of 14.6% and p=0.0124. The Applicant was also asked to recompute these analyses and provide revised samples sizes, response rates, treatment effects, and confidence intervals for the results to be presented in labeling. The Applicant's re-analysis obtained a p-value of 0.067 for the overall study, and a p-value of 0.010 for the elevated CRP subset.

Induction Study 307 (ENCORE)

This was a randomized, double-blind, placebo-controlled, twelve-week induction study in 509 adult Crohn's disease patients at 114 sites in 11 countries, mainly North America and Europe. The objective was to evaluate the efficacy and safety of Tysabri for induction in patients with elevated CRP at baseline.

To be eligible, patients had to be at least age 18 years of age and have moderately to severely active Crohn's disease and a baseline CRP > 2.87 mg/L. Reasons for exclusion included history current TNF-α blocking therapy, active fistulae, short bowel syndrome, and unstable concomitant medications. See Clinical Review for details of eligibility criteria.

Patients were randomly assigned with equal probability to receive Tysabri 300 mg IV or placebo; randomization was stratified on baseline CDAI score and use of oral steroids. Treatment was administered as intravenous infusion at Weeks 0, 4 and 8. Concomitant medication could include conventional therapy (as described above) but was to remain stable during the study. TNF-α blocking agents were not allowed. Patients who completed the study could have a follow-up assessment at Week 20 or enter an open-label extension study.

Patients were evaluated at Weeks 4, 8, and 12 following the initial infusion. The primary endpoint was defined as achieving clinical response at both Week 8 and Week 12, and the primary analysis was a comparison of Tysabri vs. placebo. Patients with missing data were considered not in remission. Secondary endpoints included clinical remission.

Of the 509 patients enrolled, the average age was 38 years, with 2% over 65. They were 59% female, and 95% were white. The mean duration of disease was 10.1 years. At baseline the mean CDAI score was 302. Despite the study design, only 94% of patients had elevated CRP at baseline, due to some variation between screening and baseline values. At baseline, 40% were taking steroids and 38% were taking immunosuppressants; 48% reported previous TNF-α blocker use.

The study succeeded on the primary analysis: 47.9% of Tysabri-treated patients had clinical response at both Week 8 and Week 12, vs. 32.4% for placebo, for a difference of 15.5% and a p-value < 0.001. The key efficacy results are shown in the following table:

Induction of Clinical Response and Remission in Study 307 (Original Results)

	TYSABRI n=259	**Placebo n=250**	**Treatment Difference (95% CI)**
Clinical Response at:			
Week 8	56%	40%	16% (8%, 26%)
Week 12	60%	44%	16% (7%, 25%)
Both Weeks 8 & 12[1]	**48%**	**32%**	**16% (7%, 24%)**
Clinical Remission at:			
Week 8	32%	21%	11% (3%, 19%)
Week 12	37%	25%	12% (4%, 21%)
Both Weeks 8 & 12[2]	26%	16%	10% (3%, 18%)

[1] primary endpoint, p <0.001
[2] p <0.002

The Statistical Reviewer concluded that the results of this study confirmed the results of a treatment effect in the elevated CRP subgroup seen in Study 301. The Statistical reviewer noted that the difference in response rates was considerably larger in Europe (23%) compared to the difference seen in North American sites (10%). She requested additional exploratory analysis from the Applicant, but they did not identify a possible explanation for the differences. The Statistical Reviewer noted that the analyses of secondary endpoints were not adjusted for multiplicity, and concluded they should be viewed as exploratory only. Additional subset analyses were performed by the reviewers and requested from the Applicant as discussed below under Supplemental Efficacy Analyses.

Maintenance Study 303

This was a continuation study for selected patients who participated in Study 301 (see above). It was a randomized, double-blind, placebo-controlled, twelve-month maintenance study of 428

Crohn's disease from 123 of the 142 sites that has participated in Study 301. The object was to evaluate the efficacy and safety of Tysabri in maintenance of clinical response.

To be eligible, patients had to have participated in Study 301 and had a clinical response at Week 10 and at Week 12, regardless of assigned treatment. In addition, patients were required to have only mildly active disease, with CDAI < 220, following the response (patients with severely active disease could have a 70-point decrease and still have CDAI ≥ 220).

Patients were randomized with equal probability to receive Tysabri 300 mg IV or placebo every month for an additional twelve months. Randomization was stratified by steroid use at entry into Study 301, immunosuppressant use at entry into Study 301, and CDAI score at Week 12 of Study 301 (i.e., at entry into Study 303).

The initial maintenance dose was timed to coincide with Week 12 of Study 301, which was designated as "Month 3" for tracking in Study 303, so that study month corresponded to time since beginning induction therapy rather than beginning of maintenance therapy. Thus, a patient participating in both Study 301 and 303 would receive essentially monthly dosing for 15 months, from Week 0 in Study 301 through Month 14 in Study 303. To preserve the integrity of the blind in the ongoing induction Study 301, patients were entered into the maintenance Study 303 without unblinding, and therefore regardless of the treatment assignment during induction, although the main objective of the maintenance study was to evaluate the results for patients who had been induced with Tysabri.

Concomitant medication could be continued, but was to be kept stable. However, patients who were on steroids at Week 10 of Study 301 were to continue the steroid taper per protocol into Study 303.

Assessments were done monthly through Month 15. The primary endpoint was clinical response. Patients who required rescue mediation or with missing data were considered not to be in response. The primary analysis was to be the comparison of the proportions of patients who remained in clinical response at every visit through Month 9 for Tysabri vs. placebo in the subgroup of patients who received Tysabri for induction. The protocol specified that clinical remission through Month 9 would be a contingent secondary analysis conducted on the subset in remission at the conclusion of induction Study 301.

Of the 428 patients enrolled, the mean age was 38 years, with 3% over age 65. There were 60% female and 94% white. The mean duration of disease was 9.6 years. The mean CDAI prior to induction was 297, but 70% had a score < 150 at entry into Study 303. Prior to induction, 75% had had elevated CRP, and at entry into Study 303, 63% had elevated CRP. A total of 36% of patients had used a TNF-α blocking agent previously. During the study, 38% used concomitant immunosuppressants, and 40% used steroids; 1% used TNF blocking agents despite that being a protocol violation.

Of the 339 patient who had responded to Tysabri and entered Study 303, 61.3% of patients treated with Tysabri were able to maintain clinical response at each visit through Month 9, vs. 28.2% for those maintained with placebo, for a difference of 33.1%, with a p-value < 0.001 for

the primary analysis. There was also a clinically and statistically significant difference in the rates of maintaining clinical remission through Month 9. For each endpoint, similar or larger treatment differences were also seen through Month 15. These results are shown in the table below:

Maintenance of Clinical Response and Remission in Study 303

	TYSABRI	Placebo	Treatment Difference (95% CI)
	n=168	**n=170**	
Clinical Response through:			
Month 9[1]	**61%**	**28%**	**33% (22%, 44%)**
Month 15	54%	20%	34% (23%, 44%)
	n=130	**n=120**	
Clinical Remission through:			
Month 9[2]	44%	26%	18% (6%, 30%)
Month 15	39%	15%	24% (13%, 36%)

[1] primary endpoint, $p < 0.001$
[2] $p = 0.003$

The disqualification of the data from the Manchester, CT site, also affected this study. Re-analyses were requested of the sponsor to provide revised samples sizes, response and remission rates, treatments differences, confidence intervals, and p-values for the table in the labeling. The changes in rates were minor (1% or less), and the p-values for the Month 9 comparisons shown in the table above remained statistically significant, with both p-values < 0.005. The Statistical Reviewer also did supplementary sensitivity analysis with that site removed.

The Clinical and Statistical reviewers considered the study to demonstrate superiority of Tysabri over placebo for maintenance of both clinical response and remission in patients that had responded to Tysabri induction. The Statistical Reviewer noted, however, that essentially no effect of Tysabri was seen in those patients who had achieved a clinical response after being treated with placebo in the induction Study 301.

The Statistical Reviewer raised concerns about the analysis of the secondary endpoints of steroid tapering (see Statistical Review for details). She noted several aspects of that analysis, namely, 1) the analysis selected patients based on their steroid use at entry into the induction Study 301, rather than at time of randomization into Study 303, 2) steroid taper was started at Week 10 of Study 301, which was two weeks before randomization into Study 303, 3) Study 303 enrolled only a subset of Tysabri responders from Study 301, and that did not include all the patients who started tapering steroids, 4) ability to taper steroids was highly correlated with response, 5) some patients restarted steroids after they had met criteria of being counted as discontinued, 6) there was no adjustment for multiplicity of endpoints, and 7) ability to taper steroids was only demonstrated in one study. She concluded that the evidence supporting a claim of reducing the need for oral steroids did not appear persuasive.

The Applicant also provided analyses and proposed labeling claims concerning the effect of Tysabri therapy on the patient-reported outcomes of IBDQ and SF-36. The SEALD review team

recommended against allowing labeling claims for these endpoints regardless of study results because of deficiencies in these endpoints (see the SEALD consultative review by A. Trentacosti).

Supplemental Efficacy Analyses

Due to the design of the clinical studies (before PML emerged), they did not incorporate elements that might be used to try to increase the benefit to risk ratio, such as more restrictive patient selection criteria or restrictions on concomitant medications. At FDA's request the Applicant performed additional subset analyses in an attempt to explore the issue. One approach was to try to identify subsets that might appear to have a greater response to treatment, thereby possibly improving the acceptability of a risk of PML. The strategy was to attempt to identify subgroups with apparently more severe disease, who would be in greater need of an effective therapy and who might show greater separation from placebo. These analyses included grouping by baseline CDAI score, by baseline CRP, by prior therapy (on the theory that prior use of immunosuppressants or TNF blockers would reflect a more severe disease course), and by inadequate response to various prior therapies (while recognizing that the documentation of that classification was usually not rigorous). The supplemental analyses also looked as treatment effects in subgroups defined by concurrent medication use of steroids or immunosuppressants to try to estimate whether effectiveness would be impacted if restrictions were placed on the types of concomitant medication allowed. Such restrictions might theoretically reduce PML risk by limiting the degree of immunologic intervention. (Unlike the situation in MS, where one of the studies evaluated Tysabri as monotherapy, none of the CD trials evaluated use of Tysabri in a regimen in which steroids or immunosuppressants were not allowed.)

The results of most of these analyses were presented at the Advisory Committee and are described in the Clinical Review and Statistical Review. In general, no clear pattern was identified regarding the effectiveness of Tysabri in any of these subgroups. Allowing for the increased variability resulting from the reduced sample size in subgroups, disease severity (as approximated by the means describe above) did not exhibit any reliable relationship to treatment effect that would help to confidently define a subgroup in which Tysabri would be expected to be especially beneficial. On the other hand analysis by concomitant medication use suggested that one could expect the treatment effect of Tysabri to be reasonably well preserved even if use of concomitant medications were restricted.

From other subgroups analyses, the Statistical Reviewer concluded that analysis of efficacy by gender did not suggest a differential effect. The numbers of subject in subgroups of race and age were deemed insufficient for meaningful analyses.

Clinical Site Inspections

The clinical sites in Atlanta, GA (Dr. Wolf), Manchester, CT (Dr. Breiter), Vancouver, Canada (Dr. Enns), and Aarhus, Denmark (Dr. Dahlerup) were inspected. The Atlanta site participated in study CD307; the other three participated in both Study CD301 and Study CD303. At the sites in Manchester, CT, inspections found some protocol violations, errors in informed consent, and lack of source documentation for certain CDAI assessments. The DSI Reviewer recommended that the efficacy data from that site be excluded in the data analysis. The DSI

Reviewer concluded that the data appeared acceptable from the other three sites. (See Clinical Inspection Summary of S. Samuels for details.)

Safety

The reader is referred to the Clinical Review for full details of the safety analysis. As of the cutoff for the supplement's safety review, a total of 1,639 patients with Crohn's disease received Tysabri, with a total of 1,897 person-years exposure. In combination with the completed MS program, this made 3,960 individuals with 3,805 person-years of exposure. In the CD program, 599 patients were exposed for at least one year, and 250 for at least two years. Postmarketing experience is estimated at about 7,000 patients, but exposures in postmarketing experience have relatively been short, due to the brief initial marketing and the slowness of the re-introduction. Most of the safety data from the CD program were previously available and were already reviewed as part of the latest MS re-introduction approval.

Clinical Study Safety Findings

There were 14 deaths in Tysabri-treated patients in the combined development programs (MS, CD, and RA). In controlled studies of CD there were 2 deaths with Tysabri vs. 0 for placebo, while in the MS controlled studies the mortality rate was lower for Tysabri than for placebo. Given the small numbers of events, neither difference is conclusive. Of particular note among the deaths were the two fatal cases of PML, two opportunistic infections (PCP pneumonia and aspergillis pneumonia, both on a background of multi-organ system failure), and a case of metastatic melanoma.

In the short-term controlled CD trials, 15% of the 1182 patients had SAE's. As it typical of CD trials, most of these were related to the GI tract. The rate of serious infections was 2.4% in both Tysabri and placebo groups. The Clinical Reviewer reported on some noteworthy serious infections in Tysabri-treated patients: two patients hospitalized for viral meningitis that ultimately resolved, and a patient with CMV colitis. An analysis by concomitant mediation subgroups found a higher rate of SAE's in patients using concomitant immunosuppressants; the Clinical Reviewer speculated that the finding could be a reflection of the disease severity in that subgroup. The rate of any infection (serious or non-serious) was only slightly higher in the Tysabri group vs. placebo in short-term controlled studies (40% vs. 36%). The common (>10%) AE's in CD studies were headache, upper respiratory tract infection, nausea, and fatigue.

In those tested for antibodies to natalizumab, the positivity rate was about 10%. In the two induction studies, the rate was highest (12% to 13%) for patients on Tysabri only, lowest (2% to 5%) for those on concomitant immunosuppressants, and intermediate for those on concomitant steroids. Patients who were positive for antibodies had a higher rate of hypersensitivity reactions; in CD induction studies the rate was 3.5%. The rate of anaphylactic reactions in patients with antibodies was less than 0.1% in CD short-term studies (compared to 0.4% in MS studies). No cases of anaphylaxis were seen in antibody-negative patients (but not all cases were tested for antibodies). The rates of clinical response in both induction studies appeared to be lower in patients who developed antibodies.

Postmarketing Safety Findings

Postmarketing data were also carefully reviewed for the Tysabri re-introduction approval in June 2006, at which time Tysabri had been off the market for over one year. Re-introduction of the product was slow initially, and there were not substantially more postmarketing data available for review for the current supplement.

Ten deaths were reported from postmarketing experience, which is estimated to derive from about 7,000 patients. Three were from infections: Herpes encephalitis after one dose of Tysabri, UTI, and GI infection with sepsis and pneumonia in an MS patient. There was one fatal case of ovarian cancer diagnosed after one month of Tysabri, a suicide, a case of progression of pre-existing ALS, and a case of progression of pre-existing paralysis. Causes of death in the remaining three cases were unclear.

There were 30 cases of serious infections. Most of these were pneumonias due to typical organisms. Of note was a second, but nonfatal, case of herpes encephalitis.

Shortly before the July Advisory Committee, the FDA became aware of postmarketing reports of several cases of liver injury in patients given Tysabri. In some cases, a positive dechallenge-rechallenge experience suggested a causal relationship. A preliminary report of this issue was presented to the Advisory Committee. Additional data were obtained subsequently, and DDRE completed a review of the cases. Several of the patients had undergone extensive evaluation without any other cause of liver injury being identified. The review team felt it was reasonable to conclude there was a causal relationship, and recommended that a new section be added to warnings and precautions to describe the potential for liver injury (see the OSE/DDRE liver injury memo of C. Flowers for additional information).

Conclusions and Recommendations

The Clinical and Statistical reviewers concluded that Studies 301 and 307, taken together, showed superiority over placebo of Tysabri for efficacy in inducing clinical response. The reviewers also concluded that Study 303 showed superiority of Tysabri over placebo for maintenance of clinical response. The Statistical reviewer concluded the finding of efficacy in reducing steroids should be considered only exploratory.

The Clinical reviewer felt that the major safety findings from the clinical studies were reasonably consistent with the safety information currently in the Tysabri labeling, but he provided a revised separate table of common adverse events for CD patients. The DDRE review team in collaboration with the DNP safety reviewers recommend a new warning be added regarding the risk of liver injury.

Consults

The Division of Neurology Products (DNP) is the "home" division for Tysabri because MS was the initially approved indication. DNP did not generate a formal consult, but they participated actively in the review of the reformatting of the labeling in the PLR format and also advised this Division during labeling negotiations with the Applicant and on issues relating to screening

patients and monitoring for PML. They also worked in conjunction with OSE to provide the wording for a new warning in the labeling regarding hepatotoxicity.

The SEALD team identified several deficiencies with the use of the IBDQ and SF-36, and recommended that results from those instruments not be presented in the labeling (see Study Endpoint Review by A. Trentacosti).

Advisory Activities

This supplemental application was presented to a joint meeting of the GI Drug Advisory Committee (GIDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) on July 31, 2007. See the transcript of that meeting for details. The Division asked the committee for input on the questions regarding the adequacy of the data to support approval, the appropriate CD population for whom Tysabri should be indicated, the concomitant therapy to be permitted, how steroids should be used in a patient taking Tysabri, the important risks to be considered, the requirements for initial patient evaluation and monitoring, recommendations regarding a restricted distribution program, and what additional information might be needed for approval.

The Committee favored approval, but subject to the restrictions that it should only be for patients who had failed other therapies and that it should be subject to a restricted distribution plan like that in effect for MS. They felt that Tysabri should not be used in conjunction with other immunosuppressant drugs; that steroids should be tapered; that treatment should be stopped if Tysabri did not appear to be producing a response or if steroids could not be tapered. The neurologist on the committee recommended a complete neurological evaluation be conducted before treatment was started. The Committee did not feel there was a need to require screening for JCV or monitoring for JCV due the lack of any clear predictive value of JCV test results. The Committee endorsed the idea of collecting additional safety date in a postmarketing safety study.

Risk Management

The reader is referred to the OSE review by OSE Tysabri RiskMAP Review Team, of the TOUCH restricted distribution program and the postmarking registry study proposals.

The applicant agreed to incorporate most of the Advisory Committee's recommendations (see above) in the Tysabri labeling for Crohn's disease. Following discussions with the Applicant and consultation with the Division of Neurology Products, it was agreed that, given the extensive monitoring integrated into the TOUCH distribution program, a baseline comprehensive neurological examination would not be a requirement, however, a baseline MRI would be suggested.

The TOUCH program was modified for the Crohn's disease indication by creating the CD-TOUCH component of the program, which has essentially the same features as the current TOUCH program for MS, but adds elements to enforce use in accordance with the CD-specific

sections of the labeling, namely, it collects information and sets up criteria to ensure patients would be continued past three months only if they were receiving a benefit from Tysabri, to ensure steroids would be tapered by six months after starting Tysabri, and to ensure patients would not be using immunosuppressants or extended courses of steroids (greater than three months per year). Apart from the CD supplement, the sponsor has been pursuing with DNP a revision to the TOUCH program to put some parts of the program online rather than relying entirely on paper forms. Following extended negotiations and revisions to the Applicants' proposals for both the CD-TOUCH and the online version, the OSE reviewers accepted the Applicant's revised TOUCH program proposal that incorporates the CD-TOUCH component as well as online features, as reflected in the January 7, 2008, submission (seq. no. 198).

The Applicant is currently conducting a registry study in MS patients, the TYGRIS study. The Applicant proposed conducting a registry for CD patients using Tysabri, but projected that use for CD would be less than for MS and anticipated more difficulty in enrolling a registry study. After negotiations with the OSE review team, the Applicant agreed to conduct the TYGRIS-CD study, a five-year registry study enrolling at least 2,000 CD patients with at least 1,000 patients followed for (b) (4) Among other information, the study will collect data on clinically significant infections and some information on clinical effectiveness outcomes. The OSE reviewers accepted the TYGRIS-CD postmarketing commitment proposal contained in the January 9, 2008, submission (seq. no. 202).

Pediatrics

This supplement included results of two open-label studies in adolescents (11 to 17), in particular, CD305, a safety and PK study with 36 adolescent patients with active disease, and CD352, an open-label study in 26 adolescents with chronic disease. The studies were viewed as insufficient to support labeling for use in pediatric Crohn's disease.

The Applicant requested a waiver for children five years and under due to the low incidence of Crohn's disease in children in that age range. They also requested a deferral for children aged six to 17 years because they do not feel studies in the pediatric population are appropriate until the safety of natalizumab is better understood. The Clinical Reviewer recommended that the Applicant be granted the requested waiver and deferral, but requested that the Applicant provide a more specific plan as to when a determination of the advisability of pediatric studies would be made, and when the studies would be conducted if it was decided they should be done. A more detailed plan was provided by the Applicant in a letter submitted 1/8/08 (seq. no. 199). The Applicant proposed first to collect additional safety data and assess the appropriateness of doing pediatric studies by 6/30/12. If pediatric studies are appropriate, the Applicant will first conduct a placebo-controlled, dose-ranging study of efficacy, safety, and pharmacokinetics in adolescents (12 to 17 years), to be submitted by 9/30/14, followed by an open-label, single-arm response, safety, and pharmacokinetic study in patients 6 to 11 years, to be submitted by 6/30/17.

The waiver and deferral request along with the pediatric plan were presented to the Pediatric Research Committee (PeRC) on January 11, 2008, and the committee found them acceptable.

Regulatory Conclusions

The data in this supplemental application support approval of Tysabri under 21 CFR 601 for Crohn's disease in adult patients at a dosage regimen of 300 mg every four weeks, and with the indication as stated in the labeling negotiated with the Applicant (see also comments on labeling below). The approval should be under the restricted distribution regulations in Subpart E (21 CFR 601.42), as requested by the Applicant in the submission of January 8, 2007 (seq. no. 200).

Evidence of Efficacy

Although Study 301 did not succeed on its formal primary endpoint analysis ($p = 0.067$ after eliminating a disqualified site), Study 307 provided statistically persuasive evidence of efficacy (one study with $p < 0.001$ provides similar statistical strength of evidence as two studies with $p < 0.05$ [both two-sided]), with evidence bolstered clinically by consistency with the effect size found in the *post hoc* analysis of Study 301 (with nominal p-value of 0.01). The two induction studies, Study 301 and Study 307, are two well-controlled studies that, considered in the entirety of data in the supplemental application, together provide substantial evidence of the efficacy of Tysabri in inducting clinical remission in patients with moderately to severely active Crohn's disease and who have elevated CRP. The observed effect sizes of 13% more patients in clinical response in Study 301 and 16% more patients in Study 307, while not dramatic, are sufficient to be considered clinically significant.

Given the substantial evidence of efficacy for induction, and given the clinically significant and statistically persuasive findings from the relatively large multicenter maintenance study, Study 303, there is also substantial evidence that Tysabri has efficacy as therapy for maintaining response and remission in Crohn's disease following induction with Tysabri.

Tysabri did not show dramatically better effectiveness compared to approved therapy for Crohn's disease they way it did for MS. The effect in CD appears to be roughly on par with what has been seen in clinical studies of the TNF blockers (infliximab and adalimumab) approved for CD. Nonetheless, a substantial fraction of CD patients with moderate to severe disease fail to obtain a clinical response from TNF blockers, some patients who respond to TNF blockers develop intolerance, and TNF blockers have serious risks of their own. There is still a place for additional therapeutic options in moderate to severe CD, particularly options that may offer a different putative mechanism of action, even if they carry significant risks.

Indication

The Application initially proposed (b) (4)

Analyses of efficacy were performed for subsets defined by disease severity, prior therapy failures, and concomitant therapy. These analyses provided reasonable assurance that Tysabri can be considered effective despite restricting the indication to a population more limited that that initially studied and despite restricting concomitant medication by precluding the use of

immunosuppressant drugs in conjunction with Tysabri. The findings were included in the presentations to the Advisory Committee in July 2007. The Advisory Committee recommended restricting use of Tysabri to patients that had failed other options, who showed a response to induction, and who were not taking concurrent immunosuppressants. They also recommended that Tysabri be discontinued if steroids could not be tapered. Because the principal evidence of efficacy in induction came from the study that required patients to have an elevated CRP, that restriction should be reflected as a limitation of the indication. Following the suggestion of the Advisory Committee, the target populations should be characterized as those with "evidence of inflammation" rather than referring to a specific laboratory test.

Following the Advisory Committee the Applicant revised the proposed indication, and after discussions with the Division, agreed to propose the following indication:

> TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α.

The dosing regimen in Crohn's disease in adult patients should be 300 mg every four weeks, as used in the clinical studies. Following the Advisory Committee's recommendations, concomitant immunosuppressants of TNF blockers should not be allowed, Tysabri should be stopped if a benefit is not obtained within three months, and Tysabri should be stopped if patients who are taking steroids when Tysabri is started cannot taper off steroids within six months. The Applicant has agreed to these provisions.

Labeling Recommendations

The labeling should include the indication for use and recommended dosing as discussed above. The Clinical Studies section of the labeling should present results from the two induction studies (Study 301 and 307), although the results of the Study 301 should be given less prominence. Major endpoint results of the maintenance Study (Study 303) should also be presented.

The primary endpoint of clinical response should be reported for the studies. It would also be reasonable the present the clinical remission rates to give some sense of the spectrum of clinical effect of treatment. For the results of maintenance Study 303, the Applicant's proposed claim of a (b) (4) should not be included (see discussion immediately below). However, because the labeling dosing recommendations state that patients should be tapered off of steroids within six months of starting Tysabri, the labeling should include some information about the rate of successful tapering in the Tysabri arm to provide the practitioner with some idea of the results to be expected when following that recommendation.

The Statistical Reviewer recommend against allowing a labeling claim for (b) (4) This reviewer does not consider the coincidence of clinical response and successful steroid tapering to be an observation that would necessarily detract from that claim. However, the Statistical Reviewer raised several additional concerns about the evidence of a (b) (4). Apart

from presenting the steroid taper rates mentioned above, the labeling (b) (4) .

In light of the deficiencies identified by the SEALD consult regarding the use of the IBDQ and SF-36 endpoints in Crohn's disease, the results for these endpoints should not be permitted as labeling claims.

Because of the cases of liver injury reported in postmarketing experience, a new Hepatotoxicity Warning/Precaution should be added to the labeling to describe that risk.

Changes should be made to the CLINICAL PHARMACOLOGY-Pharmacokinetics section as recommended by the Clinical Pharmacology reviewer.

A Medication Guide is required for the Crohn's disease indication for the same reasons it is needed for MS. The Medication Guide should be revised to be applicable to Crohn's' disease as well as MS. The Medication Guide should also be modified to provide information about the risk of hepatotoxicity as reflected in the new Warning/Precaution.

The labeling should be brought into conformance with the PLR requirements and other standard requirements as reflected in labeling review by I. Masucci and the DMETS review by J. Park, with minor exceptions as agreed to by the Division and DNP and reflected in the final labeling.

The labeling revisions the Applicant agreed to in labeling discussions as of January 11, 2007, represent a sufficient response to the above recommendations and are acceptable.

Risk Management Plan

The approval of Tysabri for Crohn's disease should be subject to a restricted distribution program (21 CFR 601.42, under Subpart E) similar to that for MS. The Applicant's proposed modification of the TOUCH program to included CD, as described in the submission dated 1/7/08 (seq. no. 198), is acceptable.

The approval should be subject to a postmarketing commitment to conduct a registry study in Crohn's disease (TYGRIS-CD) to collect additional safety data. The Applicant's proposal to conduct a five-year follow-up study in at least 2,000 Crohn's disease patients, as reflected in the commitment made in the submission dated 1/9/08 (seq. no. 202), is acceptable.

Pediatrics

The requirement to study pediatric Crohn's' disease patients aged five years and younger may be waved because of the small number of Crohn's disease patients in that age range. Because the adult indication is ready for approval, it is acceptable to defer pediatric studies. Further, given the serious safety concerns about Tysabri, it is reasonable to allow a delay in the pediatric program until additional safety date have been collected so that a better assessment can be made about the appropriateness of pediatric studies. The Applicant's requests for partial waiver and deferral should be granted, and the proposed pediatric plan in the submission of 1/8/08 (seq. no. 199) provides an acceptable basis for defining pediatric postmarketing commitments.

New Phase 4 Commitments

The Applicant committed to conduct a registry study to obtain five years of follow up in at least 2,000 adult patients with Crohn's disease as described above. This study should be formalized as a Phase 4 commitment in the approval letter.

The approval letter should contain formal Phase 4 commitments based on the Applicant's pediatric plan to 1) collect additional safety data and assess appropriateness of pediatric studies; 2) conduct an efficacy, safety, and PK study in patients of ages 12 to 17; and 3) conduct a response, safety and PK study in patients of ages 6 to 11 years.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125104/33

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA	STN 125104/33	**Submission Date(s)**	December 15th, 2006
Brand Name		Tysabri	
Generic Name		Natalizumab	
Reviewer		Abimbola Adebowale, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
Pharmacometrics Reviewer		Christoffer Tornoe, Ph.D.	
Pharmacometrics Team Leader		Joga Gobburu, Ph.D.	
OCP Division		Division of Clinical Pharmacology 3	
OND Division		Division of Gastroenterology Drug Products	
Sponsor		Biogen Idec, MA 02142	
Submission Type; Code		Supplemental BLA	Standard
Formulation; Strength(s)		Sterile liquid for intravenous infusion, containing 300 mg natalizumab drug substance	
Indication		Treatment of Crohn's Disease	

Table of Contents

1 Executive Summary

This sBLA was submitted by Biogen Idec for the additional indication of inducing and maintaining clinical response and remission in adult patients with moderately to severely

active Crohn's disease (CD). Tysabri® (natalizumab) is currently marketed for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

1.1 Recommendations

The clinical pharmacology and biopharmaceutics information included in this submission is acceptable provided that a satisfactory agreement is reached between the sponsor and the Agency regarding the language to be included in the package insert.

Signatures:

10th October, 2007

Abimbola Adebowale, Ph.D., Senior Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3, Office of Clinical Pharmacology

10/11/2007

Sue-Chih Lee, Ph.D., Team Leader, Division of Clinical Pharmacology 3, Office of Clinical Pharmacology

10th October, 2007

Christoffer Tornoe, Ph.D., Pharmacometrics Reviewer, Office of Clinical Pharmacology

10/10/07

Joga Gobburu, Ph.D., PharmacometricsTeam Leader, Office of Clinical Pharmacology

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings and Biopharmaceutics Findings

Regulatory History:

Natalizumab has been co-developed by Elan Pharmaceuticals, Inc. and Biogen-Idec, Inc. for the treatment of relapsing multiple sclerosis (MS) and moderate to severe Crohn's disease (CD). Tysabri® (natalizumab) was initially approved in the U.S. on November 23, 2004 for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Based on two reports of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab, marketing of Tysabri® was voluntarily suspended on February 28, 2005. A third case of PML was subsequently identified retrospectively in a deceased CD patient based on a review of available safety data.

Elan and Biogen Idec conducted a comprehensive safety evaluation of all clinical patients treated with natalizumab for MS, CD, or rheumatoid arthritis. There were no additional cases identified as a result of the safety evaluation. The data from this evaluation formed the basis for the sBLA submitted in September 2005 for the MS indication. Review of this information by the Food and Drug Administration and the Peripheral and Central

Nervous System Advisory Committee subsequently resulted in the sBLA being approved on June 5, 2006 and the re-introduction of Tysabri® to the market for treatment of MS.

Nomenclature:

The trade name for natalizumab (a recombinant humanized anti-α4 integrin monoclonal antibody) is Tysabri®, although originally the name Antegren® was used. Natalizumab also has been referred to as AN100226. Throughout this document, the drug substance will always be referred to as natalizumab, but the other terms are used in the original clinical study reports.

Overview of Clinical Pharmacology and Biopharmaceutics:

Clinical pharmacology and biopharmaceutics findings from 3 studies conducted in healthy volunteers (HV), and 11 studies in Crohn's disease (CD) patients were included in this submission. Doses of natalizumab ranging from 0.03 - 6.0 mg/kg (including a 300 mg fixed dose; approximately 4.3 mg/kg based on a total body weight of 70 kg) were administered in these studies. Natalizumab is intended to be given by intravenous (IV) administration over 60-minutes, however some of the early clinical trials used a 30- to 45- minute infusion period. The pharmacokinetic assessments included intense and/or sparse blood sampling for the analysis of serum natalizumab concentrations.

The pharmacokinetics of natalizumab following intense blood sampling was evaluated in a subset of patients in Study CD301 (CD patients) and Study CD306 (CD patients concurrently receiving infliximab). Natalizumab was administered in both studies as a 300 mg fixed dose, 60-minute IV infusion every 4 weeks for a total of 3 doses at Weeks 0, 4 and 8. In addition, results from a population pharmacokinetics analysis of serum natalizumab concentration-time data (including both intense and sparse blood sampling) obtained from five Phase 2 (Study #'s CD202, CD251, CD305, CD306, CD352) and three Phase 3 studies (CD301, CD303, and CD351) in patients with Crohn's disease were also included in this submission.

Immunogenicity was determined in all 11 studies conducted in CD patients and 2 studies in healthy subjects. However, the effects of anti-natalizumab antibody on natalizumab PK was evaluated in the population PK analysis as well as individual clinical studies involving healthy volunteers (C-1805 and C-1806) and CD patients (CD251, CD301, CD303, CD305, and CD306).

Pharmacokinetics

Non-Compartmental Analysis:

Following single (first) and repeat (third) dosing of 300 mg of natalizumab to CD patients (N=19) in study CD301, the mean maximum observed serum concentrations (Cmax) were 102.2 ± 30.7 and 101.2 ± 33.5 mcg/mL for the first and third doses, respectively. The Cmax was observed at approximately 1-3 hours after the start of drug infusion, followed by a somewhat rapid drop within the first 24 hours after infusion, with a slower decline thereafter over the 4 week dosing interval. The mean "trough" serum concentration was 5.2±6.3 and 8.4±8.6 mcg/mL four weeks following the first and third doses, respectively. The mean half-life, volume of distribution, and clearance (CL) of natalizumab following the third dose were 231.1 ± 172.8 hrs (= 9.6 ± 7.2 days), 5.2 ± 2.8

L and 21.9 ± 21.7 ml/hr, respectively. In Study CD306, patients received concurrent infliximab 5.0 mg/kg every 8 weeks (including one dose each at Week -2 and Week 6). PK parameters for natalizumab were generally comparable to those observed in Study CD301.

The results of the dose-ranging study CD202 indicated that natalizumab's systemic exposure was approximately dose proportional over the dose range of 3.0–6.0 mg/kg. Inter-subject variability for Cmax and AUC typically ranged from 30–60% for a 300 mg fixed monthly natalizumab dose.

Population PK Analyses:
The findings of the population PK in CD patients (N = ***1156***) from 3 phase II studies (two studies # 305 and # 352conducted in the adolescent population were excluded) and 3 phase III studies were similar to those obtained for MS patients, i.e.

- In both patient populations, an (unexplained) time dependency of CL was found to reduce CL by 25% with repeated administration.
- Anti-natalizumab antibodies occurring in approximately 10% of the patients were found to increase CL by approximately 40%. This is likely to be an underestimate of the true effect due to many antibody positive subjects having PK trough samples below LOQ.
- Body weight, age, race (categorized as black vs. other races) ALT, AST, bilirubin, and creatinine clearance had no clinically relevant influence on the PK of natalizumab suggesting that a fixed dosing regimen is appropriate.

The studies conducted in healthy volunteers (HV101 (dose escalation), C-1805 and C-1806 (bioequivalence studies) were already reviewed and found to be acceptable with the Multiple Sclerosis NDA application and therefore were not reviewed again with this submission.

Exposure-Response

Efficacy: Exposure-response relationships for efficacy was evaluated in a dose-finding study CD 202, where CD patients received two IV doses (placebo+placebo; 3+0 mg/kg; 3+3 mg/kg; or 6+6 mg/kg) separated by 4 weeks. The results of this study indicated that the probability of a clinical response defined as a decrease in Crohn's Disease Activity Index (CDAI) score of more than 70 points was found to be correlated with natalizumab exposure (AUC_τ). However, an inverse U-shaped dose- and exposure-response relationship was observed, with the highest dose group of 6 mg/kg every 4 weeks having a lower response rate compared to the 3 mg/kg every 4 weeks. The reason for observing an inverse U-shaped relationship for natalizumab was not identified.

Safety: The relationship between natalizumab exposure and serious infections, serious adverse events, urinary infections, and herpes simplex was investigated. However, only a trend towards higher incidents of herpes simplex with higher exposure was observed. Serious infections (other than PML), urinary infections, serious adverse events were not found to be correlated with natalizumab exposure.

Immunogenicity: Generally, the presence of anti-natalizumab antibodies (particularly in persistent[1] antibody–positive subjects) was observed to be associated with reduced serum natalizumab concentrations in the individual studies. In the population PK analysis, the presence of anti-natalizumab antibodies occurring in approximately 10 % of the CD patients was found to increase CL by approximately 40 %.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The active drug substance in Tysabri® is natalizumab. Natalizumab is a recombinant humanized IgG_4 isotype monoclonal antibody (mAb) produced in murine myeloma cells. The molecular weight of natalizumab is 149 kilodaltons.

2.1.3 What are the therapeutic indication(s) and proposed mechanism(s) of action?

Proposed Indication: Tysabri® is intended to be used for inducing and maintaining clinical response and remission, in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation, who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of tumor necrosis factor (TNF)-α.

Crohn's Disease: Inflammatory bowel disease (IBD) includes two autoimmune diseases, ulcerative colitis (UC) and CD. CD is characterized by chronic inflammation of all layers of the bowel and may affect any segment of the GI tract. The most common patterns of GI involvement are the distal small intestine and colon, followed by the small intestine alone and then by the colon alone. Diarrhea and abdominal pain, weight loss, fever and rectal bleeding are common symptoms of CD.

Typically, CD runs a chronic relapsing course with intermittent acute clinical episodes. The currently available drugs include aminosalicylate (5-ASA), oral corticosteroids, immunosuppressants and infliximab, a chimeric anti-TNFα antibody. Surgery is used to treat complications such as bowel obstructions or abscesses or to control the patient's symptoms when medical therapy fails.

Proposed Mechanism of Action: [redacted] (b) (4)

[1] Persistent defined as positive at two or more time points separated by at least 42 days

(b) (4)

The role of the VCAM-1 receptor in CD is however, not clear (see product review by Dr. B. Rellahan for further details).

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Natalizumab is intended to be administered as a chronic treatment. The recommended dose of Tysabri® is 300 mg (approximately 4.3 mg/kg for a 70 kg individual) IV infusion (to be infused over approximately 1 hour) every four weeks. It should be noted that this dosing regimen is identical to that currently approved for the MS indication.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Figure 1 and Table 1 below provide a summary of the clinical development plan of natalizumab in patients with CD.

(b) (4)

Figure 1 Clinical Development of Natalizumab in Crohn's Disease

Table 1 Summary of Natalizumab Efficacy Studies

Study Location; Dates	Design	Treatment Groups	No. Subjects Entered/Completed (time-point)
		Induction (Primary)	
CD307 N America, Europe, RoW; 2004-2005	Phase III R, DB, PC, PG, MC 1:1 randomization Visits at 4-week intervals	Three IV infusions separated by 4 weeks Placebo Natalizumab 300 mg	Entered/Wk 12 250/208 260[a]/220
CD301 N America, Europe, RoW; 2001-2003	Phase III R, DB, PC, PG, MC 1:4 randomization Visits at 2-week intervals	Three IV infusions, separated by 4 weeks Placebo Natalizumab 300 mg	Entered/Wk 12 181/141 724[a]/602
		Induction (Supportive)	
CD202 Europe, Israel; 1999-2001	Phase II R, DB, PC, PG, MC 1:1:1:1 randomization Visits at 2-week intervals	Two IV infusions, separated by 4 weeks Placebo + placebo Natalizumab 3 mg/kg + placebo Natalizumab 3 mg/kg + 3 mg/kg Natalizumab 6 mg/kg + 6 mg/kg	Entered/Wk 12 63/53 68[a]/59 66[a]/60 51/45
		Maintenance (Primary)	
CD303 N America, Europe, RoW; 2001-2003	Phase III R, DB, PC, PG, MC (Responders in CD301 re-randomized at entry to CD303) 1:1 randomization Visits at 4-week intervals	Twelve IV infusions, separated by 4 weeks Placebo Natalizumab 300 mg	Entered (Mo 3)/ Mo 15[b] 171[c]/51 168[c]/112

R = randomized, DB = double-blind, PC = placebo-controlled, PG = parallel group, MC = multicenter, RoW = selected countries in the rest of the world

[a] Four subjects in Study CD202 and one subject in Study CD301 did not receive natalizumab. One subject in CD307 received natalizumab but was not randomized and was excluded from the ITT Population. [b] Includes 3 months of treatment in Study CD301. [c] As pre-specified, Study CD303 primary efficacy analyses comprised subjects who had responded to natalizumab in Study CD301. Details of subjects who had responded to placebo in CD301 and were also re-randomized to natalizumab (39 subjects) or placebo (35 subjects) are provided in the CD303 CSR

The remaining studies were supportive to the efficacy trials and were primarily safety studies, open-label studies or studies in a population other than the proposed indicated patient population. These studies included a pilot study (CD201), a 2-year open-label

extension study (CD351) and, its follow-on study (CD354), an intermittent natalizumab re-treatment study (CD251), a study of natalizumab in combination with infliximab (CD306), and a study in adolescent subjects (CD305) and, its open-label extension (CD352).

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The clinical development program was designed to demonstrate the efficacy of natalizumab to induce and maintain clinical response and remission in subjects with active CD during chronic treatment. The efficacy of natalizumab, given as a fixed 300 mg dose IV infusion at 4-week intervals, was evaluated in three double-blind, placebo-controlled, Phase III studies (CD307, CD303 and CD301). Studies CD307 and CD301 (both induction studies) enrolled subjects with moderately to severely active CD (based on clinical evaluation and Crohn's disease activity index [CDAI] score $\geq$220 and $\leq$450). The primary efficacy endpoints were treatment comparisons of the proportion of subjects who had a clinical response ($\geq$70-point decrease from baseline CDAI score) or remission (CDAI score <150). The primary time-point was both Weeks 8 and 12 in CD307 and Week 10 in CD301.

Patients who met the criteria of a responder at Weeks 10 and 12 of CD301 (and had a CDAI score <220) were re-randomized in Study CD303 (Maintenance Phase) to natalizumab or placebo for up to 12 additional months (12 infusions) of treatment to assess maintenance of natalizumab response and remission. The primary efficacy endpoint was that subjects had to maintain response or remission at monthly study visits through Month 9 or Month 15 (i.e., an additional 6-month or 12-month treatment period subsequent to CD301).

Pharmacodynamic (PD) markers that were consistent with the mechanism of action of natalizumab were collected throughout clinical development. These markers included both flow cytometric determination of α4 integrin receptor occupancy (% saturation) on peripheral blood mononuclear cells (PBMCs) and also elevated peripheral lymphocyte counts. Both markers were assessed from the time of natalizumab administration to the end of the monthly dosing interval and beyond the discontinuation of natalizumab therapy.

Reviewer's Comments: Since the evaluation of these markers was exploratory in nature they were not reviewed in detail.

2.2.3 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, refer to the Analytical Section (4.3) for further details.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The dose of 300 mg natalizumab administered in the pivotal Phase 3 studies was based on data from a supportive Phase 2 Study (CD202), which evaluated various natalizumab regimens administered on a dose-by-weight basis (3 or 6 mg/kg). In this dose finding study CD202, patients received two IV doses (placebo+placebo; 3+0 mg/kg; 3+3 mg/kg; or 6+6 mg/kg) separated by 4 weeks. The study revealed that monthly dosing of 3 mg/kg resulted in the highest clinical response rate (defined as a decrease in CDAI score of more than 70 points) of approx. 70% compared to the highest dose of 6 mg/kg which had 50% response rate (see the graph in figure 2 below).

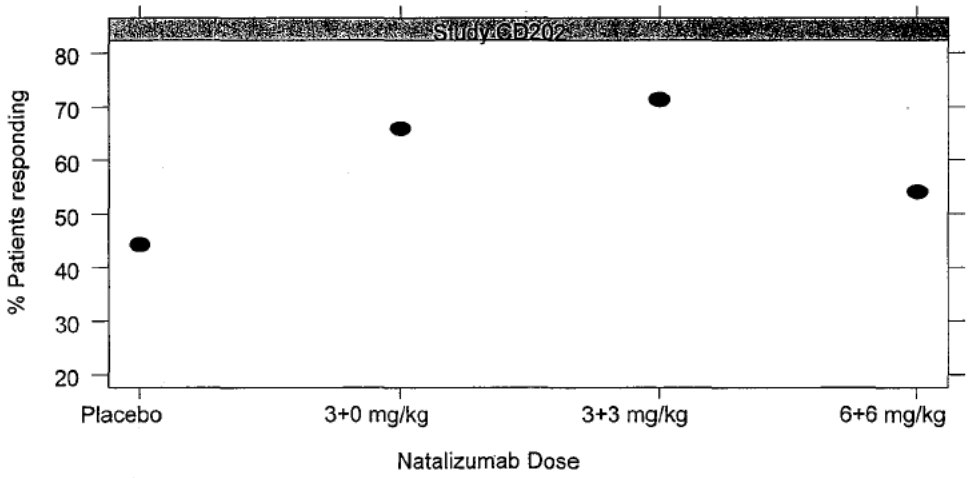

Figure 2 Exposure-Response Relationship for Natalizumab: Percentage of patients responding vs. natalizumab dose

The probability of a clinical response defined as a decrease in CDAI score of more than 70 points was found to be correlated with natalizumab exposure ($AUC_{0\text{-}6\ weeks}$) up to a certain point (i.e., $AUC_{0\text{-}6\ weeks} < 30$ ng.hr/mL) in the dose-finding study CD202 (see graph in Figure 3 below).

The placebo response rate was approx. 40%. Following the administration of natalizumab, increases to approx. 80% were observed for subjects with $AUC_{0\text{-}6\ weeks}$ around 20 mg*hr/mL whereas the upper concentration quartile of patients with $AUC_{0\text{-}6\ weeks}$ above 30 mg*hr/mL exhibited response rates of approx. 60% as illustrated in the graph in Figure 3 below where, the mid-quartile $AUC_{0\text{-}6\ weeks}$ are shown with the corresponding response rate and the $AUC_{0\text{-}6\ weeks}$ ranges for the different doses tested shown as horizontal colored bars.

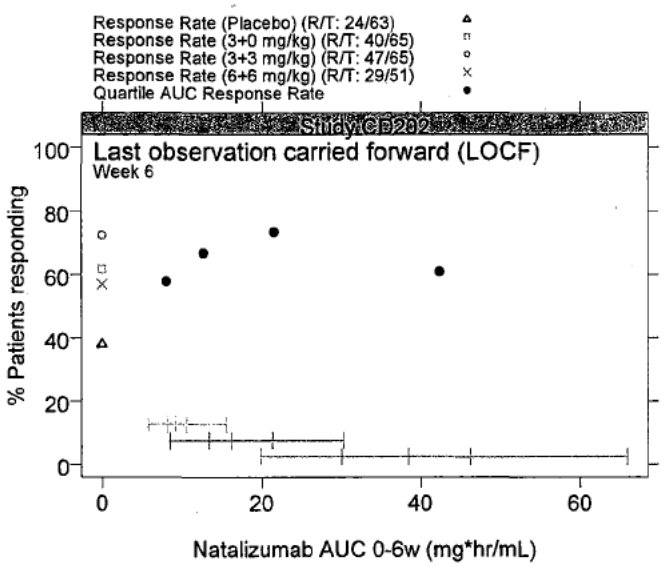

Figure 3 Exposure-Response Relationship for Natalizumab: Percentage of patients responding vs. natalizumab $AUC_{0\text{-}6\ weeks}$

In summary, an inverse U-shaped dose- and exposure-response relationship was found for efficacy with the highest dose group of 6 mg/kg q4w having lower response rate compared to 3 mg/kg q4w. The reason for observing an inverse U-shaped relationship for natalizumab was not identified.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The relationship between natalizumab exposure and serious infections, serious adverse events, urinary infections, and herpes simplex was investigated. However, only a trend towards higher incidents of herpes simplex with higher exposure was observed. Serious infections (other than PML), urinary infections, serious adverse events were not found to be correlated with natalizumab exposure.

The overall percentage of patients with herpes simplex was 2.8% (N=14) for placebo and 4.4% (N=27) for natalizumab treated patients across all studies. The probability of herpes simplex appeared to increase for patients with natalizumab AUC_{ss} above 20 mcg*hr/mL. The clinical significance of this is unknown.

2.2.4.4 Are the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?

The selection of the 300 mg fixed dose (approximately 4.3 mg/kg; 70 kg subject) every 4 weeks proposed by the applicant was found to be acceptable based on the following findings:

- 3 mg/kg dose was efficacious, with the 99th percentile weight in the Phase 2 studies being 100 kg and there was no apparent added clinical benefit of the 6 mg/kg dose over the 3 mg/kg dose.

- 6 mg/kg resulted in no dose-limiting toxicities.
- Natalizumab clearance appears to be largely independent of body weight over the body weight range of approximately 40–100 kg, such that a fixed dose is feasible.

2.2.5. Pharmacokinetic Characteristics:

2.2.5.1 What are the single dose and multiple dose PK characteristics of the drug?

Systemic Exposure:

Intensive PK samples were collected from 21 patients participating in a PK sub-study of the Phase 3 efficacy trial (study CD 301) at the following times: 0 (pre-infusion), 1, 2, and 24 hours, and at Weeks 1, 2, 3, and 4 post- infusion, for Dose 1 (Week 0) and Dose 3 (Week 8) of natalizumab or placebo intravenous (IV) infusions. Trough sampling was taken prior to the second infusion (Week 4). Typical mean serum natalizumab concentration-time profiles following single and repeat dosing of 300 mg IV at 4-weekly intervals for 3 doses in CD subjects (Study CD301) are shown in Figure 4 below.

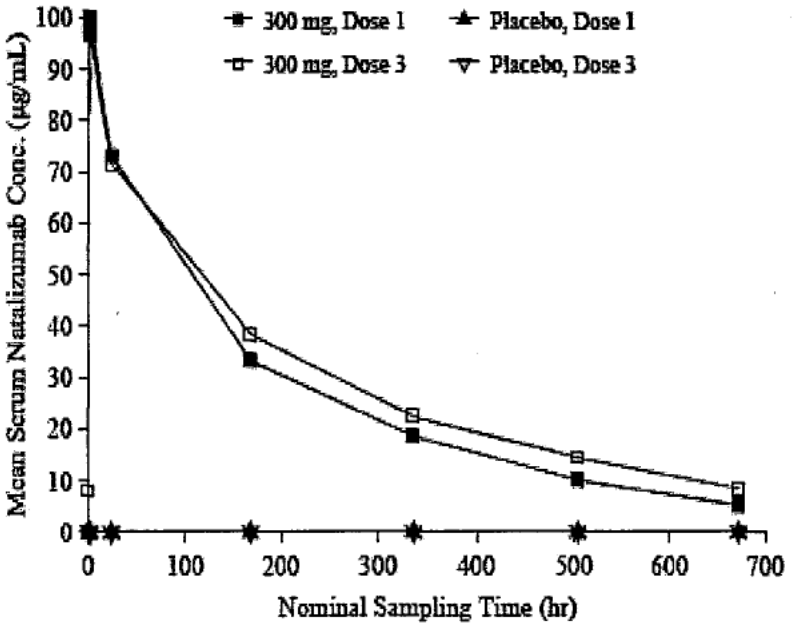

Figure 4: Linear Plots of Mean Serum Natalizumab Concentration-Time Profiles after Dose 1 and Dose 3

Table 2: Summary of Natalizumab Pharmacokinetic Parameters

Dose	Summary Statistics	T_{max} (hr)	C_{max} (µg/mL)	$AUC_{(0-672)}$ (hr*µg/mL)	$t_{½}$ (hr)	CL (mL/hr)	V_d (mL)	C_{min} (µg/mL)	C_{avg} (µg/mL)	Fluctuation (%)
1	N	19	19	19	19	19	19	0	0	0
	Mean (SD)	1.63 (0.58)	102.2 (30.7)	17980 (6730)	165.2 (63.2)	18.90 (11.03)	3934 (1278)	N/A	N/A	N/A
	Range	0.92–3.00	43.2–166.7	5240-31611	82.7-320.2	8.00-54.72	1747-7558	ND	ND	ND
	Median	1.97	92.4	18016	152.9	16.29	3720	ND	ND	ND
3	N	15	15	15	15	15	15	15	15	15
	Mean (SD)	1.45 (0.48)	101.2 (33.5)	19840 (10067)	231.1 (172.8)	21.86 (21.65)	5209 (2755)	8.0 (6.1)	29.5 (15.0)	368 (152)
	Range	0.97-2.00	37.8-152.5	3092-46606	34.4-796.5	6.44-97.03	2418-14328	0.0-19.6	4.6-69.4	178-822
	Median	1.08	97.1	19005	184.8	15.79	5163	5.5	28.3	337

As illustrated in Figure 4 and Table 2 above, the mean serum natalizumab concentration-time profiles after the first (Week 0) and third (Week 8) doses were very similar, showing mean peak concentrations of 102.2 and 101.2 µg/mL for Dose 1 and Dose 3, respectively (observed 1-2 hours after the start of drug infusion), followed by a relatively rapid drop in serum concentrations within the first 24 hrs after infusion, with a slower decline thereafter.

Distribution: Following single and multiple dosing, the volume of distribution values for natalizumab ranged from 1747- 7558 mLs and 2418-14328 mLs, respectively. The mean Vd values were 3934 ± 1278 mLs and 5209 ±2755 mLs following the first and third doses, respectively.

The applicant stated that these mean values are only slightly greater than plasma volume (approximately 3000 mL), indicating distribution of natalizumab mainly within the plasma, as well as other extracellular fluids. Therefore, no radiolabeled studies have been performed with natalizumab, to evaluate tissue distribution because negligible tissue distribution is likely based on the observed limited distribution volume and, the known properties of monoclonal antibodies (i.e. they are expected to be distributed primarily within the vascular compartment due to relatively poor vascular permeability).

Reviewer's Comments: The values of the Vd obtained with the intensive PK sampling following a single dose administration were comparable to that obtained with the POPPK analysis (Estimate of the Vd = 3560 mLs (% CV =17.6))

Metabolism: No studies were conducted to evaluate metabolism. The applicant stated that the metabolism of natalizumab is expected to follow normal proteolytic pathways (i.e. hydrolysis by various proteases and peptidases to small peptides and individual amino acids), with various organs expected to contribute to metabolism with no anticipated involvement by other Phase 1 or Phase II conjugation reactions.

Excretion: Following single and multiple dosing, the serum clearance (CL) values for natalizumab ranged from 8.0-54.7 mLs/hr and 6.4-97.0 mLs/hr, respectively. The mean CL values were 18.9 ± 11.03 mLs/hr and 21.9 ±21.7 mLs/hr following the first and third doses, respectively.

Accordingly, the half-life ($t_{1/2}$) of natalizumab was also long, ranging from 82.7-320.2 hrs (3.5-13.3 days) and 34.4-796.5 hrs (1.4-33.2 days), respectively, following the administration of the first and third doses. The mean $t_{1/2}$ values were 165.2 ± 63.2 hrs (6.9 ± 2.6 days) and 231.1 ±172.8 hrs (9.6 ± 7.2 days) following the first and third doses, respectively.

The applicant stated that significant renal elimination of natalizumab was not anticipated due to its large molecular size (146kD) and it was not evaluated in either clinical or nonclinical studies.

Reviewer's Comments: The values of the CL obtained with the intensive PK sampling following single dose administration were comparable to that obtained with the POPPK analysis (Estimate of the CL = 17.6 mLs/hr (% CV =29.4))

2.2.5.2 Based on the PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The results of the dose-ranging study (CD202) indicated that the serum natalizumab C_{max} and AUC_{last} was approximately dose-proportional over the 3 and 6 mg/kg dose range in CD patients, with minimal accumulation in serum upon multiple dosing.

Table 3:

Table A

Mean (SD) Antegren Pharmacokinetic Parameters for all Dose Groups

Dose	AUC_{last} (µg*h/mL)	C_{max} (µg/mL)	$t_{½}$ (h)	C_{min} (µg/mL)
3 mg/kg + Placebo	16781.4 (5614.7) n=60	85.1 (22.5) n=60	109.2 (23.7) n=40	1.1 (1.4) n=60
3 + 3 mg/kg Dose 1	16500.4 (4868.9) n=62	83.8 (22.0) n=62	112.3 (32.6) n=40	1.3 (2.3) n=59
Dose 2	17553.5 (6168.4) n=54	84.4 (21.5) n=54	131.9 (35.3) n=38	2.0 (3.0) n=54
6 + 6 mg/kg Dose 1	31238.6 (10740.3) n=47	147.0 (49.9) n=47	129.5 (29.8) n=38	4.6 (4.4) n=45
Dose 2	34595.9 (14045.0) n=43	147.2 (47.8) n=43	161.1 (79.3) n=37	6.6 (7.1) n=42

Reviewer's Comments: The applicant observed that given the sparse sampling approach applied in this study, the calculated PK parameters (using non-compartmental methods) needs to be interpreted with some caution.

2.2.5.3 How do the PK parameters change with time following chronic dosing?

The results of study CD 301 and CD 202 indicate that there is minimal change in time obtained for the Cmax and AUC following repeated monthly administration compared to single dosing. In addition minimal accumulation was obtained with multiple dosing.

In Study CD 301, the mean "trough" serum concentration (Ctrough) values, 28 days post-administration (C_{672}) appeared to increase following repeated (third dose) monthly administration (8.4±8.6 mcg/mL) compared to single (first dose) dosing (5.2±6.3 mcg/mL). The applicant stated that this apparent increase can be explained by time-variant clearance (e.g. an approximate 25 % reduction in clearance is observed at steady-state in CD subjects: based on the results of the population PK analysis). This reduction in clearance with multiple dosing that results in accumulation (unexpected based on the half-life of natalizumab (t1/2 ~ 6 days)) is illustrated in Figure 5 below.

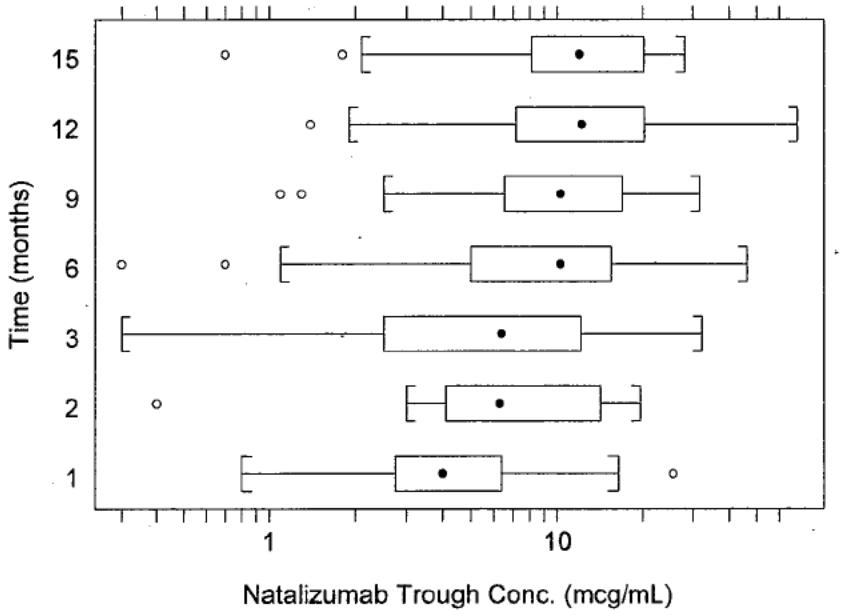

Figure 5 Box-plot of natalizumab trough concentrations from study CD-301 and CD-303.

Reviewer's Comments: The natalizumab trough concentration values obtained from Study # 301 were so variable that it would be difficult to infer any definitive conclusions from the data. However, including the data from the maintenance study # 303 showed that the mean trough concentration was more stable from 6 doses onwards indicating that steady state was achieved after approximately 4-6 doses. Therefore, the mean

Ctrough at steady state is the value (10.6 ±8.9 mcg/mL, range = 0 to 46.2 mcg/mL) that was obtained after six doses of a 300 mg fixed dose of natalizumab in study # 303.

2.2.5.4 What are the inter-and intra-subject variability of the PK parameters in patients?

Following a single dose of 300mg IV of natalizumab to CD patients in studies CD 301 and CD 306, the inter-subject variability range for most PK parameters was around 30-50 % (see Table 3 below)

Table 4: Comparison of the inter-subject variability of natalizumab PK parameters in adult CD patients

Parameter (Dose 1 Only)[1]	CD301 (CD)	CD306 (CD)
N	19	16
C_{max}	30.0	27.8
AUC	37.4	38.4
CL	58.4	39.7
V_z* or V_{ss}**	32.5*	47.0*
$t_{½}$	38.3	38.7

Reviewer's Comments: The inter-subject variability for CL and Vd shown in the table above were higher than those obtained with the POPPK analysis (29.4 and 17.6 %, respectively).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

The findings of the population pharmacokinetic analysis in Crohn's Disease patients indicated that only anti-natalizumab antibody status (categorized as negative vs. positive) appeared to affect natalizumab clearance.

Natalizumab antibody status was identified as a significant covariate (i.e. could potentially produce a 20 % or greater change in one or more PK parameters from that of the reference ('typical") patient) for natalizumab clearance with 42% increase in clearance for patients with antibodies which was comparable to the applicant's claim of 49 %. This is likely to be an underestimate of the true effect due to many antibody positive subjects having PK trough samples below LOQ.

Reviewer's Comments: The applicant also stated that their claim is likely to be an underestimate of the true effect. The applicant also conducted a supplementary analysis that included fixing BLQ trough levels to LLOQ/2 as an alternative approach. This

supplementary analysis resulted in natalizumab serum CL being predicted to be typically 114 % higher in anti-natalizumab antibody positive compared to antibody negative patients. Based on this, the applicant wants to include the following statement in the label "the presence of persistent anti-natalizumab antibodies was observed to increase natalizumab clearance [redacted] (b) (4) *". However, it is recommended that the applicant not include this value in the label because it is an estimate based on an imputation method.*

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

See 2.4.2 below

2.4.2 Drug-Drug Interactions

Study # CD 306 evaluated the safety and tolerability of natalizumab in subjects with CD concurrently receiving infliximab and not in remission (CDAI ≥150). The primary objective of this study was to evaluate the safety and tolerability of three monthly (Week 0, 4, and 8) 300 mg IV infusions of natalizumab with concurrent infliximab (5mg/kg) administrations every 8 weeks (at Weeks -2 and 6). A total of 32 subjects (18 receiving natalizumab+infliximab and 14 receiving placebo+infliximab) from 11 selected sites participated in the intensive PK/PD sub-study. Blood samples for the measurement of serum infliximab concentrations were collected from all subjects at Weeks -2, 6, 20, and any Early Discontinuation visits. The table below shows the summary statistics of serum natalizumab PK parameters for infusion 1 and 3.

Table 17 Summary Statistics for Selected Natalizumab Pharmacokinetic Parameters

Infusion		T_{max} (hr)	C_{max} (µg/mL)	$AUC_{(0-672)}$ (hr*µg/mL)	$t_{½}$ (hr)	CL (mL/hr)	V_d (mL)	C_{min} (µg/mL)
1	N	16	16	16	16	16	16	0
	Mean (SD)	1.84 (0.50)	96.0 (26.7)	16040 (6154)	158.7 (61.5)	20.44 (8.09)	4444 (2092)	ND
	Range	1.13 – 3.05	59.2 – 146.2	8436 - 29787	76.7 – 309.9	9.53 – 34.64	2148 - 10179	ND
	Median	2.00	96.1	16112	147.7	18.15	4002	ND
3*	N	11	11	11	11	11	11	11
	Mean (SD)	1.74 (0.41)	93.5 (32.8)	15411 (8422)	128.8 (68.9)	98.01 (241.19)	4349 (2640)	4.3 (4.7)
	Range	1.13 – 2.33	15.3 – 123.6	365 - 23944	10.2 – 195.1	12.53 – 822.61	2603 - 12047	0 – 15.6
	Median	2.00	107.6	16391	154.8	18.30	3818	3.2

* n= number of subjects; SD = standard deviation

Note: Calculation of some dose 3 PK parameters involved extrapolation from 368-672 hours since samples were only collected to 2 weeks post-infusion (week 10). This extrapolation was deemed to not significantly bias the results as generally comparable Dose 1 and 3 median PK parameters were obtained.

The applicant stated that the mean serum natalizumab PK parameters from this study (CD 306) for subjects receiving concomitant therapy with infliximab appeared to be generally comparable to those obtained in study CD301 in which anti-TNF therapy (including infliximab) was prohibited, indicating little or no readily apparent effect of infliximab on natalizumab PK.

Reviewer's Comments: Due to the extrapolation of data following the third dose, the AUC and half-life with multiple dosing were not really comparable to that previously obtained in study CD301. However, in the POPPK analysis, the influence of infliximab, steroids and immunosuppressants were also evaluated and the results indicated that they did not influence the PK parameters of natalizumab on co-administration. This data thus supports the results of the study # CD 306 with regards to the influence of infliximab on natalizumab.

2.5 General Biopharmaceutics

Drug Product Composition

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.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The drug product used in the Phase 3 CD studies was shown to be bioequivalent to the proposed to-be-marketed formulation in Study # C-1805. This study was previously reviewed and found acceptable during the review of the MS indication (BLA # 125104), therefore it was not reviewed again. In addition the to-be-marketed formulation was also administered in clinical study # CD351 (in patients with CD).

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

The effect of food on natalizumab was not evaluated since this is an IV formulation.

2.6 Analytical Section

2.6.4 What bioanalytical methods are used to assess concentrations?

Serum natalizumab concentrations were determined by an enzyme linked immunosorbant assay (ELISA) in which antibodies bind to both VLA-4 binding domain (capture) and the fragment crystallizable (Fc) ends of the natalizumab molecule. Plates were coated with a murine monoclonal anti-natalizumab antibody (12C4). Microplates were coated overnight with 12C4, blocked to minimize nonspecific binding, and then washed. Serum samples, reference standards, and controls were pre-diluted in assay diluent (1:1000) and

added to the microplate for incubation. After incubation, natalizumab bound to the plate was detected using a mouse anti-human immunoglobulin G4 (IgG4) antibody conjugated to alkaline phosphatase followed by the addition of a colorimetric para-nitrophenyl-phosphate (PNPP) substrate. The quantity of natalizumab in the sample was translated into absorbance units that were detected by the plate reader.

Natalizumab receptor binding saturation was determined by a flow cytometry assay for the determination of the percent saturation of α 4 –intergrin receptors by natalizumab in whole blood.

2.6.4.1 Were the assay methods adequately validated?

Yes, they were adequately validated. In addition these analytical methods and their validation data were previously reviewed in the BLA for the MS indication and found acceptable therefore they were not reviewed in detail again. Inserted below is a summary of the validation results for the serum concentration assay for natalizumab (see Appendix for the summary of the validation results for the natalizumab receptor binding assay).

Table 6: Performance Characteristics of the Colorimetric Serum Concentration Assay for Natalizumab

Intra-assay Precision	**The precision of four levels of control concentrations (625, 2500, 5000, and 20000 ng/mL), nine replicates run on a single plate, was expected to have a %CV ≤ 25% for each level.**	**The mean %CV was < 12% for all four control levels.**
Specificity - NHS interference	**The background/baseline signal in ten individual Normal Human Serum (NHS) samples should be less than the mean signal for the minimum standard (250 pg/mL). Also, spike recovery in three individual NHS is expected to be within 20% of the nominal concentration.**	**The background signal for each NHS was less than the mean signal for the 250 pg/mL standard (0.148 OD). The spike recovery in three individual NHS was within 10% of the nominal concentration.**

Validation Parameter	Proposed Acceptance Criteria	Validation Study Results
Range	The range of the assay will be determined as the interval between the upper and lower concentration of natalizumab that demonstrate a suitable level of precision, accuracy and linearity (see LLOQ and ULOQ below). An R-value for the determined range > 0.95 is acceptable.	The range of the assay standard curve was determined to be 0.25-32 ng/mL. The sample and control range was determined to be 0.25-32 µg/mL. An R-value > 0.997 was demonstrated for the assay range.
Upper Limit of Quantitation (ULOQ)	ULOQ for the assay will be defined as the highest concentration of natalizumab standard that returns an accurate value (80%-120% of nominal value) and has a coefficient of variation (CV) ≤ 25%.	The ULOQ is 32 µg/mL. The mean accuracy was within 1% of the nominal value with mean precision < 7% CV.
Lower Limit of Quantitation (LLOQ)	LLOQ for the assay will be defined as the lowest concentration of natalizumab standard that returns an accurate value (80-120% of nominal concentration) and has a %CV ≤ 25%.	The LLOQ is 0.25 µg/mL. The mean accuracy was within 5% of the nominal value with mean precision < 12% CV.
Dilutional Linearity	Samples containing high concentrations of natalizumab were prediluted with NHS into the range of the assay. The recovered concentration for these samples was required to be within 25% of the nominal value with a %CV ≤ 25%. Dilution curves were expected to exhibit linearity with R-values > 0.95	All dilutional linearity samples recovered natalizumab within 25% of the nominal concentration. The %CV was < 14%. Dilution curves exhibited linearity with R-values > 0.999.
Accuracy	The accuracy of four levels of control concentrations (625, 2500, 5000, and 20000 ng/mL) was expected to be within 20% of the nominal value for each level.	The mean accuracy was within 8% of the nominal concentration for all four control levels.
Intermediate Precision (Inter-assay)	The precision of four levels of control concentrations (625, 2500, 5000, and 20000 ng/mL) run on different days (and by different analysts for the manual method) was expected to have a %CV ≤ 25% for each level.	The mean %CV was ≤ 6% for all four control levels.

Stability of controls - Freeze/Thaw up to three times	Four levels of control samples subjected to 3 Freeze/Thaw cycles should be accurate, within 20% of the nominal concentration, and precise with a %CV ≤ 25%.	Accuracy was within 18% of the nominal value with a precision of < 6% for controls frozen and thawed up to three times.
Stability of controls - Ambient temperature	Four levels of control samples subjected to ambient temperature 24 hours should be accurate, within 20% of the nominal concentration, and precise with a %CV ≤ 25%.	Accuracy was within 12% of the nominal value with a precision of < 4% for controls held at ambient temperature 24 hours.
Stability of controls - 4°C	Four levels of control samples subjected to 4°C for two or four weeks should be accurate, within 20% of the nominal concentration, and precise with a %CV ≤ 25%.	Controls stored at 4°C for two weeks were accurate, within 18% of the nominal value, with a precision of < 6%. Controls stored at 4°C for four weeks were not accurate, with recovery 21% of the nominal concentration. Control values were, however, precise with a %CV < 10%. It was determined that storage conditions should not exceed two weeks at 4°C.
Stability of controls– Frozen (-70°C) @ one month	Four levels of control samples stored frozen for one month should be accurate, within 20% of the nominal concentration, and precise with a %CV ≤ 25%.	Accuracy was within 9% of the nominal value with a precision of < 8% for controls frozen for one month.

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4.2. Individual Study Reviews

Nomenclature: The trade name for natalizumab (a recombinant humanized anti-α4 integrin antibody) is Tysabri®, although originally the name Anteegren® was used. Natalizumab also has been referred to as AN100226 throughout this document, the drug substance will always be referred to as natalizumab, but the other terms are used in the original clinical study reports. The murine parent of natalizumab will be referred to as AN100226m.

Studies in Patients with Crohn's Disease:

Study # CD 201

Title of study: A Preliminary Study of the Effect of Intravenous Antegren on Clinical Status in Patients with Chronic Active Crohn's Disease

Investigator(s): Study was conducted at 2 centers in the UK. The sponsor's medical officer was Dr. Timothy Corn, FRCPsych, FFMP, Director of Medical Affairs, Elan Pharma, Ltd.

Phase of the Study: I/II

Study Period: 21st January 1997 to 5th February 1998

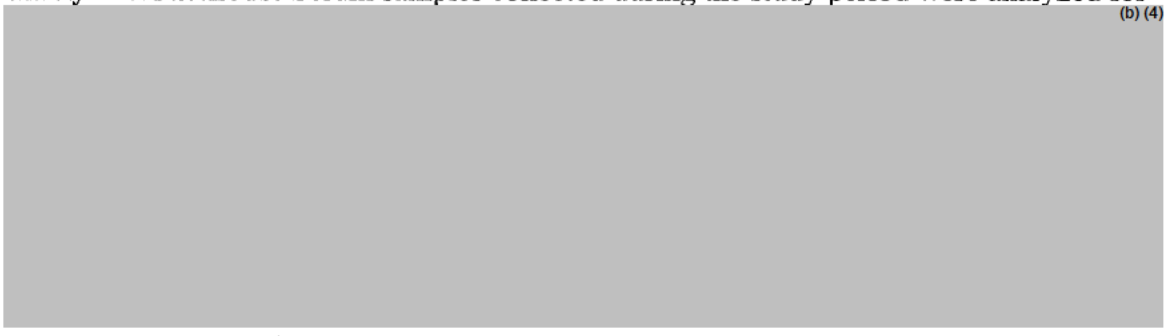
Objectives: To assess the effect of Antegren on the clinical status of patients with Crohn's disease (CD) by the Crohn's disease activity index (CDAI) and to assess the safety and tolerability of Antegren in these patients.

Study Design: This was a randomized, double-blind, placebo-controlled study in patients with active CD, not completely responsive to conventional treatment (based on clinical evaluation and CDAI >150). Patients had a pretreatment screening period of seven days. A single dose of Antegren, 3.0 mg/kg, or placebo was then given by intravenous infusion over 30 – 45 minutes. The response to treatment was assessed by CDAI activity at Weeks 1, 2, 4, 8, and 12 following administration. The total duration of the study for each patient was 13 weeks.

Test Product: Study medication was provided in clear stoppered, individual vials containing 5 mL of Antegren, 5 mg/mL, or placebo. Antegren vials contain 5 mg/mL. All patients in the Antegren group received Antegren Batch A004A. All patients in the placebo group received placebo Batch A007P.

Pharmacokinetic Sampling: Following administration of the study infusion, serum samples for Natalizumab concentrations and anti-Natalizumab antibody levels were collected predose, one hour postinfusion, and at each scheduled visit (i.e., Weeks 1, 2, 4, 8, and 12). Serum samples were frozen within one hour of sampling and stored at −70°C at the investigational sites.

Analytical Methods: Serum samples collected during the study period were analyzed for



(b) (4)

Pharmacokinetic Analysis and Statistical Methods: Pharmacokinetic parameters were estimated with the use of non-parametric (model independent) methods. Cmax, Tmax), the terminal rate constant (λz), the terminal elimination half-life (t½), AUC, Vz and the CL were estimated

Results:

Study population:

A total of 35 patients were screened, of which 30 were randomized to the study, with 18 patients in the Antegren group and 12 patients in the placebo group. Three patients were withdrawn from the study after receiving study medication, one from the Antegren group and two from the placebo group. Patient 13 (placebo) did not attend the Week 8 and 12 visits, i.e., the patient was lost to follow-up. Patient 14 (placebo) was withdrawn 28 days after the treatment infusion due to lack of efficacy and was subsequently scheduled to have surgery (ileo-caecal resection). Patient 29 (Natalizumab) was withdrawn 65 days after study medication to undergo elective surgery at another hospital (Stricturoplasty and resection).

Table 11.2.1-1: Patient Demographic Data

		Antegren	Placebo	Overall
Age (yr)	Mean (Range)	36.0 (23.0 - 67.1)	34.4 (22.5 -50.1)	35.4 (22.5 - 67.1)
Gender	Male	7 (39%)	5 (42%)	12 (40%)
Ethnic Group	White	17 (94%)	11 (92%)	28 (93%)
	Asian	1 (6%)	1 (8%)	2 (7%)
Height (cm)	Mean (Range)	166.5 (153.0 -184.0)	161.5 (151.0 -175.0)	164.5 (151.0 - 184.0)
Weight (kg)	Mean (Range)	66.4 (50.6 - 94.8)	57.5 (42.1 -67.7)	62.8 (42.1 - 94.8)

Pharmacokinetics:

Table 11.5.1: Mean (SD) Serum Natalizumab Concentration (N=18)

Time in Weeks	Mean (SD) [mcg/mL]	Range [mcg/mL]
0	0.0	—
1	14.33 (9.10)	(4.75–33.30)
2	4.91 (3.80)	(0.93–13.38)

4	0.99 (1.45)	(0.0–5.39)
8	0.01 (0.02)	(0.0–0.07)
12	0.0	—

The majority of patients had measurable serum Natalizumab concentrations at Week 4, but these were below the limit of quantitation at later times (i.e. at Week 8).

Table 11.5.2: Mean (SD) and Range Pharmacokinetic Parameters of Natalizumab in Patients with Crohn's Disease following 3 mg/kg Dose (N=18)		
Parameters	Mean (SD)	Range
Cmax (μg/mL)	52.8 (16.2)	(12.95 – 89.24)
Tmax (h)	1.0 (0)	—
T½ (h)	114.8 (54.5)	(59.7–295.2)
AUC (0-t) (μg.h/mL)	8146 (2926)	(4347–14508)
AUC (0-∞) (μg.h/mL)	8674 (3073)	(5465–14,515)
Vz (mL/kg)	65.5 (46.9)	(20.2–233.9)
Cl (mL/h/kg)	0.386 (0.124)	(0.207–0.549)

The extrapolated values of the (SD) concentration of Natalizumab at Week 4 was observed to be 0.88 (1.34) μg/mL. The mean maximum serum concentration of Natalizumab was observed to be 52.8 μg/mL. The corresponding time to maximum serum concentration was at the first sample collection point after the termination of infusion (i.e., at 1.0 hour).
The mean elimination half-life of Natalizumab was observed to be 114.8 hours with a range of 59.7 – 295 h. The mean area under the curve for interval 0–t was 8146 μg.h/mL. The mean extrapolated area to infinity was 8674 μg.h/mL, indicating that less than 7% of the area was extrapolated, which is a very small difference. The inter-patient variability in AUC of 35% was relatively low. The mean volume of distribution (Vz) for Natalizumab was observed to be 65.5 mL/kg, which for a 70 kg person is about 4.6 liters. This is slightly more than the plasma volume, indicating that the distribution is throughout the intravascular space and into limited extravascular space. The mean total body clearance of Natalizumab was 0.386 mL/h/kg - significantly lower than the normal hepatic blood flow of about 80 L/h, indicating a low intrinsic clearance compound.

Applicant's Conclusions:
The mean Cmax of Natalizumab was 52.8 ± 16.2 μg/mL (mean ± SD). The majority of patients had low but measurable serum concentrations at four weeks post-treatment (0.88 ± 1.34 μg/mL). The mean elimination half-life of Natalizumab was 114.8 hours, and the majority of the drug is distributed in the intra-vascular compartment.
Of the 18 patients who received a single dose of 3.0 mg/kg of Natalizumab, two patients (11%) developed transient, low-level (or low-titre) anti-Natalizumab antibodies. No patients had detectable anti-idiotypic antibodies.

Reviewer's Comments: The utility of the data from this study is extremely limited since the dose used in this study is lower than the therapeutic dose (approximately 4.3 mg/kg for a 70 kg individual) that is being proposed for marketing.

Study # CD 202

Title of study: A phase II, double-blind, placebo-controlled study of the efficacy, safety and tolerability of intravenous Antegren™ (natalizumab) (3 + 0, 3 + 3, 6 + 6 mg/kg) in subjects with chronic active Crohn's disease.

Investigator(s): (b) (4)

Study center(s): The study was conducted in 36 centers including four centers in Belgium, one center in The Netherlands, seven centers in the Czech Republic, five centers in Denmark, three centers in Germany, seven centers in Israel, two centers in Sweden and seven centers in the United Kingdom.

Study Period: 7th September, 1999 to 30th April, 2001

Phase of the Study: II

Objectives: The primary objective was to evaluate the effect of natalizumab on the clinical status of patients with Crohn's disease (CD), as assessed by the Crohn's Disease Activity Index (CDAI). The primary endpoint of remission was defined as a decrease in the CDAI to <150 at 6 weeks and the primary comparison were between the 6 + 6 mg/kg natalizumab treatment group and placebo. The secondary and tertiary objectives were to assess the safety and tolerability of natalizumab in CD, to further evaluate natalizumab in CD by assessment of changes in the CDAI score, rescue medication requirements, C-reactive protein and albumin levels, the Inflammatory Bowel Disease Questionnaire (IBDQ) and, in a subgroup of patients with Crohn's colitis, the appearance of the mucosa by colonoscopy using the Crohn's Disease Endoscopic Index of Severity (CDEIS) and to determine the serum natalizumab levels and α4 integrin saturation.

Study Design: Phase II, multicenter, double-blind, placebo-controlled, parallel group, randomized study in patients with active CD (based on clinical evaluation and CDAI ≥220 and ≤450). . Patients were randomized (1:1:1:1) at Week 0 to one of four treatment groups:

Table 1:	**Dosing Details**		
Treatment Group*	**Dose group***	**Week 0 infusion**	**Week 4 Infusion**
3 mg/kg natalizumab	3 mg/kg	3 mg/kg	Placebo
3 + 3 mg/kg natalizumab	6 mg/kg	3 mg/kg	3 mg/kg
6 + 6 mg/kg natalizumab	12 mg/kg	6 mg/kg	6 mg/kg
Placebo	Placebo	Placebo	Placebo

*The treatment groups 3 + 0 mg/kg, 3 + 3 mg/kg and 6 + 6 mg/kg are described in this study report and employed in the statistical tables. However, the corresponding dose groups of 3 mg/kg, 6 mg/kg, and 12 mg/kg are employed in the statistical listings.

Intravenous infusion was administered over 60 minutes. Patients were dosed twice during the study, at Weeks 0 and 4. The patients returned to their study center every 2 weeks for 8 weeks and then at Weeks 12, 16, 24, and 36. Patients were followed up by telephone at Weeks 52, 78, and 104. This report includes all data up to and including Week 36.

Patients were permitted to receive other medication for CD, which was to remain at the same dose during Weeks 0 to 12 unless rescue medication was required. This included oral corticosteroids (such as prednisolone, prednisone, methylprednisolone and budesonide), oral 5-ASA (5-aminosalicyclic acid) compounds (such as sulfasalazine, mesalazine or olsalazine), antibiotics (such as metronidazole, tinidazole, ciprofloxacin or clarithromycin) and the immunosuppressants azathioprine. Doses of all therapy, except azathioprine, had to be stable for the 2 weeks prior to the Week 0 visit. Patients receiving oral prednisolone were limited to a dose of <25 mg/day (or equivalent) at enrollment. The only exception was that the dose of oral prednisolone (or equivalent) could be tapered after the Week 6 visit to a dose ≥10 mg/day. Doses of azathioprine had to be stable for the 4 months prior to the Week 0 visit.

The severity of the patients' Crohn's disease was assessed using the CDAI score of the study protocol, see Appendix 16.1.1). This score included assessments of the patient's bowel activity, abdominal pain, overall well being over the previous 7 days, and clinical evaluation of extraintestinal symptoms, presence or absence of an abdominal mass, use of anti-diarrheals, hematocrit values and weight. The assessment produced a single score in which <150 represents quiescent disease, 150–450 represents active disease and >450 represents severe disease.

Test product, dose and mode of administration, batch number: Natalizumab solution supplied in 5 and 20 mL vials at a concentration of 5 mg/mL and 20 mg/mL, with matching 5 and 20 mL vials containing placebo. All infusions were made up in 100 mL bags of 0.9% saline and administered over 60 minutes. Lot numbers B81003B, C24001 and C23001 were employed.

Reviewer's Comments: *Not TBMF, however sponsor did conduct a bioequivalence study (C-1806) to link this drug product to the TBMF*

Reference therapy, dose and mode of administration, batch number: Placebo solution supplied in 5 and 20 mL vials. All infusions were made up in 100 mL bags of 0.9% saline and administered over 60 minutes. Lot numbers C85002 and C85001 were employed.

Pharmacokinetic and Pharmacodynamic Sampling: Serum natalizumab levels and α4 integrin saturation in a subgroup of patients. Blood samples for analysis of natalizumab concentrations following the first infusion were collected at time 0 (pre-dose), at 2 hours and week 2 post-dose. Following the second infusion, blood samples were collected at time 0 (pre-dose), 2 hours and 2, 4 and 8 weeks post-dose.

A few patient blood samples collected from selected study centers were analyzed for α4 integrin saturation. The samples were collected at time 0 (pre-dose), 2 and 24 hours and at week 2 after each dose. After the second dose of natalizumab, additional samples were collected at week 8 and 12.

Immunogenecity (anti-natalizumab antibodies), assessed at Weeks 0 (pre-infusion), 2, 4 (pre-infusion), 6, 8, and 12 (or early discontinuation), was evaluated in 181 subjects to

determine the rate of occurrence of both screening and anti-idiotypic antibodies during the study.

Analytical Methods: The Elan analytical development department analyzed serum

(b) (4)

Pharmacokinetic Analysis and Statistical Methods: Pharmacokinetic parameters were estimated with the use of non-parametric (model independent) methods. Cmax, Tmax), the terminal rate constant (λz), the terminal elimination half-life (t½), AUC, Vz and the CL were estimated

Results:

Study Population: A total of 248 male and female patients were randomized to the study: 63 to the placebo group and 68, 66, and 51 to the 3 + 0, 3 + 3, and 6 + 6 mg/kg natalizumab treatment groups at weeks 0 and 4, respectively.

Serum samples for the assessment of pharmacokinetic parameters were collected from a total of 60, 62, and 47 patients in the 3 + 0, 3 + 3, and 6 + 6 mg/kg natalizumab treatment groups, respectively. Ambient whole blood samples for the assessment of α4 integrin saturation were collected from a very small subset of patients (ranging from 2 to 9 patients per treatment group at different time points).

Table A

Mean (SD) Antegren Pharmacokinetic Parameters for all Dose Groups

Dose	AUC_{last} (μg*h/mL)	C_{max} (μg/mL)	$t_{½}$ (h)	C_{min} (μg/mL)
3 mg/kg + Placebo	16781.4 (5614.7) n=60	85.1 (22.5) n=60	109.2 (23.7) n=40	1.1 (1.4) n=60
3 + 3 mg/kg Dose 1	16500.4 (4868.9) n=62	83.8 (22.0) n=62	112.3 (32.6) n=40	1.3 (2.3) n=59
Dose 2	17553.5 (6168.4) n=54	84.4 (21.5) n=54	131.9 (35.3) n=38	2.0 (3.0) n=54
6 + 6 mg/kg Dose 1	31238.6 (10740.3) n=47	147.0 (49.9) n=47	129.5 (29.8) n=38	4.6 (4.4) n=45
Dose 2	34595.9 (14045.0) n=43	147.2 (47.8) n=43	161.1 (79.3) n=37	6.6 (7.1) n=42

Applicant's Conclusions:

In summary, the serum natalizumab C_{max} and AUC_{last} appeared to increase proportionally with dose for both the 3 and 6 mg/kg doses in CD patients, with minimal accumulation in serum upon repeat dosing. As expected, patients receiving the single infusion of 3 mg/kg (3 + 0 mg/kg dose group) had minimal natalizumab exposure 4 weeks following the first infusion.

Reviewer's Comments: The applicant observed that given the sparse sampling approach applied in this study, the calculated PK parameters (using non-compartmental methods) in this study should be evaluated with some caution.

Pharmacodynamics:

Mean (SD) Percent α4-integrin saturation for All Dose Groups

Time	Dose Groups		
	3 mg/kg + Placebo	3 + 3 mg/kg	6 + 6 mg/kg
Week 0 (Baseline)	9.4 (6.2) (n=5)	29.5 (47.9) (n=5)	5.0 (3.0) (n=6)
Week 0 (2 hr)	116.4 (17.6) (n=9)	115.1 (25.9) (n=4)	107.1 (15.9) (n=6)
Week 0 (24 hr)	109.6 (64.8) (n=6)	96.6 (18.6) (n=3)	162.9 (149.3) (n=5)
Week 2	76.0 (20.6) (n=6)	74.8 (26.3) (n=6)	65.7 (NA) (n=2)
Week 4 (0 hr)	42.5 (14.5) (n=4)	54.0 (18.1) (n=6)	58.1 (47.4) (n=5)
Week 4 (2 hr)	52.3 (24.9) (n=6)	109.9 (52.0) (n=6)	111.6 (49.8) (n=5)
Week 4 (24 hr)	57.0 (24.0) (n=3)	90.6 (28.3) (n=4)	162.4 (83.8) (n=4)
Week 6	11.6 (6.8) (n=4)	82.5 (NA) (n=2)	106.0 (88.6) (n=3)
Week 8	6.7 (5.5) (n=6)	23.4 (18.5) (n=4)	77.0 (20.1) (n=3)
Week 12	5.4 (6.2) (n=5)	27.5 (35.9) (n=3)	52.8 (NA) (n=2)
Week 16	8.3 (5.5) (n=3)	4.4 (2.9) (n=4)	5.2 (NA) (n=2)
Week 24	10.1 (NA) (n=2)	13.1 (15.2) (n=5)	3.8 (1.0) (n=4)

NA = Not Applicable

Applicant's Conclusions:

Based on the available α4 integrin saturation data, saturation >60% was maintained for at least 2 weeks following each of the 3 and 6 mg/kg infusions of natalizumab. In addition, the mean saturation at Week 4 was 42%, 54% after the 3 mg/kg dose (3 + 0 and 3 + 3 mg/kg groups, respectively) and 58% after the 6 mg/kg dose. Likewise, after the second doses of 3 and 6 mg/kg the mean saturation at Week 8 was 23% and 77%, respectively. The reason for the lower than expected saturation levels, compared to previous studies with natalizumab, could be due to the small number of patients contributing to the data.

Applicant's Conclusions:

Immunogenecity: A total of 13 (7.2 %) of the 181 natalizumab-treated subjects developed anti-natalizumab antibodies during the main treatment phase: 8, 4, and 1 in the 3.0 mg/kg, 3.0 + 3.0 mg/kg and 6.0 + 6.0 mg/kg natalizumab groups, respectively.

Study # CD 251 (*Synopsis only because study only investigated the intermittent prn infusion of the 6.0 mg/kg dose, however data was included in PopPK analysis)*

Title of study: Intermittent Re-treatment Study of Natalizumab for Crohn's Disease
Study Design: This was a Phase 2, multicenter, open-label, chronic re-treatment study of the safety, tolerability and effectiveness of repeated courses of IV natalizumab in 96 subjects with active CD (confirmed by CDAI score >150) who had completed Study CD202. The minimum period of drug holiday between the last infusion of natalizumab in CD202 and the Week 0 infusion at treatment course 1 (TC1) was 43 weeks and the maximum 127.9 weeks. Eligible subjects received courses of treatment, each of which comprised an infusion of 6.0 mg/kg natalizumab at Weeks 0 and 4, with assessments at Weeks 0, 2, 4, 6, and 12. After completing a TC and the associated assessments, subjects initiated a repeat course following the Week 12 visit if disease was active (confirmed by

CDAI score >150), or entered the follow-up phase. Subjects were not considered for a repeat course before the Week 12 visit of the existing course. If at any time during the follow-up phase the subject experienced a recurrence of active disease (CDAI score >50), the subject could receive a repeat course of treatment, providing they still met the eligibility criteria.

Pharmacokinetic and Pharmacodynamic Sampling: Serum samples were collected for natalizumab concentration analysis from all subjects during the study. Similarly, WBC and circulating absolute lymphocyte response and immunogenicity (anti-natalizumab antibodies) were assessed in all subjects. All these measures were performed during each TC at the following time-points: screening visit for the TC and Weeks 0 (pre-infusion), 2, 4 (pre-infusion), 6, and 12. Further, subjects who did not go immediately onto another TC with natalizumab following the Week 12 visit of a TC went into a follow-up phase with the above measures performed at Month 4 (Week 16), Month 6 (Week 24), and Month 9 (Week 36).

Results: ***[Applicant's Summaries]***

Pharmacokinetics:

Serum Natalizumab Concentrations:

Generally comparable natalizumab serum concentrations were observed for the total population and also for those subjects who were antibody negative at the equivalent visits between TCs. For each TC, the mean serum natalizumab concentrations post-infusion (excludes Week 0 concentrations which were typically BLQ) were highest at Weeks 2 and 6, and lowest by Week 12, where mean levels were below that associated with an adequate degree of α4 integrin receptor percent saturation. Week 6 serum concentrations appeared to be somewhat higher than the corresponding Week 2 serum concentrations in each TC.

Serum Natalizumab Concentrations and antibody status:

In antibody-negative subjects, median serum natalizumab concentrations ranged from 17.3–32.4 μg/mL and 27.4–41.8 μg/mL at Weeks 2 and 6, respectively, for TCs 1 through 7. Corresponding Week 4 and 12 median concentrations ranged from 5.0–10.4 μg/mL and 0.0–0.0 μg/mL, respectively. Mean and median serum natalizumab levels were markedly lower in antibody positive subjects compared to antibody negative subjects. At Week 6 of TC1, the mean serum natalizumab level in antibody positive subjects was one-fourth of the mean serum level in the antibody-negative subjects. In addition, mean serum natalizumab levels at Week 4 were also below that associated with an adequate degree of α4 integrin receptor percent saturation in the antibody-positive subjects.

Table 25 **Mean Serum Natalizumab Concentration (µg/mL) by Visit and Treatment Course for Antibody Negative Subjects**

	TC						
	TC1	TC2	TC3	TC4	TC5	TC6	TC7
Week 0 (N)	71	37	17	9	5	1	1
Mean (SD)	0.1 (0.5)	0.1 (0.6)	0	1.0 (2.9)	0	0	0
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Week 2 (N)	71	35	16	9	5	1	1
Mean (SD)	22.7 (10.7)	27 (11.6)	24.8 (11.7)	28.8 (21)	22.5 (12.4)	32.4 (0)	22.1 (0)
Median	23.3	27.9	23.6	20.7	17.3	32.4	22.1
Week 4 (N)	67	35	17	8	5	1	1
Mean (SD)	7.4 (5.6)	10 (7.3)	9.5 (9.3)	7 (3.9)	6.2 (3.3)	10.4 (0)	5 (0)
Median	6.0	8.5	8.0	7.7	7.5	10.4	5.0
Week 6 (N)	70	36	17	9	5	1	1
Mean (SD)	30.8 (17.4)	34.6 (16.5)	35.9 (18.6)	28.9 (18.8)	29.5 (16.3)	41.8 (17.3)	30.8 (0)
Median	30.6	36.9	39.5	33.2	27.4	41.8	30.8
Week 12 (N)	66	35	17	8	4	1	1
Mean (SD)	1.3 (2.6)	1.9 (3.7)	2 (4.4)	0.8 (1.9)	0.1 (0.2)	0	0.3 (0)
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Source: Table 4.3.2a, Listing 4.3

In antibody-positive subjects, median serum concentrations ranged from 0.0–19.9 µg/mL and 0.0–35.5 µg/mL at Weeks 2 and 6, respectively, for TCs 1 through 7. Corresponding Week 4 and 12 median concentrations ranged from 0.0–8.2 µg/mL and 0.0–0.0 µg/mL, respectively.

Table 26 **Mean Serum Natalizumab Concentration (µg/mL) by Visit and Treatment Course for Antibody Positive Subjects**

	TC						
	TC1	TC2	TC3	TC4	TC5	TC6	TC7
Week 0 (N)	25	15	9	3	2	1	0.0
Mean (SD)	0.2 (1.0)	0	0.7 (2.2)	0	0	0	0.0
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Week 2 (N)	24	14	9	3	2	1	0.0
Mean (SD)	5.6 (9.0)	5.7 (9.7)	8 (9.5)	15.9 (14.3)	10.9 (15.4)	0	0.0
Median	0.0	0.0	3.3	19.9	10.9	0.0	0.0
Week 4 (N)	23	13	9	3	2	1	0.0
Mean (SD)	1.7 (4.4)	0.8 (2.6)	2.2 (3.5)	6 (5.3)	2.7 (3.8)	0	0.0
Median	0.0	0.0	0.0	8.2	2.7	0.0	0.0
Week 6 (N)	23	14	9	3	2	1	0.0
Mean (SD)	7.3 (14.0)	9 (13.6)	15.6 (14.6)	25 (21.8)	14.2 (20.1)	0	0.0
Median	0.0	0.0	14.3	35.5	14.2	0.0	0.0
Week 12 (N)	23	13	9	3	2	1	0.0
Mean (SD)	0.1 (0.3)	0	0.2 (0.5)	1.4 (2.5)	0	0	0.0
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Immunogenicity: The number of subjects with detectable antibodies was 25 (26%). This was comparable to the preceding Study CD202. Six of these 25 subjects had detectable antibodies prior to first exposure to natalizumab in this study, whilst the remaining 19 subjects developed antibodies during TC1. No subjects initially tested positive for anti-natalizumab antibodies between TC2 and TC7 or any of the follow-up periods. As

expected, a lower proportion of subjects taking concomitant immunosuppressants developed antibodies (11.4%) than subjects not taking immunosuppressants (34.4%).

Study # CD 301

Title of study: A Phase III, International, Multicenter, Double-Blind, Placebo-Controlled Study of the Safety, Efficacy, and Tolerability of Intravenous Antegren™ (Natalizumab) in Subjects with Moderately to Severely Active Crohn's Disease

Investigator(s): This study was conducted in 142 investigational sites in North America, Europe, and selected countries from the rest of the world (ROW).

Study Period: 4th December 2001 to 3rd September 2003

Pharmacokinetics/Pharmacodynamics Objectives:

1. To determine the pharmacokinetics of natalizumab in subjects with moderately to severely active Crohn's disease as assessed by Pharmacokinetic parameters
2. To determine saturation (natalizumab binding) of alpha-4 (α4) integrin receptors on circulating peripheral blood leukocytes as assessed by α4 integrin receptor saturation levels.
3. To determine changes in circulating absolute lymphocyte count as assessed by Mean change in absolute lymphocyte count from baseline (Week 0) at Weeks 2, 4, 6, 8, 10, and 12.

Immunogenicity Objective: To determine the immunogenicity of natalizumab in subjects with moderately to severely active Crohn's disease, as assessed by the formation of anti-natalizumab antibodies.

Study Design: This was a Phase 3, international, multicenter, double-blind, placebo-controlled study of the safety, efficacy, and tolerability of natalizumab in subjects with moderately to severely active CD (CDAI score ≥220 and ≤450). The study was designed to evaluate the efficacy and safety of a total of 3-monthly (every 4 weeks) infusions of 300 mg natalizumab in 905 subjects with moderately to severely active disease, using a 4:1 active to placebo randomization ratio. 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.

Treatments: Natalizumab was provided in clear, stoppered individual 5–mL vials at a concentration of 20 mg/mL in 10 mM phosphate buffer, 140 mM NaCl and 0.02% polysorbate 80. Natalizumab was administered as an intravenous (IV) infusion of 300 mg once every 4 weeks. Subjects in the natalizumab group received natalizumab from drug product lot numbers F23001, F23002, and F23003. Placebo vials were provided in matching 5–mL vials and comprised 10 mM phosphate buffer, 140 mM NaCl and 0.02% polysorbate 80. Subjects in the placebo group received placebo from lot numbers E85001, F85002, and G85001.

Duration of Treatment: Study drug (either natalizumab or placebo) was administered monthly (i.e., every 4 weeks) for a total of three doses (12 weeks). The safety follow-up period consisted of a clinic visit at Week 20 and a telephone follow-up at Week 32. Therefore, study participation could be up to approximately 34 weeks if the subject did not enroll in Study CD303 or Study CD351.

Pharmacokinetic and Pharmacodynamic Sampling: Blood samples for serum natalizumab concentration analysis were to be collected from all subjects at their Week

12, 20, or Early Discontinuation visits. Serial natalizumab concentrations in serum were obtained from subjects enrolled in the intensive PK/PD sub-study for Dose 1 (Week 0) and Dose 3 (Week 8) of natalizumab or placebo intravenous (IV) infusions, and at 1, 2, and 24 hours, and at Weeks 1, 2, 3, and 4 following the start of infusion. Trough sampling was taken prior to the second infusion (Week 4). Pharmacodynamic samples for α4 integrin receptor saturation determination were collected at pre-dose, and at 2 hours and Weeks 1, 2, 3, and 4 following the start of infusion of Doses 1 and 3.

Visit	Anti-natalizumab Antibody	(PK) Natalizumab Concentration	(PD) α4 integrin receptor saturation
Screening			
Week 0 (preinfusion) (immediately postinfusion) (2 h after start of infusion) (24 h after start of infusion)	√	X X X X	X X
Week 1		X	X
Week 2		X	X
Week 3		X	X
Week 4 (preinfusion)	*	X	X
Week 8 (preinfusion) (immediately postinfusion) (2 h after start of infusion) (24 h after start of infusion)	*	X X X X	X X
Week 9		X	X
Week 10		X	X
Week 11		X	X
Week 12	√	√	X
Week 20	√	√	
Early discontinuation	√	√	X
Infusion reaction SAE/AE	√	√	

X Only taken on a subset of subjects at selected sites US only.

√Taken on all randomized subjects.

Note: Samples were obtained, where possible, ± 2 hours for the 24-hour post infusion blood draws and ± 1 day for all additional post infusion samples.

*Only obtained from subjects randomized in Denmark

Immunogenicity (anti-natalizumab antibodies) was assessed at Week 0 (pre-infusion), Week 12, and Week 20 (or Early Discontinuation).

Analytical Methods: The concentration of natalizumab in serum was determined using an enzyme-linked immunosorbant assays (ELISA) "sandwich" assay in which antibodies bind to both VLA-4 binding domain (capture) and the fragment crystallizable (Fc) ends

of the natalizumab molecule. Plates were coated with a murine monoclonal anti-natalizumab antibody (12C4). Microplates were coated overnight with 12C4, blocked to minimize nonspecific binding, and then washed. Serum samples, reference standards, and controls were pre-diluted in assay diluent (1:1000) and added to the microplate for incubation. Standards and quality controls were added to the plates in triplicates. Samples and Dilution Controls were added to the plates in duplicates. After incubation, natalizumab bound to the plate was detected using a mouse anti-human immunoglobulin G4 (IgG4) antibody conjugated to alkaline phosphatase followed by the addition of a colorimetric para-nitrophenyl-phosphate (PNPP) substrate. The quantity of natalizumab in the sample was translated into absorbance units that were detected by the plate reader. The final concentration of natalizumab present was interpolated from the natalizumab standard curve. The sensitivity of the assay was 250 pg/mL (250 ng/mL allowing for the 1:1000 minimum serum dilutions). This assay was validated prior to testing any of the study samples.

Pharmacokinetic Analysis and Statistical Methods:

Pharmacokinetics: Concentration-time profiles after the first (Dose 1) and third (Dose 3) intravenous infusions were plotted for subjects receiving natalizumab treatment. Individual subject natalizumab pharmacokinetic parameters (Cmax, Tmax, AUC0-last, AUC (0-672), Kel, t½, CL, Vd, Vss, Caverage, and Cmin) were calculated using noncompartmental methods and summarized for both Dose 1 and Dose 3. Natalizumab trough concentration data collected at Week 12, Week 20, Early Discontinuation, and unscheduled visits were summarized.

Pharmacodynamics: In the PK/PD substudy, individual and mean α4 integrin receptor saturation versus time profiles after Dose 1 and Dose 3 were plotted and summary statistics generated. For enrolled study subjects, mean absolute lymphocyte counts and their changes from baseline versus time profiles were plotted and summary statistics generated.

Immunogenicity: The number and percentage of subjects who tested positive for screening and blocking anti-natalizumab antibodies were tabulated by visit.

Results:

Study Population:

Serum samples for natalizumab concentration analysis were collected from 816 (652 natalizumab-treated) randomized subjects at their Week 12, 20, or Early Discontinuation visits. Evaluable Week 12 serum concentration data were measured in samples collected from 731 subjects (589 natalizumab-treated). At Week 20 and Early Discontinuation visits, 256 and 90 subjects provided evaluable serum natalizumab concentration data, respectively.

In addition, intensive PK (serum) and PD (blood) samples were collected from 26 subjects (21 natalizumab; 5 placebo) participating in a PK/PD sub-study conducted at 7 US sites. The PD samples were collected for assessment of α4 integrin receptor percent saturation on circulating peripheral blood leukocytes. Nineteen of the 21 natalizumab-treated subjects provided evaluable PK and PD data. Circulating absolute lymphocyte response was assessed in 873 subjects (699 natalizumab, 174 placebo) based on hematology assessments throughout the study. Lastly, immunogenicity (anti-natalizumab

antibodies), typically assessed at Week 0 (pre-infusion), Week 12, and Week 20 (or Early Discontinuation), was evaluated in 650 subjects to determine the rate of occurrence of both screening and blocking antibodies during the study.

PK/PD Sub-Study

A total of 26 subjects (21 received natalizumab and 5 received placebo) at seven selected US sites participated in the intensive PK/PD substudy. Two subjects (CD133-006 and CD 528-009) in the natalizumab group had only one PK sample collected at Week 12 Visit (no sample collected at any other time points) and were, therefore, excluded from the intensive PK/PD analyses. For Subject CD592-004, PK/PD samples collected after the second dose were excluded from the PK/PD analyses because these were not collected at the protocol-designated sample collection times.

Data from 19 of the 21 subjects treated with natalizumab in the intensive PK/PD sub-study were included in the analyses and 15 of the 19 subjects received all three scheduled 300-mg doses. The mean total body weight (TBW) of the 19 subjects (8 male and 11 female) was 73.5 kg and the mean age was 39.8 years. All were Caucasian and two were smokers (1 male and 1 female). The mean natalizumab dose per total body weight for these 19 subjects was 4.29 mg/kg and for the 15 subjects who received Dose 3 was 4.25 mg/kg (mean TBW was 74.2 kg). There were four males and one female subject in the placebo group. All were Caucasian, with one male smoker

Pharmacokinetics:

Intensive PK/PD Substudy: Comparable PK profiles and parameters were observed after the first (Dose 1) and third infusions (Dose 3) of natalizumab in subjects participating in the PK/PD substudy (n=19).

For the 19 natalizumab-treated subjects with evaluable intensive PK data, their individual and mean natalizumab concentrations in serum after Dose 1 (Week 0, N = 19) and Dose 3 (Week 8, N = 15) are presented in the table below:

Table 4.1 Summary of Serum Natalizumab Concentrations (ug/mL) After Dose 1 (Week 0) and Dose 3 (Week 8): PK/PD Substudy

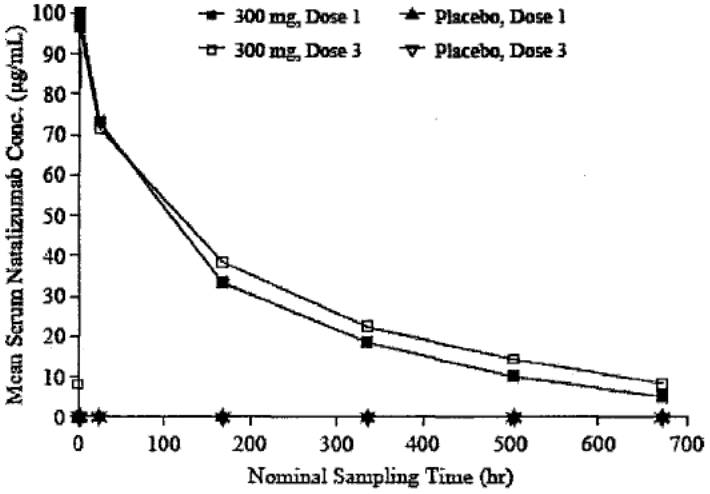
	Dose 1 (Week 0)				Dose 3 (Week 8)			
Scheduled Time	N	Mean	s.d.	CV (%)	N	Mean	s.d.	CV (%)
0 Hour Pre-Infusion	19	0.0	0.00	.	15	8.1	6.09	75.0
Immediately Post-Infusion	19	97.4	28.26	29.0	15	97.2	30.35	31.0
2 Hour Post-Infusion	19	99.9	31.19	31.0	14	96.9	33.44	35.0
24 Hour Post-Infusion	18	73.2	20.52	28.0	15	71.7	23.09	32.0
1 Week Post-Infusion	19	33.4	14.20	43.0	15	38.5	28.04	73.0
2 Week Post-Infusion	18	18.7	9.46	51.0	14	22.5	11.80	52.0
3 Week Post-Infusion	19	10.1	6.53	65.0	13	14.5	10.12	70.0
4 Week Post-Infusion	19	5.2	6.27	120.0	18	8.4	8.57	102.0
12 Week Post-Infusion (Wk 20)	.	.	.	.	2	0.0	0.00	.

Notes:Trough serum concentration level of natalizumab at Week 8 is the pre-infusion level of Dose 3 assessed at Week 8. Serum natalizumab concentrations below the lower limit of quantification (LLOQ) 0.25 ug/mL were treated as zero for calculation purposes.

As illustrated in Figure 5 and Figure 6 below, the mean serum natalizumab concentration-time profiles after the first (Week 0) and third (Week 8) doses were very similar, showing

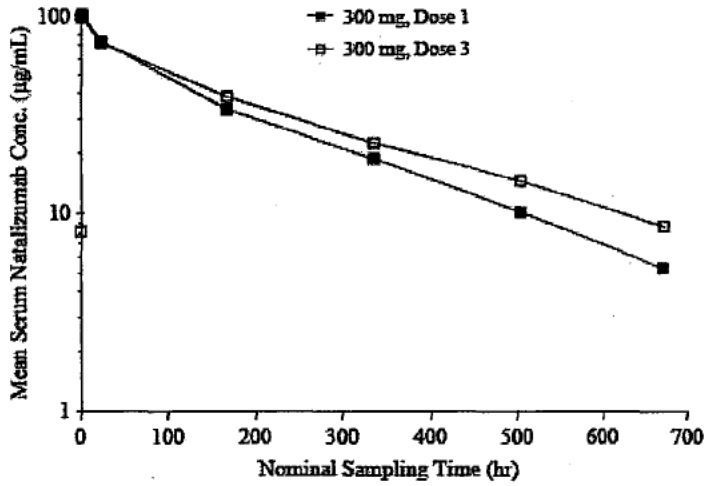
mean peak concentrations of 102.2 and 101.2 μg/mL for Dose 1 and Dose 3, respectively (observed 1-2 hours after the start of drug infusion), followed by a multi-exponential decline in serum concentrations (i.e., relatively rapid drop within the first 24 hrs after infusion, with a slower decline thereafter). By 4 weeks post-infusion, mean serum natalizumab concentrations had decreased to 5.2, 8.1, and 8.4 μg/mL after infusion of Doses 1, 2 and 3, respectively. Therefore quantifiable concentrations were still observed at the end of each 28-day-dosing interval (means >5.0 μg/mL).

Figure 5 Linear Plots of Mean Serum Natalizumab Concentration-Time Profiles after Dose 1 and Dose 3



Note: Hours 168, 336, 504, and 672 = Weeks 1, 2, 3, and 4 after dosing, respectively.
For the natalizumab treatment group, each point represents data collected from 18–19 and 13–15 subjects for Dose 1 and Dose 3, respectively. For the placebo group, each point represents data collected from 5 and 2-3 subjects for Dose 1 and Dose 3, respectively.

Figure 6 Semi-Logarithmic Plots of Mean Serum Natalizumab Concentration- Time Profiles after Dose 1 and Dose 3



Note: Hours 168, 336, 504, and 672 = Weeks 1, 2, 3, and 4 after dosing, respectively.
For the natalizumab-treated group, each point represents data collected from 18–19 and 13–15 subjects for Dose 1 and Dose 3, respectively. For the placebo treatment group, all mean concentrations were below the LLQ (<0.25 µg/mL; treated as zero) and hence cannot be displayed on a semi-logarithmic plot.

Pharmacokinetic Parameters:

For the PK/PD sub-study, natalizumab pharmacokinetic parameters were calculated from serum concentrations following IV infusions of the study drug at Week 0 (Dose 1) and Week 8 (Dose 3). Comparable serum natalizumab pharmacokinetics for the first and third infusions of natalizumab were observed in the PK/PD sub-study, indicating generally time-invariant pharmacokinetics and little or no accumulation of natalizumab upon repeated monthly dosing. Summary statistics for selected serum natalizumab PK parameters are shown in the following table:

Table 30 Selected Natalizumab Pharmacokinetic Parameters

Dose	Summary Statistics	T_{max} (hr)	C_{max} (µg/mL)	$AUC_{(0-672)}$ (hr*µg/mL)	$t_{½}$ (hr)	CL (mL/hr)	V_d (mL)	C_{min} (µg/mL)	C_{avg} (µg/mL)	Fluctuation (%)
1	N	19	19	19	19	19	19	0	0	0
	Mean (SD)	1.63 (0.58)	102.2 (30.7)	17980 (6730)	165.2 (63.2)	18.90 (11.03)	3934 (1278)	N/A	N/A	N/A
	Range	0.92–3.00	43.2–166.7	5240-31611	82.7-320.2	8.00-54.72	1747-7558	ND	ND	ND
	Median	1.97	92.4	18016	152.9	16.29	3720	ND	ND	ND
3	N	15	15	15	15	15	15	15	15	15
	Mean (SD)	1.45 (0.48)	101.2 (33.5)	19840 (10067)	231.1 (172.8)	21.86 (21.65)	5209 (2755)	8.0 (6.1)	29.5 (15.0)	368 (152)
	Range	0.97-2.00	37.8-152.5	3092-46606	34.4-796.5	6.44-97.03	2418-14328	0.0-19.6	4.6-69.4	178-822
	Median	1.08	97.1	19005	184.8	15.79	5163	5.5	28.3	337

NA = Not Applicable and ND = Not determined
Note: Trough serum concentration level of Dose 3 is the Pre-infusion level of Dose 3 assessed at Week 8.

Pharmacodynamics:

Pharmacodynamic samples for α4 integrin receptor saturation determination were collected at pre-dose, and at 2 hours and Weeks 1, 2, 3, and 4 following infusion of Dose 1 (Week 0) and Dose 3 (Week 8) from 26 subjects (21 natalizumab, 5 placebo) participating in the intensive PK/PD sub-study that was conducted at seven selected sites in the US. Two subjects (CD133-006 and CD528-009) receiving natalizumab had only one PD sample collected (Week 12 Visit only), which were excluded from the intensive PD analysis. Hence, data from only 19 of the 21 natalizumab-treated subjects were included in the α4 integrin receptor saturation PD analysis; of these 19 subjects, 15 received all three natalizumab doses per protocol.

Table 4.3 Alpha-4 Integrin Receptor Saturation Levels (%) After Dose 1 (Week 0) and Dose 3 (Week 8): PK/PD Substudy

	Dose 1 (Week 0)				Dose 3 (Week 8)			
Scheduled Time	N	Mean	s.d.	Min., Max.	N	Mean	s.d.	Min., Max.
0 Hour Pre-Infusion	16	4.1	2.06	2, 10	15	68.3	20.17	8, 88
2 Hour Post-Infusion	18	99.0	6.22	87, 113	14	101.0	10.32	88, 130
1 Week Post-Infusion	19	92.8	7.94	77, 108	14	91.1	10.28	80, 123
2 Week Post-Infusion	17	90.3	10.54	73, 109	14	85.4	8.06	74, 95
3 Week Post-Infusion	19	85.4	11.67	55, 115	12	81.3	13.79	46, 94
4 Week Post-Infusion	19	69.6	26.26	3, 97	13	65.5	22.25	7, 94

Note: Trough alpha-4 integrin receptor saturation levels (%) at Week 8 is the pre-infusion level of Dose 3 assessed at Week 8.

The mean α4 integrin receptor saturation level measured at baseline, before the first natalizumab infusion, was only 4.1–5.9%. For both Doses 1 and 3, the observed mean percent α4 integrin receptor saturation was maximal (~100%) at the first scheduled sampling within each dosing interval (2 hours after the start of IV infusion), consistent with the achievement of peak mean serum natalizumab concentrations near the end of the 1-hour IV infusion. Whereas mean serum natalizumab concentrations declined relatively quickly (from approximately 100 μg/mL to less than 9 μg/mL; mean percent α4 integrin receptor saturation values declined relatively slowly (from approximately 100% to 70%) during the monthly dosing interval. Percentage saturation at 4 weeks after the first, second, and third infusions was comparable (69.6%, 68.3%, and 65.5%, respectively).

Reviewer's Comments: The circulating lymphocyte count is being reviewed by the clinical reviewer since the analysis as described above involved subjects from the whole ITT population and not just the PK/PD sub-study.

Applicant's Conclusions:

PK

Comparable serum natalizumab pharmacokinetics for the first and third infusions of natalizumab was observed in the PK/PD sub-study, suggesting no accumulation occurred.

Immunogenecity:

The presence of antibodies to natalizumab has been detected in 8% [53/650] of subjects tested; the majority of these subjects did not experience infusion reactions. The incidence of adverse events was comparable between subjects who tested positive or negative for anti-natalizumab antibodies, except for Crohn's disease and pruritus, which showed a higher incidence for subjects who tested positive for screening anti-natalizumab antibodies. However, the overall frequency of these events was low. Additionally, there was a trend for lower response and remission rates in natalizumab treated subjects with anti-natalizumab antibodies compared to those without anti-natalizumab antibodies.
Reviewer's Comments: The clinical reviewer is currently reviewing this immunogenecity data.

Study # CD 303 (Maintenance Study)
Title: A Phase III, International, Multicenter, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Intravenous Antegren™ (Natalizumab) (300 mg Monthly) in Maintaining Clinical Response and Remission in Subjects with Crohn's Disease
PK/PD objective: The PK and PD objectives of this study were to assess and summarize peak and trough serum natalizumab concentration and the effect of natalizumab on circulating lymphocyte counts in the CD301 Natalizumab Responders Population.
Study Design: This was a Phase 3, randomized, international, multicenter, double-blind, placebo-controlled, parallel-group study that enrolled subjects with CD who had responded to treatment with monthly infusions of either natalizumab 300 mg or placebo for 3 months in Study CD301. Informed consent was obtained at Week 10 in Study CD301, at which point subjects on oral steroids began reducing their doses according to a fixed algorithm. Subjects who continued to meet eligibility criteria at Week 12 (Month 3) were re-randomized to receive monthly IV infusions of natalizumab 300 mg or placebo (ratio 1:1) for up to 12 consecutive months in Study CD303. Subjects were centrally randomized and enrollment was stratified according to 3 factors: disease status at Week 12 (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 1 month after their last study drug infusion (Month 15). Efficacy assessments and safety evaluations were scheduled to occur during monthly (every 4 weeks) clinic visits (Months 3 through 15). A total of 428 subjects (214 natalizumab and 214 placebo) were randomized and all received treatment.
Subjects completing the treatment phase (i.e., up to Month 15) were eligible to enter an open-label, chronic treatment study (ELN100226-CD351) in which all subjects received natalizumab. Subjects who completed the treatment phase but declined to enter Study CD351 were followed for an additional 6 months (after the last infusion) and were evaluated for safety during a clinic visit at Month 17 and a telephone contact at Month 20.
Pharmacokinetics: Trough serum concentrations of natalizumab was assessed at Months 3, 6, 9, 12, and 15, and at any Early Termination and Unscheduled visits in subjects previously treated with natalizumab in Study CD301.
Pharmacodynamics:

Mean change from baseline in circulating absolute lymphocyte count was also assessed at Months 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15, and at Follow-up Visit at Month 17.
Immunogenicity: This was assessed by evaluating the rate of occurrence of anti-natalizumab screening and blocking antibodies at Months 3, 6, 9, 12, and 15, and at the Follow-up Visit at Month 17.
Pharmacokinetic and Pharmacodynamic Analysis: Serum natalizumab concentrations and circulating absolute lymphocyte count data obtained from all randomized subjects were listed by subject. For the CD301 Natalizumab Responders Population, appropriate summary statistics of serum natalizumab concentrations during the Month 3, 6, 9, 12, and 15 Visits were prepared using data included in the PK analysis. Pharmacokinetic data collected at Early Discontinuation and Unscheduled visits also were summarized for the CD301 Natalizumab Responders Population. Mean circulating absolute lymphocyte counts at Months 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 in the CD301 Natalizumab Responders Population were summarized and plotted as a PD measure of natalizumab.

Reviewer's Comments: All the data on lymphocyte counts were reviewed by the clinical reviewer.
Immunogenicity: The number (%) of subjects who tested positive for screening anti-natalizumab antibodies and blocking anti-natalizumab antibodies was tabulated by visit for three subsets of subjects:

- natalizumab (CD301 treatment) + natalizumab (CD303 treatment)
- natalizumab (CD301 treatment) + placebo (CD303 treatment)
- placebo (CD301 treatment) + natalizumab (CD303 treatment)

Screening antibody positive status was defined by an anti-natalizumab antibody concentration $\geq$0.5 µg/mL. For blocking anti-natalizumab antibodies, any result not reported as "negative" was considered positive. A subject was considered to have persistent anti-natalizumab antibodies if two positive tests occurred at least 42 days apart, or if the subject's last observation was positive.

Pharmacokinetics:
A total of 1938 serum natalizumab concentration measures were obtained from 427 randomized subjects (213 natalizumab, 214 placebo) between Month 3 and Month 15. The 213 subjects randomized to the natalizumab group (300 mg fixed dose) received a mean actual natalizumab dose per total body weight (TBW) of 4.47 mg/kg (range: 1.79 – 7.89 mg/kg).
Serum Natalizumab Concentrations at Scheduled Visits (Months 3, 6, 9, 12, and 15):

Of the 1938 available serum natalizumab concentration measures, 1768 serum measures (91%) were obtained from samples collected from 420 subjects during scheduled visits at Months 3, 6, 9, 12, and 15. Of these, only 1382 serum measures from 400 subjects were considered evaluable and were included in the summary statistical analyses, with the remainder (386 serum measures) excluded. The 1382 evaluable serum natalizumab concentrations were summarized for the CD301 Natalizumab Responders Population, CD301 Placebo Responders Population, and ITT Population respectively.

Reviewer's Comments: Applicant stated the following: For the purposes of PK and PD analysis, excluded serum sample or circulating lymphocyte count data were those collected beyond ±3 days (72 hours) of the protocol designated scheduled sampling window at a certain visit, or from subjects who did not receive a designated dose at the corresponding month.

The majority (353; 91%) of the 386 sample results excluded from the PK summary statistical analyses met the exclusion criteria. However, two sample results from two subjects in the placebo treatment group were deemed anomalous and were excluded (14.0 µg/mL, collected 1 hour following dose conclusion at Month 12, and 59.8 µg/mL collected at Month 15 trough). Nine additional trough sample results in the natalizumab treatment group were deemed anomalous because they were more than three standard deviations above the group mean at the corresponding visits. Another 22 sample results from the natalizumab treatment group (11 each apparently collected 1 hour following dose conclusion at Month 6 and Month 12) with relatively low peak serum natalizumab concentrations (range: 0–24.0 µg/mL) also appeared anomalous and were thus excluded. For the purpose of comparison, summary statistics of serum natalizumab concentrations at evaluated time-points are presented in Table 28 for subjects receiving natalizumab treatment in the CD301 Natalizumab Responders, CD301 Placebo Responders, and the entire PK-evaluable ITT population (which also includes any subjects not included in either of the two subpopulations).

Table 28 Summary Statistics of Serum Natalizumab Concentration (Months 3, 6, 9, 12, and 15)

CD301 Response Category	Summary Statistics	Serum Natalizumab Concentrations (µg/mL)						
		Month 3 (Pre-Dose)	Month 6 (Pre-Dose)	Month 6 (Post-Dose)	Month 9 (Pre-Dose)	Month 12 (Pre-Dose)	Month 12 (Post-Dose)	Month 15 (Pre-Dose)
Natalizumab Responders	N	98	87	116	91	69	95	36
	Mean (SD)	7.1 (7.2)	11.1 (9.1)	92.2 (24.7)	10.7 (7.2)	14.7 (12.0)	102.4 (26.1)	13.8 (8.2)
	Range	0 – 32.2	0 – 46.2	53.8 – 208.3	0 – 31.6	0 – 69.2	54.4 – 210.3	0.7 – 28.1
	Median	5.9	9.5	90.2	9.6	12.1	100.1	12.0
Placebo Responders	N	20	21	24	14	11	17	9
	Mean (SD)	0 (0)	5.1 (6.7)	83.4 (14.5)	10.3 (9.2)	11.8 (8.5)	96.7 (24.7)	15.1 (8.8)
	Range	0	0 – 21.1	53.0 – 112.7	0.5 – 30.9	0.8 – 27.1	58.9 – 148.8	6.4 – 29.5
	Median	0	1.6	82.2	7.7	9.8	97.6	13.9
ITT Population	N	127	116	146	111	82	117	45
	Mean (SD)	6.0 (7.2)	10.0 (8.9)	91.2 (23.6)	10.9 (7.4)	14.2 (11.6)	100.4 (26.2)	14.0 (8.2)
	SD	7.2	8.9	23.6	7.4	11.6	26.2	8.2
	Range	0 – 32.2	0 – 46.2	53.0 – 208.3	0 – 31.6	0 – 69.2	35.0 – 210.3	0.7 – 29.5
	Median	3.9	8.0	88.6	9.6	11.9	97.2	12.1

This table includes only subjects randomized to receive natalizumab in Study CD303.
N/A = Not Available; Pre-Dose = pre-dose for trough concentration; Post-Dose = 1-hr after dose stopped for peak concentration.

In the natalizumab treatment group, trough serum natalizumab concentrations were quite variable but generally comparable across Months 3–15. However, mean trough serum

natalizumab concentrations did appear to increase slightly during repeated administration, possibly reflecting a small degree of drug accumulation that is unlikely to be clinically relevant.

Generally comparable Month 3 trough serum natalizumab concentrations were observed between the placebo and natalizumab treatment groups. In the placebo treatment group, quantifiable trough serum natalizumab concentrations observed at Month 3 can be attributed to natalizumab infusions administered during Study CD301. Nonetheless, no quantifiable trough and/or peak serum natalizumab concentrations in the placebo group were observed at Months 6, 9, 12, or 15, with the exception of three subjects (Subjects 561-010, 022-003, and 030-014) with serum natalizumab concentrations of only 0.3 μg/mL (1 hour after conclusion of placebo infusion at Month 6), 0.4 μg/mL (pre-dose at Month 9), and 0.3 μg/mL (pre-dose at Month 12). These three measurements were low and approached the LLQ of the assay for serum natalizumab concentrations (0.25 μg/mL).

Placebo Responders Population: In the CD 301Placebo Responders Population, a total of 67 subjects (34 natalizumab, 33 placebo) provided a total of 240 evaluable serum natalizumab concentration measures (116 and 124, respectively). The 34 subjects in the natalizumab treatment group received a mean actual natalizumab dose per TBW of 4.68 mg/kg (range: 2.80 – 6.12 mg/kg).

In the placebo treatment group, no quantifiable trough serum natalizumab concentrations were observed at Month 3 nor were they observed at Months 6, 9, 12, or 15 visits, with the exception of two subjects (Subjects 064-016 and 044-010) with serum natalizumab concentrations of 0.9 and 1.9 μg/mL, respectively, 1 hour after conclusion of placebo infusion at Month 12). These two measurements were low and approached the LLQ of the assay for serum natalizumab concentrations (0.25 μg/mL).

Intent-to-Treat Population:
Results for the ITT population were generally comparable to those of the CD301 Natalizumab Responders population. Peak and trough serum natalizumab concentrations during visits at Months 6 through 15 generally were generally comparable among the three evaluated populations. Natalizumab peak and trough profiles for the ITT population also were generally comparable to those observed in subjects participating in an intensive PK/PD substudy in Study CD301.

Study # CD 305 (Safety Study)
Title: A Phase II, International, Multicenter, Open Label Study of the Safety, Tolerability and Effectiveness of Three Intravenous Infusions of Antegren™ (Natalizumab) in Adolescents with Moderately to Severely Active Crohn's Disease
Study Sites: This study was conducted at 16 sites (by 16 investigators) in 3 countries, including 8 sites (7 of which enrolled subjects) in the United States (USA), 5 sites in the United Kingdom (UK), and 3 sites in Australia.
Study Period: Date First Site Initiated: 12 September 2002 and Date Last Subject Completed Week 20 Visit: 25 September 2003
Objectives:

Primary Objective: The primary objective of this study was to evaluate the safety and tolerability of natalizumab in an adolescent population of subjects with moderately to severely active Crohn's disease (CD).
Secondary Objective: The secondary objective of this study was to conduct a pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of treatment with natalizumab in an adolescent CD population, including analyses of natalizumab serum concentration, natalizumab binding to α4 integrin receptors, and changes in absolute lymphocyte counts.
Tertiary Objective: The tertiary objective of this study was to evaluate the effect of natalizumab on the clinical status of adolescent subjects with CD, assessed primarily by changes in subjects' Pediatric Crohn's Disease Activity Index (PCDAI) scores and quality-of-life assessments.
Methodology: This was a multicenter, open-label, single-arm study designed to examine the safety, tolerability, and effectiveness of IV infusions of natalizumab (3.0 mg/kg) administered once a month for up to 3 months in adolescent subjects (12–17 years of age) with moderately to severely active CD (PCDAI >30). The treatment period spanned 12 weeks. Thirty-eight subjects received IV infusions of natalizumab (3.0 mg/kg) at Weeks 0, 4, and 8 and were assessed through Week 12. The follow-up phase for this study comprised a visit at Week 20 and a telephone follow up of AEs at Week 32. During the study, subjects were allowed to remain on stable doses of oral 5-ASA compounds, oral steroids, antibiotics, and specified immunosuppressants, as well as nasogastric/nasoenteric tube feeding and elemental/polymeric diets. Herbal preparations, rectal 5-ASA compounds, rectal steroids, total parenteral nutrition (TPN), anti-tumor necrosis factor (TNF) therapy, and experimental agents were prohibited.
Test Product, Dose and Mode of Administration, Batch Number: Natalizumab was administered by IV infusion over approximately 60 minutes at a dose of 3 mg/kg from lot number F23003A.

Reviewer's Comments: The dose administered in this study is weight based compared to the fixed dosing regimen that is proposed for use in adults. Applicant stated that dosing was based on individual body weights due to the weight variability of the adolescent population.
Pharmacokinetics/Pharmacodynamics Sampling: The PK evaluation was based on analysis of natalizumab serum concentrations. The PD evaluations included assessments of saturation levels of α4 integrin receptor on circulating peripheral lymphocytes and changes in levels of circulating lymphocytes.

Serum samples for measurement of natalizumab concentrations were collected weekly from the 38 enrolled subjects (with the exception of Weeks 5, 6, and 7) during the 12-week treatment phase, including Week 12 and any Early Discontinuation visit, and then at Week 20. Subjects underwent additional, more intensive sampling around the first (Week 0) and third infusion (Week 8) (see Table 3 below). Blood samples for α4 integrin receptor saturation on circulating peripheral blood leukocytes were collected weekly (with the exception of Weeks 5, 6, and 7) up to and including Week 12 and any Early Discontinuation visit from 19 subjects enrolled at US study sites. At the time of the first (Week 0) and third (Week 8) infusions, additional samples were taken pre-infusion and 2

hours post-infusion. Circulating lymphocyte response was also assessed in the 38 enrolled subjects based on hematology assessments throughout the study. Lastly, immunogenicity (anti-natalizumab antibodies), assessed at Week 0 (pre-infusion), Week 12, and Week 20 (or Early Discontinuation), was evaluated in all 38 subjects to determine the rate of occurrence of both screening and blocking antibodies during the study.

Table 3 Blood Samples for Pharmacokinetic, Pharmacodynamic, and Immunogenicity Measurements

Visit	Anti-Natalizumab Antibodies	Natalizumab PK [a]	Natalizumab PD [b]
Screen			
Week 0 (pre-infusion)	√	√	√
(immediately post-infusion)		√	√
(2 hr. post-start of infusion)		√	√
(24 hr. post-start of infusion)		√	√
Week 1		√	√
Week 2		√	√
Week 3		√	√
Week 4 (pre-infusion)		√	√
Week 8 (pre-infusion)		√	√
(immediately post-infusion)		√	√
(2 hr. post-start of infusion)		√	√
(24 hr. post-start of infusion)		√	√
Week 9		√	√
Week 10		√	√
Week 11		√	√
Week 12	√	√	√
Week 20	√	√	
Early discontinuation	√	√	√
Infusion reaction SAE/AE	√	√	

[a] Taken at all study sites.
[b] Taken at USA sites only.
NOTE: Samples were obtained, when possible, ±2 hours for the 24-hour post-infusion blood draws and ±1 day for all additional post-infusion samples.

Eligible subjects who completed the treatment phase of the study (i.e., through Week 12) were given the opportunity to enroll into an open-label, chronic treatment protocol (Study ELN100226-CD352 [CD352]). Study CD352 would allow subjects to continue with monthly dosing of natalizumab. Subjects who declined or were not eligible to enter Study CD352 were followed for safety in Study CD305 up to Week 32.

Analytical Methods: (b)

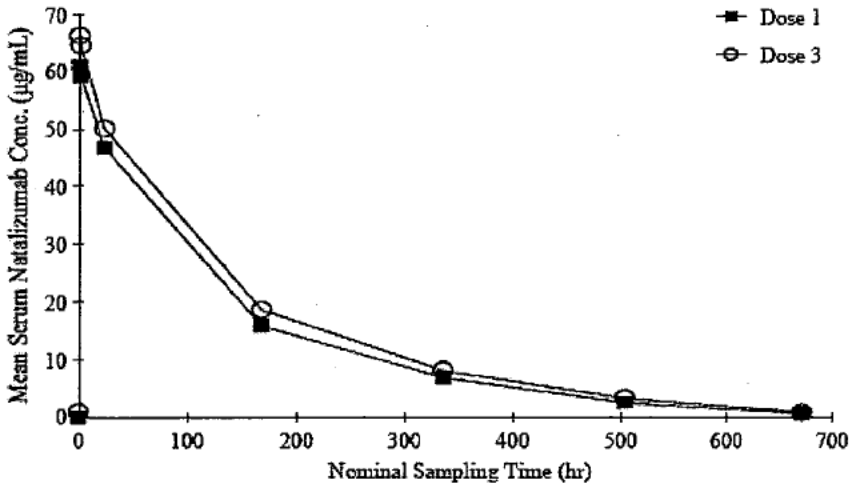
(b) (4)

Results:

Pharmacokinetics:

Natalizumab Serum Concentrations:

Serial blood samples for measuring natalizumab serum concentration were collected from 38 subjects after Dose 1 (Week 0) and 30 subjects after Dose 3 (Week 8) following IV infusion of the study drug (3 mg/kg). As illustrated in Figure 5, the mean serum natalizumab concentration-time profiles after the first (Week 0) and third (Week 8) infusions were very similar, showing peak concentrations immediately after drug infusion (61.0 and 66.3 µg/mL for Doses 1 and 3, respectively), followed by a multi-exponential decline in serum concentrations (i.e., relatively rapid drop within the first 24 hours after infusion, with a slower decline thereafter). By four weeks post-infusion, mean serum natalizumab concentrations had decreased to 0.6, 0.9, and 0.8 µg/mL (Doses 1, 2, and 3, respectively), approaching the lower limit of quantitation of the assay (0.25 µg/mL).



Natalizumab Pharmacokinetic Parameters:

Natalizumab PK parameters were calculated from serum concentrations following IV infusions of study drug at Weeks 0 and 8. Data were available from 38 subjects at Week 0 and 30 subjects at Week 8.

Serum natalizumab PK parameters for Doses 1 and 3, were generally comparable between the two infusions. The median peak level and t½ of natalizumab appeared to be comparable following the first (Week 0) and third (Week 8) infusions, respectively, and

little or no accumulation of natalizumab was observed with the repeated monthly dosing. A relatively high degree of inter-subject variability (coefficient of variation percent [CV%] ranging from approximately 29-177%) was observed for the selected PK parameters. Table 15 below shows summary statistics for serum natalizumab PK parameters for Doses 1 and 3.

Table 15 Selected Natalizumab Pharmacokinetic Parameters after Doses 1 and 3

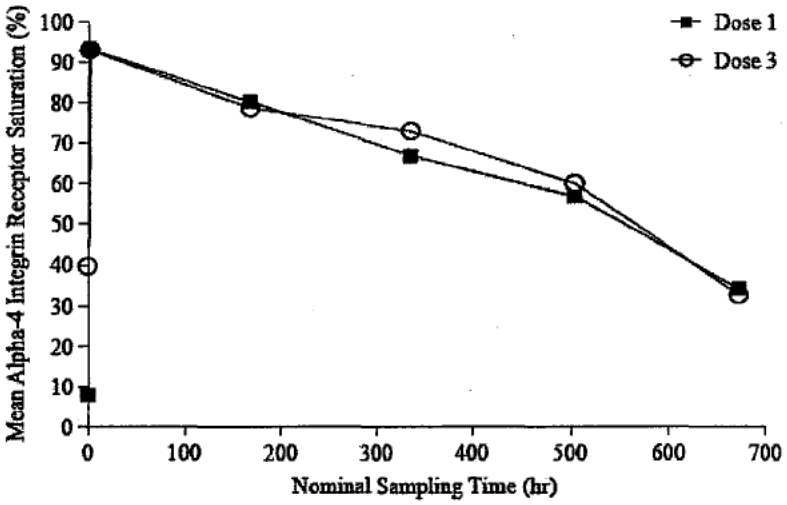
Dose		Cmax (µg/mL)	AUC(0-672)(hr*µg/mL)	t1/2(hr)	CL (mL/hr)	CL/TBW(mL/hr/kg)	Vd (mL)	Cmin (µg/mL)
1	N	38	38	38	38	38	38	0
	Mean (SD)	63.8 (18.7)	8910 (3347)	94.9 (29.3)	17.37 (5.51)	0.38 (0.14)	2305 (828)	ND
	CV%	29.4	37.6	30.9	31.7	36.6	35.9	ND
	Range	40.5 – 114.3	4464 -18466	48.7 – 170.6	5.63 – 34.10	0.16 – 0.70	668 – 4456	ND
	Median	57.4	8234	92.3	17.43	0.36	2158	ND
3	N	30	30	30	30	30	30	30
	Mean (SD)	70.3 (24.3)	9954 (3959)	111.0 (59.2)	17.64 (9.05)	0.37 (0.21)	2482 (1021)	0.9 (1.5)
	CV%	34.6	39.8	53.4	51.3	56.3	41.1	177.3
	Range	42.0 – 163.8	2959 -18066	47.4 – 262.7	7.45 – 52.72	0.17 – 1.01	771 – 4853	0.0 – 6.1
	Median	66.7	10730	96.3	17.06	0.28	2369	0.0

Pharmacodynamics

Serial blood samples for measuring percent α4 integrin receptor saturation were collected from 19 subjects after Dose 1 (Week 0) and 13 subjects after Dose 3 (Week 8) following IV infusion of the study drug.

The mean α4 integrin receptor saturation (%) *versus* nominal sampling time plots for Dose 1 and 3 are presented in Figure 6 and show that the profiles are generally comparable.

Figure 6 Mean Alpha-4 Integrin Receptor Saturation Levels (%) Over Time after Dose 1 (Week 0) and Dose 3 (Week 8)



Mean α4 integrin receptor percent saturation-time profiles were comparable for Doses 1 and 3, falling from approximately 93% at 2 hours after the start of infusion to 34.1% and 32.6% at 4 weeks post-infusion. Saturation levels four (4) weeks after the first, second, and third infusions were comparable (34.1%, 39.7%, and 32.6%, respectively).

Immunogenicity

Only 3 (7.9%) subjects were anti-natalizumab antibody-positive (screening and blocking antibodies) in this study. Screening antibody concentrations in these subjects ranged from 0.59–7.85 μg/mL, and blocking antibody titers ranged from 80–674.

Pharmacokinetic/Pharmacodynamic Conclusions

- The peak level (57.4 and 66.7 μg/mL) and half-life (92.3 and 96.3 h) of natalizumab appeared to be comparable following the first (Week 0) and third (Week 8) infusions, respectively,
- Generally time-invariant pharmacokinetics, and little or no accumulation of natalizumab were observed with repeated monthly dosing of natalizumab in adolescents.
- A relatively high degree of intersubject variability was observed for the calculated PK parameters.
- Mean α4 integrin receptor saturation fell from approximately 93% (2 hours after the start of IV infusion) to <40% four weeks post-infusion.
- The ranges for median change (%) in absolute lymphocyte counts from baseline at two and four weeks post-infusion of natalizumab were 106 – 122% and 45 – 65%, respectively.

The relatively low α4 integrin receptor saturation levels and fluctuating changes in absolute lymphocyte counts from baseline observed four weeks post-infusion suggest dose response studies in adolescent subjects might be of interest, but may not be necessary given the safety and effectiveness observed with the dose used in this study.

Reviewer's Comments: Applicant is not proposing the use of this product in the adolescent population at this time however, if they decide to in the future, the appropriate dose for this population will need to be further explored.

Study # CD 306

Title of study: A Phase II, Multicenter, Double-Blind, Placebo-Controlled Pilot Study of the Safety, Tolerability, and Efficacy of Intravenous Antegren™ (Natalizumab) in Crohn's Disease Subjects Concurrently Receiving Remicade® (Infliximab) and not in Remission (CDAI ≥150)

Investigator(s): This study was conducted in 17 investigational sites in the United States.

Study Period: Date First Site Initiated: 20 November 2002

Date Last Subject Completed Week 10 Visit: 24 July 2003

Objectives:

Primary: To evaluate the safety and tolerability of natalizumab in subjects with Crohn's disease (CD) concurrently receiving infliximab and not in remission.

Pharmacokinetic (PK)/Pharmacodynamic (PD) Objectives:

1. To determine the PK of natalizumab in subjects with CD receiving concomitant infliximab.
2. To determine and compare the PK of infliximab in subjects with CD receiving placebo or natalizumab.
3. To determine saturation (natalizumab binding) of α4 integrin receptors on circulating peripheral blood leukocytes in subjects receiving natalizumab and infliximab.
4. To determine changes in circulating lymphocyte count in subjects with CD receiving natalizumab and infliximab.

Study Design: This was a Phase 2, multicenter, double-blind, placebo-controlled, pilot study of the safety, tolerability and efficacy of natalizumab in CD subjects concurrently receiving infliximab (Remicade®) and not in remission (CDAI score □150). The primary objective of this study was to evaluate the safety and tolerability of three monthly (Week 0, 4, and 8) infusions of natalizumab with concurrent infliximab administrations every 8 weeks (at Weeks -2 and 6). Subjects were randomized in a 2:1 ratio to receive intravenous (IV) infusions of either natalizumab 300 mg or placebo at Weeks 0, 4, and 8. Subjects were stratified on the basis of baseline CDAI score (<250 or ≥250). Following the Week 0 Visit, subjects returned to the clinic for safety and efficacy assessments every two weeks until the Week 10 visit. Upon completion of the Week 10 visit of this study, subjects could elect to enroll in the open-label extension study, ELN100226-CD351.

Treatments: Natalizumab (300 mg) or placebo was administered as an IV infusion over approximately 60 minutes at a flow rate of approximately 2 mL/min at Weeks 0, 4, and 8. The lot numbers of study drug used in this study were G23001 for natalizumab and F85002 for placebo.

The Sponsor provided commercially available infliximab for use in the treatment phase of this study. Each single-use vial of Remicade® contained 100 mg infliximab. Following reconstitution with 10 mL of sterile water for injection, the resulting pH was approximately 7.2. The lot numbers used in this study were 02F113A, 02J091A, 02K131A, 03A085A, 03A023A, and 02L042A. Intravenous infliximab was administered according to the directions provided in the package insert at a dose of 5 mg/kg over a period of not less than two hours.

Pharmacokinetic/Pharmacodynamic Sampling:

Visit	Screening and blocking natalizumab antibody, infliximab concentration, and anti-infliximab antibody (HACA)	Natalizumab concentration (PK)	α4 integrin saturation (PD)
Screening (Week – 2	√(infliximab only)		
Week 0 (pre-infusion) (immediately post-infusion) (2 hr. post-start of infusion) (24 hr. post-start of infusion)	√(natalizumab only)	X X X X	X X
Week 1		X	X
Week 2		X	X
Week 3		X	X
Week 4 (pre-infusion)		X	X
Week 6	√ (infliximab only)		
Week 8 (pre-infusion) (immediately post-infusion) (2 hr. post-start of infusion) (24 hr. post-start of infusion)		X X X X	X X
Week 9		X	X
Week 10	√	√	X
Week 20	√	√	
Early discontinuation	√	√	X
Infusion reaction SAE/AE	√	√	

X Only drawn from a subset of subjects at selected sites.

√Drawn from all randomized subjects.

Note: Samples were obtained, where possible, ± 2 hours for the 24-hour post-infusion blood draws and ± 1 day for all additional post-infusion samples.

Blood samples for measurement of serum levels of natalizumab were collected from all subjects at Week 10, Week 20, and any Early Discontinuation Visit. Subjects participating in a PK/PD sub-study at selected sites only were to undergo more frequent blood testing. Serum concentrations of natalizumab were evaluated around Infusion 1 (Week 0) and Infusion 3 (Week 8) at pre-dose, and at 1, 2, and 24 hours, and at 1 and 2 weeks (Infusions 1 and 3), and at 3 and 4 weeks (Infusion 1 only) post-start of infusion. The week-4 sample for Infusion 1 was to be collected prior to the second infusion

Blood samples for the measurement of serum infliximab concentrations were collected from all subjects at Weeks -2, 6, 20, and any Early Discontinuation visits.

The α4 integrin receptor percent saturation levels were to have been evaluated for the first (Week 0) and third (Week 8) infusions as shown in table 3 above.

Immunogenicity was assessed by evaluating the rate of occurrence of screening natalizumab antibodies, blocking natalizumab antibodies, and anti-infliximab antibodies (human anti-chimeric antibody, HACA). Blood samples for screening natalizumab antibody measurement were collected from all subjects at Weeks 0, 20, and any Early Discontinuation visit.

Analytical Methods: The concentration of natalizumab in serum was determined using

(b) (4)

[redacted]

Results:

A total of 103 subjects were screened, of whom 52 were randomized to natalizumab and 27 to placebo at 17 sites.

Table 9: Demography and Baseline Characteristics (ITT Population)

Variable Statistic or Category	Placebo + Infliximab (n=27)	Natalizumab + Infliximab (n=52)	Overall (n=79)
Age (yr)			
N	27	52	79
Mean	38.9	39.9	39.5
SD	13.20	12.60	12.73
Median	35.0	38.5	38.0
Min., Max.	19, 72	20, 69	19, 72
Age Group (yr) N (%)			
<=65	26 (96)	51 (98)	77 (97)
>65	1 (4)	1 (2)	2 (3)
Gender N (%)			
Female	10 (37)	28 (54)	38 (48)
Male	17 (63)	24 (46)	41 (52)
Race N (%)			
Black	2 (7)	2 (4)	4 (5)
White	23 (85)	49 (94)	72 (91)
Asian	0 (0)	0 (0)	0 (0)
Hispanic	1 (4)	0 (0)	1 (1)
Other	1 (4)	1 (2)	2 (3)
Smoking Status of More Than 10 Cigarettes per Day N (%)			
Yes	3 (11)	7 (13)	10 (13)
No	24 (89)	45 (87)	69 (87)

Variable Statistic or Category	Placebo + Infliximab (n=27)	Natalizumab + Infliximab (n=52)	Overall (n=79)
Weight (kg)			
N	27	52	79
Mean	74.8	72.6	73.4
SD	16.81	17.98	17.51
Median	70.9	69.7	70.2
Min., Max.	45, 127	44, 117	44, 127
Weight Group (kg) N (%)			
<50	1 (4)	5 (10)	6 (8)
50-75	15 (56)	25 (48)	40 (51)
76-100	10 (37)	17 (33)	27 (34)
>100	1 (4)	5 (10)	6 (8)
Height (cm)			
N	27	52	79
Mean	173.2	170.1	171.2
SD	10.62	12.02	11.59
Median	174.0	170.2	172.0
Min., Max.	150, 189	147, 193	147, 193
Body Mass Index (kg/m^2)			
N	27	52	79
Mean	24.8	24.9	24.9
SD	4.43	4.95	4.75
Median	24.9	24.0	24.6
Min., Max.	17, 39	17, 45	17, 45

All 79 subjects randomized received at least one infusion of one of the study drugs. Natalizumab PK parameters were calculated for individual subjects in the PK/PD sub-study. In addition, change in circulating absolute lymphocyte counts was assessed in the 79 randomized subjects. Infliximab PK data from 78 subjects were used in the analysis.

Natalizumab Pharmacokinetics:

Serum Natalizumab Concentrations:

Serum samples for natalizumab concentrations were collected from 72 randomized subjects, of whom 25 subjects received placebo+infliximab and 47 subjects received natalizumab (300 mg) +infliximab. The mean actual natalizumab dose per total body weight for the 47 subjects in the natalizumab+infliximab group was 4.35 mg/kg (range: 2.56 – 6.51 mg/kg).

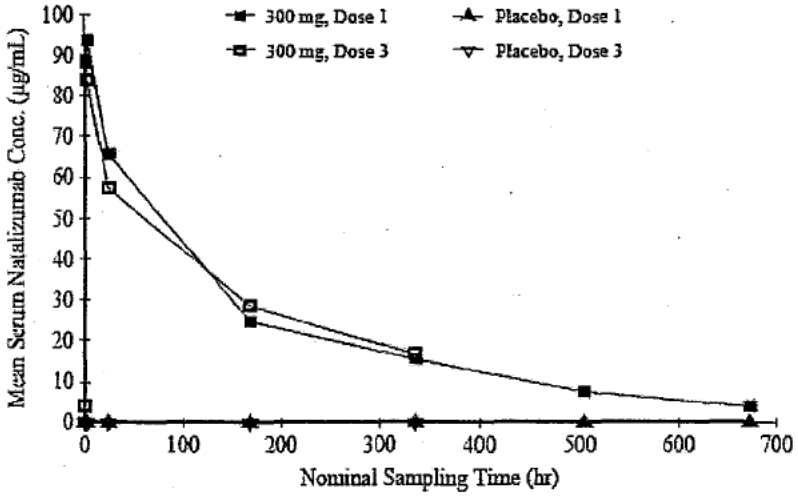
PK/PD Sub-Study:

A total of 32 subjects (18 receiving natalizumab+infliximab providing 195 natalizumab concentration-time results; 14 receiving placebo+infliximab providing 142 natalizumab concentration-time results) from 11 selected sites participated in the intensive PK/PD substudy. There were eight male and ten female subjects in the natalizumab+infliximab group, and all subjects were Caucasians. There were eight male and six female subjects in the placebo+infliximab group, and all subjects, with one exception, were Caucasian. Based on the sample exclusion criteria 11 serum natalizumab concentration results (nine from natalizumab+infliximab and two from placebo+infliximab group) were excluded from summary statistics and mean concentration-time plots, leaving a total of 186 data points for natalizumab+infliximab group (122 from Infusion 1 and 64 from Infusion 3) and 140 data points for placebo+infliximab group (84 from Infusion 1 and 56 from Infusion 3) included in the summary analyses.

Nearly all of the 142 serum samples collected from the 14 subjects receiving placebo had no measurable natalizumab concentrations, except for one sample collected from Subject 820-002 (Week 1; 0.3 µg/mL), which was only slightly above the LLOQ of the assay (0.25 µg/mL).

Inserted below (Figure 8) is a plot of mean serum natalizumab concentration versus-nominal sampling time As illustrated in Figure 8, the mean serum natalizumab concentration-time profiles after the first (Week 0) and third (Week 8) infusions were very similar, showing peak concentrations of 93.7 and 88.3 µg/mL for Infusion 1 and Infusion 3, respectively (observed approximately 1 - 2 hours after the start of the study drug infusion, followed by a multi-exponential decline in serum concentrations (i.e., relatively rapid drop within the first 24 hours after infusion, with a slower decline thereafter). By four weeks post-infusion, mean serum natalizumab concentrations had decreased to 3.9 and 4.3 µg/mL for Infusions 1 and 2, respectively.

Figure 8 Linear Plots of Mean Serum Natalizumab Concentration-Time Profiles after Infusion 1 and Infusion 3



Inserted below is a tabular summary of natalizumab serum concentrations after the first and second infusion:

Table 4.1 Summary of Natalizumab Serum Concentrations (ug/mL) After Dose 1 (Week 0) and Dose 3 (Week 8): PK/PD Substudy

	Dose 1 (Week 0)				Dose 3 (Week 8)			
Scheduled Time	N	Mean	s.d.	CV (%)	N	Mean	s.d.	CV (%)
0 Hour Pre-Infusion	16	0.0	0.00	.	11	4.3	4.71	110.2
Immediately Post-Infusion	15	87.9	27.30	31.1	11	88.3	32.05	36.3
2 Hour Post-Infusion	16	93.7	27.65	29.5	8	83.9	36.36	43.3
24 Hour Post-Infusion	14	65.9	19.77	30.0	10	57.5	24.40	42.5
1 Week Post-Infusion	12	24.8	12.13	49.0	9	28.5	21.68	76.0
2 Week Post-Infusion	18	15.5	7.46	48.1	15	16.7	9.68	58.0
3 Week Post-Infusion	16	7.5	4.50	59.9	.	.	.	.
4 Week Pre-Infusion	15	3.9	3.20	82.0	.	.	.	.

Note 1: Trough serum concentration level of natalizumab at Week 8 is the pre-infusion level of Dose 3 assessed at Week 8.
2: Serum natalizumab concentrations below the lower limit of quantification (LLOQ) 0.25 ug/mL were treated as zero for calculation purposes.
3: Data excluded from PK/PD analysis:- CD816001 and CD816007- CD816001, week 1; CD820004, Week 4, Pre-Infusion and Week 8, 2 Hours Post-Start Infusion.

Pharmacokinetics of Natalizumab

PK/PD Sub-Study

Eighteen subjects in the PK/PD sub-study received natalizumab in addition to infliximab. Infusion 1 PK parameters were not calculated for two of these subjects, 816-001 and 816-007, because missing samples immediately post-infusion precluded unbiased estimation of C_{max} and volume of distribution. In addition, four subjects (806-002, 813-002, 815-001, and 816-007) had only a Week 10 PK sample collected after Infusion 3 and thus Infusion 3 PK parameters for these subjects could not be calculated. Subjects 818-002 and 818-003 did not receive Infusions 2 and 3, so their natalizumab pharmacokinetic parameters after Infusion 3 could not be calculated. Lastly, for Subject 820-004, two serum samples were deemed anomalous and excluded from the PK parameter calculations: Week 4, pre-infusion sample, 120.1 µg/mL; and Week 8, 2-hours post-start of infusion sample, 4.0 µg/mL.

Overall, pharmacokinetic parameters were calculated from 16 of the 18 subjects enrolled in the PK/PD sub-study who were treated with natalizumab. Eleven of these 16 subjects received all three scheduled natalizumab 300-mg doses. The mean total body weight and actual natalizumab dose per total body weight for these 16 subjects (seven male and nine female, all Caucasian) were 74.3 kg and 4.23 mg/kg, respectively. For the 11 subjects completing all three infusions, the mean total body weight and actual natalizumab dose per total body weight were 75.0 kg and 4.24 mg/kg, respectively.

Summary statistics for all calculated natalizumab PK parameters are shown in Table 4.2. Table 17 shows summary statistics of selected serum natalizumab PK parameters for Infusion 1 and Infusion 3, which were generally comparable between infusions. For both infusions, mean serum natalizumab concentrations were observed to reach maximum levels at approximately 1 - 2 hours after the start of infusion.

Table 4.2 Summary of Natalizumab Pharmacokinetic Parameters After Dose 1 (Week 0) and Dose 3 (Week 8): PK/PD Substudy

	Dose 1 (Week 0) (n=16)					Dose 3 (Week 8) (n=11)				
Variable	N	Mean	S.D.	Median	Min., Max	N	Mean	S.D.	Median	Min., Max
Tmax (hr)	16	1.8	0.50	2.0	1, 3	11	1.7	0.41	2.0	1, 2
Cmax (ug/mL)	16	96.0	26.72	96.1	59, 146	11	93.5	32.79	107.6	15, 124
AUC (0-last) (ug*hr/mL)	16	15900	6185.7	15460	8425, 29802	11	12533	6610.7	13756	166, 19594
Kel (1/hr)	16	0.005	0.0017	0.005	0.002, 0.009	11	0.013	0.0197	0.004	0.004, 0.068
T 1/2 (hr)	16	158.7	61.49	147.7	77, 310	11	128.8	68.86	154.8	10, 195
AUC (0-672 hr) (ug*hr/mL)	16	16040	6154.0	16112	8436, 29787	11	15411	8422.3	16391	365, 23944
CL (mL/hr)	16	20.4	8.09	18.1	10, 35	11	98.0	241.19	18.3	13, 823
VD (mL)	16	4444.2	2092.1	4002.2	2148, 10179	11	4348.9	2639.6	3818.3	2603, 12047
VSS (mL)	16	3704.9	1519.3	3655.6	1024, 6700	10	3006.6	1011.2	3019.3	1190, 4822
Cavg (ug/mL)						11	22.9	12.53	24.4	1, 36
Cmin (ug/mL)						11	4.3	4.71	3.2	0, 16
% Fluctuation						11	705.7	761.30	354.3	292, 2819

Table 17 Summary Statistics for Selected Natalizumab Pharmacokinetic Parameters

Infusion		T_{max} (hr)	C_{max} (µg/mL)	$AUC_{(0-672)}$ (hr*µg/mL)	$t_{½}$ (hr)	CL (mL/hr)	V_d (mL)	C_{min} (µg/mL)
1	N	16	16	16	16	16	16	0
	Mean (SD)	1.84 (0.50)	96.0 (26.7)	16040 (6154)	158.7 (61.5)	20.44 (8.09)	4444 (2092)	ND
	Range	1.13 – 3.05	59.2 – 146.2	8436 - 29787	76.7 – 309.9	9.53 – 34.64	2148 - 10179	ND
	Median	2.00	96.1	16112	147.7	18.15	4002	ND
3*	N	11	11	11	11	11	11	11
	Mean (SD)	1.74 (0.41)	93.5 (32.8)	15411 (8422)	128.8 (68.9)	98.01 (241.19)	4349 (2640)	4.3 (4.7)
	Range	1.13 – 2.33	15.3 – 123.6	365 - 23944	10.2 – 195.1	12.53 – 822.61	2603 - 12047	0 – 15.6
	Median	2.00	107.6	16391	154.8	18.30	3818	3.2

ND = Not Determined.
*Descriptive statistics for Infusion 3 parameter values include results obtained from Subject 811-005 (anti-natalizumab antibody positive) who had very low natalizumab serum exposure; mainly accounting for the very wide range of observed PK parameter values after Infusion 3.
Note: Calculation of some Infusion 3 PK parameters involved extrapolation from 336 – 672 hours (or 2 - 4 weeks after Infusion 3, since serum samples were only collected up to two weeks post-infusion [Week 10 of the study]).
This extrapolation was deemed not to have significantly biased the results as the magnitude of the extrapolation was typically low, and generally comparable Infusion 1 and 3 PK parameter values were obtained.

Pharmacodynamics

From the 32 subjects (18 natalizumab+infliximab, 14 placebo+infliximab) participating in the intensive PK/PD substudy, a total of 227 α4 integrin receptor percent saturation values (136 from natalizumab+infliximab and 91 from placebo+infliximab subjects) were measured from collected samples. Among those 227 measurements, only 10 were excluded from the summary statistics calculations and mean α4 integrin receptor percent saturation versus nominal sampling time plots. Among the 18 subjects receiving natalizumab+infliximab who provided evaluable α4 integrin receptor percent saturation data, 13 received all three natalizumab infusions per protocol.

Table 4.3 Alpha-4 Integrin Receptor Saturation Levels (Percent) After Dose 1 (Week 0) and Dose 3 (Week 8): PK/PD Substudy

	Dose 1 (Week 0)						Dose 3 (Week 8)					
Scheduled Time	N	Mean	s.d.	Median	Min	Max	N	Mean	s.d.	Median	Min	Max
0 Hour Pre-Infusion	15	7.5	3.00	6.7	3.2	12.8	11	56.1	33.50	72.8	4.5	86.4
2 Hour Post-Infusion	14	98.1	5.04	97.2	91.1	108.9	8	96.9	2.53	96.9	93.0	101.1
1 Week Post-Infusion	12	88.7	7.76	87.5	75.6	100.4	8	73.4	30.18	83.4	2.7	92.6
2 Week Post-Infusion	17	80.1	11.41	78.7	59.7	101.4	11	72.1	31.20	89.1	2.7	94.6
3 Week Post-Infusion	16	71.3	12.55	70.6	41.8	89.9	.	.	.	.	.	.
4 Week Pre-Infusion	15	62.2	24.82	64.8	5.3	94.7	.	.	.	.	.	.

In the natalizumab-treated subjects, mean α4-integrin receptor percent saturation at baseline, before the first infusion, was 7.5 ± 3.0%. For both Infusions 1 and 3, the observed median α4 integrin receptor percent saturation was maximal (~100%) at the first scheduled sampling within each infusion interval (2 hours after the start of IV infusion), consistent with the achievement of peak serum natalizumab concentrations near the end of the 1-hour IV infusion. Median α4 integrin receptor percent saturation values declined thereafter during each monthly infusion interval. Median α4 integrin receptor percent saturation levels four (4) weeks after the first and second infusions were comparable (65% and 73%, respectively; Table 4.3), as well as to those of a previous Phase III study AN100226-CD301 in which anti-TNF-αtherapy (including infliximab) was prohibited, indicating little or no readily apparent effect of infliximab on natalizumab PD.

As expected, placebo-treated subjects demonstrated relatively low percentage saturation of α4 integrin receptors (mean values < 8%) at all evaluated time points (data on file at Elan Pharmaceuticals).

Immunogenicity

One (2%) natalizumab + infliximab subject tested positive for anti-natalizumab antibodies in the screening assay and 2 (4%) natalizumab + infliximab subjects tested positive for blocking anti-natalizumab antibodies (at Week 10). One of these subjects also tested positive for HACA at Weeks -2 and 6.

Ten (12.7%) of the 79 subjects tested positive for HACA; 2 subjects in the natalizumab + infliximab group were positive for HACA at Week -2 (prior to the first infliximab infusion in the study; subjects were required to have had prior treatment with infliximab prior to randomization), while 8 subjects became positive for HACA after randomization (i.e., post-baseline or after the first infusion of study drug). Of the 8 subjects who tested positive for HACA post-baseline (i.e., randomization), 6 (12%) of the 52 subjects were in the natalizumab + infliximab group and 2 (7%) of the 27 subjects were in the placebo + infliximab group.

Applicant's Conclusions:

Based on the following pharmacokinetic, pharmacodynamic, and immunogenicity results, there was no evidence to suggest any drug-drug interactions exist with the co administration of natalizumab and infliximab:

- Serum natalizumab pharmacokinetics was time-invariant and indicated little or no accumulation upon repeated infusion. Adequate α4 integrin receptor saturation and elevation of circulating lymphocyte levels were generally maintained throughout the 10-week study treatment phase in subjects receiving natalizumab+infliximab treatment. Based on comparisons to a previous Phase III study in which anti-TNFα therapy (including infliximab) was prohibited, little or no effect of infliximab on natalizumab serum concentrations or pharmacokinetics/pharmacodynamics was observed in this study.
- Natalizumab treatment had no readily apparent effect on trough infliximab concentrations during co-administration of both compounds, though the likely high intra-subject variability precluded a more definitive assessment.
- Two (4%) natalizumab+infliximab subjects tested positive for blocking anti-natalizumab antibodies and eight subjects, 6 (12%) of 48 natalizumab+infliximab subjects and 2 (8%) of 26 placebo+infliximab subjects tested positive for anti-infliximab antibodies during the treatment phase. The presence of HACA did not appear to increase the risk of developing anti-natalizumab antibodies and although the numbers are very small, the presence of either anti-natalizumab or anti-infliximab antibodies did not appear to affect efficacy measures in this study.

Reviewer's Comments: The lymphocyte count data is being reviewed by the clinical reviewer.

Study # 307

Title of study: A Phase III, Multicenter, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Intravenous Natalizumab in Subjects with Moderately to Severely Active Crohn's Disease with Elevated C-reactive Protein

Investigator(s): This study was conducted in 114 investigational sites in North America, Europe, and selected countries from the rest of the world (RoW).

Study Period: Date First Subject Enrolled: 29 March 2004; Date Last Efficacy (Week 12) Visit Completed: 14 March 2005

Objectives: Pharmacokinetic/Pharmacodynamic Objectives and Endpoints:

1. To determine the pharmacokinetics of natalizumab in subjects with moderately to severely active CD and elevated CRP as measured by:
   - Serum concentrations of natalizumab (pre- and post-infusion) at Weeks 0, 4, and 8.
2. To determine changes in circulating absolute lymphocyte count as determined by:
   - Mean change and percent change from baseline (Week 0) in circulating absolute lymphocyte count at Weeks 4, 8, 12, and 20 or Early Discontinuation.

Immunogenicity Objective and Endpoint:

To evaluate the immunogenicity of natalizumab in subjects with moderately to severely active CD and elevated CRP as measured by:

- Proportion (%) of subjects who develop screening and blocking anti-natalizumab antibodies by Week 12 and Week 20

Methodology: This was a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study in subjects with moderately to severely active CD (based on clinical evaluation and CDAI score ≥220 to ≤450) and elevated CRP levels (defined as >2.87 mg/L, the upper limit of normal [ULN]) as assessed by the study central laboratory at the screening visit. 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. Randomization was stratified by site of enrollment.

Following the Week 0 visit, subjects returned to the clinic for safety and efficacy assessments at Weeks 4, 8, and 12. Subjects returned for safety assessments at Week 20 unless they enrolled into the open-label extension study, ELN100226-CD351 (CD351), after completing all visits up to Week 12 of Study ELN100226-CD307 (CD307). All subjects enrolling in Study CD351 did so without knowledge of their treatment assignment in Study CD307.

Treatments: Natalizumab was provided in clear, stoppered, individual 15–mL vials at a concentration of 20 mg/mL in 10 mM phosphate buffer, 140 mM NaCl and 0.02% polysorbate 80. All infusions were made up in 100–mL bags of 0.9% saline provided by Elan Pharmaceuticals, Inc (Elan). Natalizumab was administered as an IV infusion of 300 mg over approximately 60 minutes at a flow rate of 2 mL/min. All subjects were observed for 2 hours following the start of each infusion. Subjects in the natalizumab group received natalizumab from drug product lot numbers H48003, H48006, and J48002.

Placebo vials were provided in matching 15–mL vials containing 10 mM phosphate buffer, 140 mM NaCl and 0.02% polysorbate 80. All placebo infusions were made up in 100–mL bags of 0.9% saline provided by Elan and administered IV over approximately 60 minutes at a flow rate of 2 mL/min. All subjects were observed for 2 hours following the start of each infusion. Subjects in the placebo group received placebo from lot number H85001.

Duration of Treatment: Study drug (either natalizumab or placebo) was administered monthly (i.e., every 4 weeks) for a total of three doses in 12 weeks. The safety follow-up period consisted of a clinic visit at Week 20. Therefore, a subject's study participation in the study could be up to 13 to 14 weeks (including the 7- to 14-day screening period) if they enrolled into an open-label extension study (CD351), or 21 to 22 weeks if they continued through the follow-up phase of Study CD307. For those subjects who did not enroll in the open-label extension study, the safety follow-up period was extended beyond the Week 20 Visit in order to complete additional testing related to the risk of developing PML.

Pharmacokinetic Sampling: Serum concentrations of natalizumab were assessed pre-dose and a single sample 1–3 hours post-dose at Weeks 0, 4, 8, 12, and Early Discontinuation prior to Week 12.

Pharmacodynamics: The absolute and percent change in circulating absolute lymphocyte count from baseline was assessed at Weeks 4, 8, 12, and 20 or Early Discontinuation in all subjects.

Immunogenicity: This was assessed by evaluating the rate of occurrence of anti-natalizumab antibodies.

Analytical Methods: The concentration of natalizumab in patient sera was determined using an ELISA "sandwich" assay in which antibodies bind to both VLA-4 binding domain (capture) and the fragment crystallizable (F_c) ends of the natalizumab molecule (enzyme conjugate). LOQ was 250 pg/mL.

Pharmacokinetic Analysis and Statistical Methods: Serum natalizumab concentration versus time profiles were presented as box plots for subjects receiving natalizumab treatment. For all randomized subjects serum natalizumab concentration data collected pre- and post-infusion at Weeks 0, 4, and 8 (infusions 1, 2, and 3) were summarized and tabulated. The potential effects of subject demographics, pharmacodynamic measures, and immunogenicity data on serum natalizumab concentrations were explored.

Pharmacodynamics: Individual circulating absolute lymphocyte data (absolute count, absolute change and percent change from baseline) were listed by treatment (placebo or 300 mg natalizumab), subject number, and visit number (Weeks 0, 4, 8, 12, and 20, or Early Discontinuation), and summarized (n, mean, SD, min, median, max) by treatment and visit number. The mean circulating absolute lymphocyte data were plotted versus the visit week (0 to 20), and visually inspected and compared between natalizumab- and placebo-treated subjects.

Reviewer's Comments: This is being reviewed by the clinical reviewer.

Immunogenicity: The number and percentage of subjects who developed antibodies were tabulated with or without immunosuppressant use.

Results:

Serum Natalizumab Concentrations Results

A total of 3260 serum natalizumab concentration measures were obtained from 503 subjects (257 natalizumab-treated and 246 placebo-treated) participating in Study CD307, which included peak and/or trough samples collected from Week 0 to Week 12. The date of last sampling for this dataset was 14 March 2005. A copy of the final Bioanalytical Report with testing dates of 06 January 2005 to 18 August 2005 was provided.

A total of 3125 (95.9%) serum natalizumab concentration measures were considered evaluable from 503 randomized subjects (257 natalizumab-treated and 246 placebo-treated). The remaining 135 (4.1%) measures were excluded based on the following criteria:

- Collected beyond the protocol-designated sampling time window (±3 days of a protocol-designated visit).
- Deemed anomalous by the study pharmacokineticist based on calculation and/or scientific judgment (e.g., a concentration value that is beyond mean ±3 SD at a protocol-designated nominal sampling time).

One subject (CD807-702) was randomized to placebo, but received natalizumab infusions in this study and thus was included in the natalizumab treatment group for the analysis of serum natalizumab concentration data. The 257 subjects randomized to the natalizumab treatment group received a mean actual natalizumab dose per total body weight (TBW) of 4.43 mg/kg (range: 1.66–7.52 mg/kg).

Summary statistics of evaluable trough (Weeks 0, 4, 8, and 12) and peak (Weeks 0, 4, and 8) serum natalizumab concentrations are presented in Table 41 stratified by study week and treatment group.

Table 41 Summary of Serum Natalizumab Concentrations (mcg/mL)

	Nominal Sampling Time / Sample Relative to Infusion							
	Week 0		Week 4		Week 8		Week 12	ED
Treatment Group / Statistic	Pre-Infusion	Post-Infusion	Pre-Infusion	Post-Infusion	Pre-Infusion	Post-Infusion	Not Applicable	Not Applicable
Placebo								
N	241	238	226	223	210	198	222	30
Mean	0.03	0.00	0.00	0.01	0.00	0.05	0.00	0.00
s.d.	0.329	0.019	0.039	0.141	0.000	0.375	0.000	0.000
Min.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Max.	5.0	0.3	0.5	1.8	0.0	3.9	0.0	0.0
Natalizumab								
N	251	248	209	217	187	213	193	19
Mean	0.00	91.29	4.13	90.07	5.72	91.26	5.66	15.32
s.d.	0.000	55.626	3.727	32.805	6.138	43.751	6.383	23.996
Min.	0.0	11.2	0.0	19.1	0.0	11.7	0.0	0.0
Median	0.00	81.70	3.20	85.60	4.20	81.80	3.90	2.80
Max.	0.0	701.0	17.7	240.8	39.4	359.1	32.7	84.6

Note 1: ED = Early Discontinuation

In the natalizumab-treated group (1537 evaluable sample measures total), peak and trough serum natalizumab concentrations were variable between individuals, but mean values of the respective measures at the evaluated time points were comparable throughout the evaluation period. Mean (SD) peak (post-infusion) serum natalizumab concentrations were 91.3 (55.6), 90.1 (32.8), and 91.3 (43.8) μg/mL at Weeks 0, 4, and 8, respectively. Mean (SD) trough serum natalizumab concentrations were 4.1 (3.7), 5.7 (6.1), and 5.7 (6.4) μg/mL at Weeks 4, 8, and 12, respectively.

As expected, non-quantifiable (below level of quantitation, BLQ) serum natalizumab concentrations were obtained in all natalizumab-treated subjects pre- infusion at Week 0. Serum natalizumab concentrations, collected at variable times after the last dose administered from natalizumab-treated subjects who discontinued early, ranged from 0.0–84.6 μg/mL. As expected, in the placebo-treated group (1588 evaluable sample measures total) nonquantifiable (BLQ) serum natalizumab concentrations were typically obtained (1577 evaluable samples; 99.3%) at all evaluated collection time points, with the exception of 11 (0.7%) evaluable sample measures (all ≤5.0 μg/mL) from 10 subjects.

The presence of anti-natalizumab antibodies results in very low (non-quantifiable) natalizumab serum trough concentrations, which are likely due to increased serum clearance.

Table 41 Summary of Serum Natalizumab Concentrations (mcg/mL)

	Nominal Sampling Time / Sample Relative to Infusion							
	Week 0		Week 4		Week 8		Week 12	ED
Treatment Group / Statistic	Pre-Infusion	Post-Infusion	Pre-Infusion	Post-Infusion	Pre-Infusion	Post-Infusion	Not Applicable	Not Applicable
Placebo								
N	241	238	226	223	210	198	222	30
Mean	0.03	0.00	0.00	0.01	0.00	0.05	0.00	0.00
s.d.	0.329	0.019	0.039	0.141	0.000	0.375	0.000	0.000
Min.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Max.	5.0	0.3	0.5	1.8	0.0	3.9	0.0	0.0
Natalizumab								
N	251	248	209	217	187	213	193	19
Mean	0.00	91.29	4.13	90.07	5.72	91.26	5.66	15.32
s.d.	0.000	55.626	3.727	32.805	6.138	43.751	6.383	23.996
Min.	0.0	11.2	0.0	19.1	0.0	11.7	0.0	0.0
Median	0.00	81.70	3.20	85.60	4.20	81.80	3.90	2.80
Max.	0.0	701.0	17.7	240.8	39.4	359.1	32.7	84.6

Note 1: ED = Early Discontinuation.
2: Subject 807-702 was randomized to placebo, but received natalizumab infusions in this study and is included in the natalizumab group for analysis of PK data.

Immunogenicity:
Overall, 23 (9.5%) of the 241 natalizumab-treated subjects were reported to have tested positive for screening anti-natalizumab antibodies (concentration ≤0.5 µg/mL) through Week 12. A total of 19 (86%) of 22 anti-natalizumab antibody-positive and 187 (86%) of 218 antibody-negative subjects developed AEs. Given that the incidence rate due to positive anti-body in this study was based on the Week 12 assessment, no determination of antibody persistence was done.

Applicant's Conclusions:

Pharmacokinetics:
In natalizumab-treated subjects, mean values of the various PK measures at the evaluated time points were generally comparable throughout the evaluation period.

An immunogenic response to natalizumab appears to result in very low (non-quantifiable) natalizumab serum trough concentrations, which may be due to increased serum clearance.

Study # 351
Title of study: A Phase III, Multicenter, Open-Label, Long-Term Study of the Safety, Tolerability, and Efficacy of Intravenous Antegren™ (Natalizumab) in Crohn's Disease Subjects Who Have Previously Participated in Antegren™ Crohn's Disease Studies

Investigator(s): 181 investigational sites in North America, Europe, and selected countries from the rest of the world (RoW) have enrolled subjects in this study.
Study Period: Date First Subject Enrolled: 12 January 2003; Date Last Visit Completed: 30 March 2005
Objectives: This study did not have any PK or PD objectives it was mainly a long-term safety study however, serum samples were collected and included in the population pK analysis.
Methodology: This was a Phase III, multicenter, open-label, long-term study in Crohn's disease (CD) enrolled subjects who had participated in Studies CD251, CD301, CD303, CD306, or CD307. In Study CD351 subjects received their first 300-mg natalizumab infusion at Week 0 (the baseline visit) and returned to the clinic at monthly intervals (defined as a 4-week period) to receive subsequent natalizumab infusions and for assessments of safety and efficacy until the Month 24 Visit. All subjects were followed for safety for an additional 3 months after the last infusion. Those subjects who withdrew from the study, where possible, completed an Early Discontinuation Visit and also were followed for safety for an additional 3 months following their last infusion. At each study visit, all, or a combination of some of the following procedures were conducted: Medical history, Physical examination, Vital signs, Laboratory evaluations, Crohn's Disease Activity Index (CDAI), Study drug administration by infusion, Blood sample collection for assessment of hematology, biochemistry, anti-nuclear antibodies (ANA), serum natalizumab levels, anti-natalizumab antibodies, and pregnancy testing, Urine sample collection for urinalysis and pregnancy testing, Assessment of adverse events (AEs) (including a telephone call 24 hours after each of the first of three infusions, Recording of concomitant medications and rescue intervention.
Treatments: Natalizumab (300 mg) was administered by intravenous infusion once every 4 weeks. Clinical Trial Product (Product Code AN100226): A total of 630 subjects received natalizumab (AN100226) from lot numbers G23001A, G23001B, G23005A, and G23005C.
Commercial Process Product (Product Code BG00002-B): Once the appropriate regulatory and ethical approvals were granted, a phased introduction of natalizumab commercial process product (BG00002-B) was undertaken to replace the natalizumab clinical trial process product (AN100226). A total of 965 subjects had received at least one infusion of commercial process product (BG00002-B) from lot numbers H48001A, H48002A, J48003D, H48006B, H48006D, and H48007A.
Duration of Treatment: Up to 23 months, comprising a total of 24 infusions administered monthly (defined as a 4-week period). Subjects were followed for safety for 3 months after the last infusion of natalizumab.
Pharmacokinetic Sampling: Serum natalizumab concentrations were measured immediately pre-infusion at Months 0, 3, and 12.
Immunogenicity: This was assessed by evaluating the occurrence of anti-natalizumab antibodies at the time of the first infusion and at Months 0, 3, 6, 12, and 24 using a screening assay. Samples positive in the screening assay were evaluated for the presence of blocking antibodies.
Analytical Methods: Samples for natalizumab concentration were forwarded from the central laboratory to Elan for analysis. The methodology for Serum Natalizumab Assay is described below:

Pharmacokinetic Analysis and Statistical Methods: All non-quantifiable serum natalizumab concentrations (< 0.25 µg/mL) were set to zero prior to summary statistical analysis.

Individual serum natalizumab concentration data collected pre-infusion at Week 0, and Months 3, 12 were listed by subject number, visit month, dosing date and time, and sample collection date and time. Serum natalizumab concentrations were summarized (n, mean, SD, minimum, median, maximum) by visit month and nominal sampling time. Serum natalizumab concentration data were excluded from the calculation of summary statistics and box plots if at least one of the following criteria were met:

- The sample was collected beyond □3 days of a protocol-designated visit;
- The sample was collected after the start of the infusion rather than prior to the start of the infusion; or
- The value was deemed anomalous by the study pharmacokineticist based on calculation and/or scientific judgment (e.g., a concentration value that is beyond mean ± 3 SD at a protocol-designated nominal sampling time).

Results:
Serum natalizumab concentrations were assessed for the total population and by anti-natalizumab antibody status.

Serum Natalizumab Concentrations:
A total of 1110 subjects were enrolled in the study, however, 1100 were dosed and included in the analysis population (defined as all subjects enrolled into the study with at least one infusion of study drug).
Table 10 presents a summary of trough (pre-infusion) serum natalizumab concentrations by prior natalizumab exposure and by Type 1 patients (i.e., those with more than 4 weeks elapsed since the last natalizumab infusion in the prior study) or Type 2 patients (those with ≤ 4 weeks elapsed since the last natalizumab infusion in the prior study) at baseline and thereafter by all subjects at Months 3 and 12. In general, serum natalizumab concentrations were undetectable at baseline in subjects with no prior exposure to natalizumab. Mean trough serum natalizumab concentrations were slightly higher at Month 12 (11.2 µg/mL; n=311) compared with Month 3 (7.8 µg/mL; n=586). Mean

trough serum natalizumab concentrations were the similar at Month 0 for Type 2 subjects (7.8 μg/mL; n=185) and at Month 3 for all subjects (7.8 μg/mL; n=586).

Table 10 Summary of Serum Natalizumab Concentrations (μg/mL) by Natalizumab Exposure at Months 0, 3, and 12

Month 0

Visit	Statistic	No Previous Natalizumab Exposure	Previous Natalizumab Exposure	
		Type I & II	Type I	Type II
Month 0	N	203	5	185
	Mean	0.0	5.4	7.8
	s.d.	0.46	6.36	6.78
	Median	0.0	1.5	6.3
	Min., Max.	0.0,6.4	0.0,14.2	0.0,29.5

Month 3 and Month 12

Visit	Statistic	No Previous Natalizumab Exposure	Previous Natalizumab Exposure	Overall
Month 3	N	131	455	586
	Mean	6.0	8.3	7.8
	s.d.	6.04	7.22	7.04
	Median	4.3	6.6	6.1
	Min., Max.	0.0,36.6	0.0,33.6	0.0,36.6
Month 12	N	43	268	311
	Mean	10.2	11.3	11.2
	s.d.	8.01	7.91	7.92
	Median	7.2	9.4	9.3
	Min., Max.	0.0,32.9	0.0,38.4	0.0,38.4

Serum Natalizumab Concentrations by Anti-natalizumab Antibody Status:

Table 11 summarizes serum natalizumab concentrations by visit for subjects with and without detectable anti-natalizumab antibodies, and in Table 12 the results for subjects with detectable anti-natalizumab antibodies are stratified further by persistent and transient antibody status.

Among antibody-negative subjects, trough (pre-infusion) serum natalizumab concentrations observed at Month 0 in Type 2 subjects were higher than those in Type 1 subjects and approached the mean values observed in the overall population at Months 3 and 12. The mean concentrations observed in antibody-negative subjects were consistently higher than those observed for the overall population. Mean serum natalizumab concentrations in subjects with detectable anti-natalizumab antibodies were much lower than the concentrations observed in antibody-negative subjects and the overall population. The serum natalizumab concentrations in subjects with persistent anti-

natalizumab antibodies were either below or close to the lower limit of quantitation (mean concentration of 0.0 μg/mL [n=24] at Month 3 and 0.4 μg/mL [n=8] at Month 12), whereas the serum concentrations were higher in subjects with transient anti-natalizumab antibodies (mean concentration of 1.5 μg/mL [n=13] at Month 3 and 11.3 μg/mL [n=5] at Month 12).

Table 11 Summary of Serum Natalizumab Concentrations (μg/mL) by Antibody Status at Months 0, 3, and 12

Month 0

Visit	Statistic	Antibody Negative		Antibody Positive	
		Type I	Type II	Type I	Type II
Month 0	N	72	300	2	19
	Mean	0.5	4.8	0.0	0.0
	s.d.	2.17	6.53	0.00	0.00
	Median	0.0	1.6	0.0	0.0
	Min., Max.	0.0,14.2	0.0,29.5	0.0,0.0	0.0,0.0

Table 12 Summary of Serum Natalizumab Concentrations (μg/mL) by Persistent and Transient Antibody Status at Months 0, 3, and 12

Month 0

Visit	Statistic	Persistent Antibody Positive (a)		Transient Antibody Positive (b)		Antibody Negative (c)	
		Type I	Type II	Type I	Type II	Type I	Type II
Month 0	N	2	15	0	4	72	300
	Mean	0.0	0.0	NA	0.0	0.5	4.8
	s.d.	0.00	0.00	NA	0.00	2.17	6.53
	Median	0.0	0.0	NA	0.0	0.0	1.6
	Min., Max.	0.0,0.0	0.0,0.0	NA	0.0,0.0	0.0,14.2	0.0,29.5

Month 3 and Month 12

Visit	Statistic	Persistent Antibody Positive (a)	Transient Antibody Positive (b)	Antibody Negative (c)
Month 3	N	24	13	549
	Mean	0.0	1.5	8.3
	S.d.	0.10	2.25	7.00
	Median	0.0	0.6	6.5
	Min., Max.	0.0,0.5	0.0,7.2	0.0,36.6
Month 12	N	9	5	298
	Mean	0.4	11.3	11.4
	S.d.	1.10	12.27	7.76
	Median	0.0	6.2	9.6
	Min., Max.	0.0,3.1	0.4,30.3	0.0,38.4

(a) Defined as >=0.5 ug/mL at two or more visits >= 42 days apart or >=0.5 ug/mL at the last visit during study CD351.
(b) Defined as >=0.5 ug/mL at any visit during study CD351 excluding subjects in (a).
(c) Defined as < 0.5 ug/mL in all visits during study CD351.

Immunogenicity

Of the 1090 subjects tested for anti-natalizumab antibodies in Study CD351, a total of 72 (7%) subjects tested positive for anti-natalizumab antibodies (of whom 33 entered the study positive). Fifty-six (5%) subjects were considered to have developed persistent anti-natalizumab antibodies and 16 (1%) developed transient anti-natalizumab antibodies. The incidence of antibody formation was lower in subjects receiving concurrent immunosuppressants, steroids, or both than in subjects receiving natalizumab alone. The incidence of antibody formation after an interruption in therapy of >12 weeks was 11%, compared to 5% for subjects receiving continuous therapy. The design of the CD short-term studies primarily used only 3-month therapy with only a single antibody test at study end in a large number of patients, which could result in a falsely high proportion of antibodies being considered persistent, as subjects with a single positive antibody test were considered to have persistent antibodies.

Reviewer's Comments: Take note of this when interpreting the population PK analysis.

Applicant's Conclusions: Trough serum natalizumab concentrations increased slightly over time but no clinically significant accumulation occurred. Serum natalizumab concentrations were markedly lower in subjects with persistent anti-natalizumab antibodies compared with antibody-negative subjects.

Study # CD 352

Title of study: A Phase II, Multicenter, Open-Label, Long-Term Study of the Safety, Tolerability, and Efficacy of Intravenous Antegren™ (Natalizumab) in Adolescent Crohn's Disease Subjects Who Have Previously Participated in Study CD305

Investigator(s): 12 investigational sites in 3 countries, including 2 sites in Australia, 3 sites in the United Kingdom (UK) and 7 sites in the United States of America (USA)

Study Period: Date First Subject Enrolled: 19 December 2002; Date Last Subject Visit Completed: 30 March 2005

Objectives: No PK objectives were stated however, serum samples were collected and included in the POPPK analysis.
Methodology: This was a Phase 2, multicenter, open-label, long-term study of the safety, tolerability and efficacy of natalizumab in adolescent subjects who previously participated in Study CD305. At the Week 12 visit of CD305, subjects may have elected to continue natalizumab treatment every 4 weeks by enrolling in this open-label extension study. Initially the dose was 3 mg/kg of natalizumab and the treatment phase was to span 24 months, but the protocol was amended: 1) to allow the dose to be increased at the Investigators' discretion to 6 mg/kg in subjects who were not achieving an optimal clinical benefit from the 3 mg/kg dose; and 2) to extend the treatment phase to 48 months, with a follow-up period of 3 months after the last infusion.

However, dosing was suspended in all natalizumab clinical trials, including CD352, on 28 February 2005 in response to the diagnosis of progressive multifocal leukoencephalopathy (PML) in 2 study subjects with MS and one with CD. A total of 26 subjects were enrolled and all had received at least 6 infusions in Study CD352. Further study is necessary to determine appropriate dosing for adolescent subjects.
Treatments: Natalizumab was provided as a liquid in clear, stoppered, individual vials of 20 mg/mL natalizumab in 10 mM phosphate buffer, 140 mM sodium chloride (NaCl), and 0.02% polysorbate 80, adjusted to pH 6.1 with phosphoric acid. At the start of the study, natalizumab was supplied as the clinical trials product in 5 mL vials, and the dose administered was 3 mg/kg. However, a protocol amendment, dated 23 March 2004, called for a phased introduction of the natalizumab commercial process product, which was to replace the clinical trials product, and allowed for the option of a dose increase to 6 mg/kg. The commercial process product was provided in 15 mL vials, also at a concentration of 20 mg/mL. Natalizumab was diluted in 100 mL normal saline and administered by IV infusion over approximately 60 minutes at a flow rate of 2 mL/min. Lot numbers used for the clinical trials product were G23005B, G23001C and F23003A. Lot numbers used for the commercial process product were H48006A and J48003C.
Pharmacokinetic Sampling: Serum natalizumab concentrations were measured immediately prior to the start of the natalizumab infusion at Months 0, 3, 12, 24, 36, and 48. Additionally, samples for serum natalizumab concentration (pre- and post-infusion) were collected for any subject whose dose was increased to 6 mg/kg; these additional samples were collected at the first study visit that a subject's dose was increased, as well as at the two subsequent visits following the dose-increase visit.
Analytical Methods: Same as Study # 305
Pharmacokinetics/Pharmacodynamics: Evaluations were based on analysis serum natalizumab concentration and pharmacodynamic (PD) evaluations were based on change in circulating lymphocyte counts.
Immunogenicity: This was assessed by evaluating the proportion of subjects who developed anti-natalizumab antibodies.
Results:
Pharmacokinetics
Table 5 Demography and Baseline Characteristics by Drug Product and Dose

Variable Statistic or Category	Overall (n=26) N (%)	AN100226 (n=8) N (%)	AN100226 and BG00002-B (3mg/kg only) (n=8) N (%)	AN100226 and BG00002-B (6mg/kg only) (n=9) N (%)	AN100226 and BG00002-B (3mg/kg and 6mg/kg) (n=1) N (%)
Age (yr)					
N	26	8	8	9	1
Mean	14.7	15.0	15.3	14.3	12.0
s.d.	1.76	2.07	1.39	1.66	N/A
Median	15.0	15.5	16.0	14.0	12.0
Min., Max.	12.0,17.0	12.0,17.0	13.0,17.0	12.0,17.0	12.0,12.0
Gender N (%)					
Female	8 (30.8)	5 (62.5)	1 (12.5)	2 (22.2)	0 (0.0)
Male	18 (69.2)	3 (37.5)	7 (87.5)	7 (77.8)	1 (100.0)
Race N (%)					
Black	1 (3.8)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
White	24 (92.3)	8 (100.0)	7 (87.5)	8 (88.9)	1 (100.0)
Asian	1 (3.8)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AN100226 = Clinical Trial Product of Natalizumab; BG00002-B = Commercial Process Product of Natalizumab. AN100226 was only administered at a dose of 3 mg/kg.

For subjects receiving 3 mg/kg natalizumab infusions, pre-infusion serum natalizumab concentrations at visit Months 0, 3, 12, and 24 are summarized in Table 10. Their pre-infusion serum natalizumab concentrations were highly variable, but showed an increasing trend in median values from 0.0 μg/mL, 0.5 μg/mL, and 3.4 μg/mL at Months 0, 3 and 12. Only three subjects had measurements at Month 24. The limited and variable data available preclude any definitive conclusions.

Table 10 Pre-Infusion Serum Natalizumab Concentration Summary Statistics (3 mg/kg Dosing)

Visit Month	Statistic	3 mg/kg Pre-Infusion Serum Natalizumab Concentrations (μg/mL)
0	N	25
	Mean (s.d.)	0.9 (1.84)
	Median (Range)	0.0 (0.0, 6.3)
3	N	26
	Mean (s.d.)	3.4 (6.49)
	Median (Range)	0.5 (0.0, 29.2)
12	N	17
	Mean (s.d.)	5.3 (5.87)
	Median (Range)	3.4 (0.0, 19.3)
24	N	3
	Mean (s.d.)	6.2 (1.01)
	Median (Range)	6.0 (5.3, 7.3)

N = number of subjects; s.d. = standard deviation

Ten (38.5%) subjects also received at least one dose of 6 mg/kg natalizumab during the study. For subjects receiving 6 mg/kg natalizumab infusions who had pre- and post-infusion serum natalizumab concentrations prior to the first, second, and third infusions are summarized in Table 11. For subjects receiving 6 mg/kg natalizumab infusions, pre-infusion serum natalizumab concentrations were highly variable, with generally comparable median (0.7 and 0.8 μg/mL) and mean (7.9 and 7.6 μg/mL) values observed prior to Infusions 2 and 3, respectively. For subjects receiving 6 mg/kg natalizumab infusions, post-infusion (peak) serum natalizumab concentrations were variable, but generally comparable median values (range: 98.5-103.6 μg/mL) and mean values (range: 95-117.1 μg/mL) were observed for Infusions 1, 2, and 3. These results suggest little or no drug accumulation upon repeat administration at the 6 mg/kg dose level, and are generally consistent with an expected approximate doubling of peak concentrations from those of the 3 mg/kg dose level in Study CD305, where mean post-infusion (peak) concentrations ranged from 63.8-70.3 μg/mL and median values ranged from 57.4–66.7 μg/mL.

Table 11 Pre- and Post-Infusion Serum Natalizumab Concentration Summary Statistics (6 mg/kg Dosing)

Infusion Number	Statistic	6 mg/kg Serum Natalizumab Concentrations (μg/mL)	
		Pre-Infusion	Post-Infusion
1	N	10	10
	Mean (s.d.)	2.4 (3.89)[a]	117.1 (38.10)
	Median (Range)	0.0 (0.0, 9.6)[a]	102.9 (72.5, 182.0)
2	N	9	9
	Mean (s.d.)	7.9 (11.88)	114.4 (50.06)
	Median (Range)	0.7 (0.0, 31.2)	103.6 (49.4, 207.4)
3	N	8	8
	Mean (s.d.)	7.6 (16.22)	95.0 (24.37)
	Median (Range)	0.8 (0.0, 47.2)	98.5 (46.0, 132.8)

[a]Reflects the trough level of the previous 3 mg/kg dose, N = number of subjects; s.d. = standard deviation.

Due to the limited amount of data, analyses comparing serum natalizumab concentrations by anti-natalizumab antibody status were not performed.

Pharmacodynamics

Blood samples for absolute lymphocyte counts were collected at the Screening visit (if applicable), Month 0, and then every three months thereafter or at the Early Discontinuation visit. Additionally, samples for serum absolute lymphocyte counts were collected for any subject whose dose was increased to 6 mg/kg.

Applicant's Conclusions:

Pharmacokinetics

- The serum natalizumab concentrations in this study were highly variable within a dose (3 mg/kg or 6 mg/kg). A review of data from Study CD305 showed that the 3 mg/kg natalizumab dose produced: 1) serum natalizumab concentrations lower than in adult patients receiving a fixed dose of 300 mg; and 2) lymphocyte elevations and α4-integrin saturation that were not maintained over the dosing interval. Therefore, the 3 mg/kg natalizumab was not considered to be a sufficient dose in adolescent patients and the Study CD352 protocol was amended to allow investigators the discretion to increase the dose to 6 mg/kg if clinical remission had not been achieved. The limited and variable results precluded any definitive conclusions concerning pharmacokinetic parameters over long-term exposure to the higher dose.
- Median serum natalizumab trough concentrations ranged from 0.0–3.4 μg/mL at Months 0, 3, and 12 for the 3 mg/kg dose level and 0.7–0.8 μg/mL prior to Infusions 2 and 3 at the 6 mg/kg dose level.
- Median post-infusion (peak) serum natalizumab concentrations ranged from 98.5-103.6 μg/mL after Infusions 1, 2, and 3 of the 6 mg/kg dose level. These results suggest little or no drug accumulation upon repeat administration at the 6 mg/kg dose level and are generally consistent with an expected approximate doubling of peak concentrations from those of the 3 mg/kg dose level in Study CD305, where median post-infusion (peak) concentrations ranged from 57.4-66.7 μg/mL.
- Analyses comparing pharmacokinetics by anti-natalizumab antibody status were not performed.

Pharmacodynamics:

- An approximate two-fold elevation of median circulating absolute lymphocyte counts above Study CD305 baseline levels was maintained through Study CD352.
- Median values remained below the upper limit of normal (ULN) (5.25 x 10^9/mL) at all evaluated time points.
- The limited and variable circulating absolute lymphocyte count data precluded a meaningful comparison between natalizumab dose levels (3 mg/kg and 6 mg/kg).

Studies in Healthy Volunteers

Study # HV101, # C-1805 and # C-1806 were already reviewed with MS application and found acceptable, therefore I did not review them again.

Study # HV101was a randomized, double blind, placebo-controlled, dose-escalation study in healthy male volunteers to evaluate the safety, tolerability, PK, and PD of natalizumab (AN100226) following IV infusion. Doses of 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg were evaluated. In each of the 2 lowest dose groups, 4 subjects received natalizumab, and in each of the 0.3, 1.0, and 3.0 mg/kg dose groups, 6 subjects received natalizumab. Nine subjects received placebo.

Study # C-1805 was a randomized, double-blind, 2-period crossover study comparing the PK, PD, and immunogenicity of AN100226 (used in Phase 3 CD studies) and BG00002-B (commercial material) in healthy male and female volunteers. Subjects received a single 300 mg IV infusion of natalizumab over 60 minutes.

Study # C-1806 was a randomized, double-blind, 2-period crossover study comparing the PK, PD, and immunogenicity of BG00002-A (used in Phase 3 MS studies) and BG00002-B (commercial material) in healthy male and female volunteers. Subjects received a single 300 mg IV infusion of natalizumab over 60 minutes.

Bioanalytical Methods:

Table 1: Summary of Bioanalytical Methods

Serum Natalizumab Concentration Assay	ELISA assay for determination of total natalizumab concentration in serum
Anti-Natalizumab Antibody Screening ELISA	ELISA assay for measurement of total anti-natalizumab antibodies in serum
Anti-Natalizumab Idiotype Assay	ELISA assay for measurement of anti-idiotypic antibodies to natalizumab in serum
Anti-Natalizumab Blocking Assay	Flow cytometry assay for characterization of anti-natalizumab antibodies that block natalizumab binding to VLA4 on the surface of α4 transfected K562 cells
Natalizumab Receptor Binding Saturation Assay	Flow cytometry assay for determination of the percent saturation of VLA4 receptors by natalizumab in whole blood. A flow cytometer based binding assay to demonstrate ability of natalizumab to bind and saturate α4-integrin expressed on peripheral blood mononuclear cells (PBMC) *in vivo* was developed and validated. The whole blood based assay measured the percent saturation of natalizumab bound to the surface of PBMC collected from animals or subjects enrolled in the trials at fixed time points. Natalizumab bound to the cells was detected using an anti- IgG4 antibody conjugated to a fluorochrome.

Reviewer's Comments: Validated bioanalytical methods were developed and validated to determine human serum natalizumab concentrations using enzyme linked immunosorbant assays (ELISAs), α4 integrin receptor saturation of human peripheral blood lymphocytes was determined using a receptor binding assay, and three different measures of immunogenicity to natalizumab (screening ELISA assay, anti-idiotype assay and a blocking assay) were also developed. All methods were also used for the studies conducted in the MS application and found to have adequate validation. Therefore, the assay method validation was not reviewed again.

Table: Performance Characteristics of the Flow-Cytometer Based PD Saturation Assay for Natalizumab

Validation Parameter	Proposed Acceptance Criteria	Validation study results
Specificity	Natalizumab concentration-dependent increase in MFI, 4-parameter curve fit $r \geq 0.95$.	Natalizumab concentration-dependent MFI, 4-parameter curve fit r =0.999, mean of n=5.
	Inhibition by monoclonal anti-natalizumab antibody (12C4) such that MFI in presence of 12C4 = MFI ± 20%in the absence of natalizumab	Inhibition by 12C4 MFI =32, no natalizumab MFI=31. 12C4 inhibition MFI is within 3.2% of MFI without natalizumab.
	Copaxone: Natalizumab concentration-dependent MFI, 4-parameter curve fit $r \geq 0.95$	Binding assay in the presence of Copaxone: Natalizumab concentration-dependent MFI, 4-parameter curve fit r = 0.998, no significant effect on % saturation (ANOVA, $p \geq 0.99$)
Precision (intra and inter-assay)	Intra-assay precision Coefficient of Variance at % saturation ≤ 20% of 5 replicates;	Intra-assay precision was ≤ 20% CV for all natalizumab concentrations tested.
	Inter-assay precision Coefficient of Variance at % saturation ≤ 20% among 3 analysts on 3 days.	Inter-assay precision was ≤ 20%CV except at % saturation levels approaching the detection limit of approximately 14%. Therefore, this assay does not provide acceptable precision at < 15% saturation.
Robustness	%CV of MFI ≤ 20% in the presence of natalizumab for 20 to 40 min.	Natalizumab incubation time at 20 minutes was comparable to 40 minutes with 2% CV.
	%CV of MFI ≤ 20% in the presence of anti-IgG4-PE and anti-VLA-4 (anti-CD49d) for 5 to 20 min.	Anti-IgG4-PE %CV= 11 at 5 and 20 minutes incubation with saturating concentration of natalizumab and anti VLA-4 (anti-CD49d) %CV = 8.
	%CV of percentage of mononuclear cells ≤ 20% in the presence of FACS lysis reagent for 10 to 40 min.	FACS lysis reagent at 10 to 40 min resulted in %CV =5 among the percentage of mononuuclear cells

MFI = Mean Fluorescence Intensity

4.3 Consult Reviews (including Pharmacometric Reviews)

PHARMACOMETRIC REVIEW

BLA:	125104
Drug name:	Tysabri (natalizumab)
Indication:	Treatment of Crohn's Disease
Proposed Regimen (Sponsor):	300 mg IV q4w
Applicant:	Biogen Idec

OCP Reviewer	Abimbola O. Adebowale, Ph.D.
PM Reviewer:	Christoffer W. Tornoe, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	BLA
Submission Date:	December 15, 2006
PDUFA Date:	October 15, 2007

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Executive Summary

A fixed dose of 300 mg q4w proposed by the sponsor is acceptable based on the following findings:

- 3 mg/kg dose was efficacious, with the 99th percentile weight in the Phase 2 studies being 100 kg and there was no apparent added clinical benefit of the 6 mg/kg dose over the 3 mg/kg dose.
- 6 mg/kg resulted in no dose-limiting toxicities.
- Natalizumab clearance appears to be largely independent of body weight over the body weight range of approximately 40–100 kg, such that a fixed dose is feasible.
- The probability of clinical response defined as a decrease in CDAI score of more than 70 points was found to be correlated with natalizumab exposure ($AUC_{\square}$in the dose-finding study CD202. However, an inverse U-shaped dose- and exposure-response relationship was found with the highest dose group of 6 mg/kg q4w having lower response rate compared to 3 mg/kg q4w. The reason for observing an inverse U-shaped relationship for natalizumab was not identified.

The percentage of patients with herpes simplex in the natalizumab treated subjects was double that of placebo patients, i.e. 2.8% (N=14) for placebo and 4.4% (N=27) for natalizumab treated patients across all studies. The probability of herpes simplex appeared to increase for patients with natalizumab AUC_{ss} above 20 mcg*hr/mL.

The findings of the population pharmacokinetic analysis in Crohn's Disease patients (N = 1156) from 1 phase II study and 3 phase III studies were similar to those obtained for MS patients, i.e.

- In both patient populations, an (unexplained) time dependency of CL was found to reduce CL by 25% with repeated administration.
- Anti-natalizumab antibodies occurring in approximately 10% of the patients were found to increase CL by 42%. This is likely to an underestimate of the true effect due to many antibody positive subjects had PK trough samples below LOQ.
- Body weight, age, race, ALT, AST, bilirubin, and creatinine clearance were not found to have any clinical relevant influence on the PK of natalizumab.

Question Based Review

Is a fixed dose of 300 mg q4w justified?

The 300 mg fixed dose (approximately 4.3 mg/kg; 70 kg subject) was based on the following:

- 3 mg/kg dose was efficacious, with the 99th percentile weight in the Phase 2 studies being 100 kg and there was no apparent added clinical benefit of the 6 mg/kg dose over the 3 mg/kg dose.
- 6 mg/kg resulted in no dose-limiting toxicities.
- Natalizumab clearance appears to be largely independent of body weight over the body weight range of approximately 40–100 kg, such that a fixed dose is feasible.

The reviewer agrees with sponsor's assessment and finds a fixed dose of 300 mg q4w acceptable.

Furthermore, a time-dependent decrease in clearance was identified leading to a doubling of the median trough concentrations (from approx. 4 to 10 mcg/mL) between from month 1 to month 12. There is however no need to decrease dosing with repeated administration to prevent accumulation due to time-dependent decrease in clearance since the more adverse events where not identified with time and higher trough concentrations should result in better efficacy.

Natalizumab antibody status was identified as a significant covariate for natalizumab clearance with a 42% increase in clearance for patients with persistent antibodies compared to sponsor's claim of more than 100%. A dose adjustment based on the patient's antibody status was not found necessary.

Is there evidence of exposure-response?

The probability of clinical response defined as a decrease in CDAI score of more than 70 points was found to be correlated with natalizumab exposure ($AUC_{0\text{-}6\ weeks}$) in the dose-finding study CD202. However, an inverse U-shaped dose- and exposure-response relationship was found with the highest dose group of 6 mg/kg q4w having lower response rate compared to 3 mg/kg q4w. The reason for observing an inverse U-shaped relationship for natalizumab was not identified.

Is there evidence of adequate safety data?

Serious infections (other than PML), urinary infections, serious adverse events were not found to be correlated with natalizumab exposure.

The percentage of patients with herpes simplex was 2.8% (N=14) for placebo and 4.4% (N=27) for natalizumab treated patients across all studies which is similar to the findings in multiple sclerosis patients. The probability of herpes simplex appeared to increase for patients with natalizumab AUC_{ss} above 20 mcg*hr/mL.

Are claims based on population PK analysis acceptable?

Below are recommendations for the proposed label regarding population PK claims:

12.3 Pharmacokinetics

The effects of covariates such as total body weight, age, gender, race, selected hematology and serum chemistry measures, co-administered medications (infliximab, immunosuppressants, or steroids), and the presence of anti-natalizumab antibodies were investigated in a population pharmacokinetic analysis (n=1156). (b) (4) The presence of (b) (4) anti-natalizumab antibodies was observed to increase natalizumab clearance (b) (4)

Pharmacokinetics of TYSABRI® in patients with renal or hepatic insufficiency have not been studied. (b) (4)

Recommendations

The Pharmacometrics Staff in Office of Clinical Pharmacology finds that the BLA is acceptable.

Introduction

Background

Natalizumab (Tysabri) is a recombinant humanized anti-α4 integrin monoclonal antibody (mAb) that is produced in murine myeloma cell line (NS0) cells and binds to the α4 subunit of human integrin, expressed at high levels on all circulating leukocytes except polymorphonuclear leukocytes (PMNs). Natalizumab binds to and blocks the interaction of α4β1 integrin (also known as very late antigen-4, VLA-4) on leukocytes with its counter receptor, vascular cell adhesion molecule-1 (VCAM-1), on endothelial cells. Likewise, natalizumab blocks the interaction of α4β7 integrin expressed on leukocytes interacting with mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Disruption of these cell adhesion molecule interactions prevents trafficking of mononuclear leukocytes across the endothelium and into the parenchymal tissue. Increased leukocyte trafficking into the parenchyma of the brain and gut is believed to play a role in the pathogenesis of multiple sclerosis (MS) and inflammatory bowel disease (IBD), respectively.

This supplemental BLA is to support an indication for treatment of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy.

The sponsor included 1 phase II and 3 phase III studies in patients with Crohn's disease to demonstrate the effectiveness of natalizumab.

Aims of Analysis

The aims of the analysis are:

- To describe the typical natalizumab pharmacokinetic (PK) parameters in the evaluated human Crohn's disease (CD) patient population, using an assembled data set incorporating selected Phase 2 and Phase 3 clinical studies.
- To estimate potential effects of intrinsic (e.g., demographics) and extrinsic (e.g., co-administered medication) patient factors that may help explain the observed variability in natalizumab serum systemic clearance, volume of distribution, and the resulting serum exposure for a given dose.
- To investigate the exposure-response and exposure-safety relationships of natalizumab.

Sponsor's Population PK Analysis

Background

The primary objectives of the sponsor's population PK analysis were to:

1) Describe the typical natalizumab pharmacokinetic (PK) parameters in the evaluated human CD patient population.

2) Estimate potential effects of intrinsic (e.g., demographics) and extrinsic (e.g., co-administered medication) patient factors that may help explain the observed variability in natalizumab serum systemic clearance, volume of distribution, and the resulting serum exposure for a given dose.

Studies

An overview of the natalizumab studies in Crohn's disease patients is graphically illustrated in Figure 1 and further described in the following paragraphs.

Figure 1 Clinical development of natalizumab in Crohn's disease.

CD202

Study CD202 was a Phase 2, multi-center, randomized, double blind, placebo-controlled parallel group, multiple-dose safety, tolerability and dose-evaluation study of IV natalizumab in subjects with active CD. Concomitant treatment with other agents, including 5-aminosalicylic acid (5-ASA) compounds, oral corticosteroids, azathioprine,

and 6-mercaptopurine was permitted providing that doses were stable in the period leading up to enrollment. A total of 248 male and female subjects with moderate to severely active CD (defined by a CDAI score ≥220) were enrolled: 63 subjects received placebo (at Weeks 0 and 4) and 68, 66, and 51 subjects received a single 3.0 mg/kg infusion, two 3.0 mg/kg infusions, or two 6.0 mg/kg infusions of natalizumab (at Weeks 0 and 4), respectively. Four subjects did not receive a single infusion (3 subjects randomized to the single 3.0 mg/kg infusion group and one subject to the two 3.0 mg/kg infusion group).

Blood samples for serum natalizumab concentration analysis were collected from a total of 64, 65 and 50 subjects following single 3.0 mg/kg IV infusion, two 3.0 mg/kg IV infusions, and two 6.0 mg/kg IV infusions of natalizumab, respectively. Serum samples for natalizumab concentration analysis were collected following the first infusion at time 0 (pre-infusion), at 2 hours, and Week 2 post-dose. Further, blood samples were collected at time 0 (pre-infusion) and 2 hours, and 2, 4, and 8 weeks following the second infusion. Immunogenicity was also assessed at Weeks 0 (pre-infusion), 2, 4 (preinfusion), 6, 8, and 12 (or Early Discontinuation). Data from all subjects who received at least one complete dose of natalizumab and provided evaluable serum natalizumab concentration data were used in this analysis.

CD251

Study CD251 was a Phase 2, multi-center, open-label, chronic re-treatment study of the safety, tolerability, and effectiveness of repeated courses of IV natalizumab in 96 subjects with active CD (confirmed by CDAI >150) who had completed Study CD202. The time between the last infusion of natalizumab in CD202 and the Week 0 infusion at Treatment Course (TC) one (TC1) ranged from 43 to 128 weeks. Eligible subjects received courses of treatment, each of which comprised an IV infusion of 6.0 mg/kg natalizumab at Weeks 0 and 4. After completing a TC and the associated assessments, subjects received a repeat course following the Week 12 visit if disease was active (confirmed by CDAI >150), or entered the follow up phase. Subjects were not considered for a repeat course before the Week 12 visit of the existing course. If at any time during the follow up phase the subject experienced a recurrence of active disease (CDAI >150), the subject could receive a repeat course of treatment, providing they still met the eligibility criteria.

Blood samples were planned to be collected for serum natalizumab concentration analysis and immunogenicity assessments at Weeks 0, 2, 4, 6, and 12 during each TC. Data from all subjects who received at least one complete infusion of natalizumab and provided evaluable serum natalizumab concentration data were used in this analysis.

CD301

Study CD301 was a Phase 3, international, multi-center, double blind, placebo-controlled study of the safety, efficacy, and tolerability of natalizumab in subjects with moderately to severely active CD (CDAI score ≥220 and ≤450). The study was designed to evaluate the efficacy and safety of a total of 3 monthly (every 4 weeks) IV infusions of 300 mg natalizumab in 905 subjects with moderately to severely active disease, using a 4:1 active to placebo randomization ratio.

Blood samples for serum natalizumab concentration analysis were to be collected from all subjects at their Week 12, 20, or Early Discontinuation visits. In addition, intensive serum samples were collected from 21 subjects receiving natalizumab, who participated in a PK/PD sub-study conducted at 7 US sites. For these 21 subjects, blood samples for natalizumab were to be collected at 0 hour (pre-infusion), immediately post-infusion, 2 hours, 24 hours and 1, 2, 3, and 4 weeks post-infusion for Doses 1 and 3. Immunogenicity was assessed at Week 0 (pre-infusion), Week 12, and Week 20 (or Early Discontinuation). Data from all subjects who received at least one complete dose of natalizumab and provided evaluable serum natalizumab concentration data were used in this analysis.

CD303

Study CD303 was a Phase 3, randomized, international, multi-center, double blind, placebo-controlled, parallel-group study that enrolled subjects with CD who had responded to treatment with monthly IV infusions of either natalizumab 300 mg or placebo for 3 months in Study CD301. Informed consent was obtained at Week 10 in Study CD301, at which point subjects on oral corticosteroids began reducing their doses according to a fixed algorithm. Subjects who continued to meet eligibility criteria at Week 12 (Month 3) were re-randomized to receive monthly IV infusions of natalizumab 300 mg or placebo (ratio 1:1) for up to 12 consecutive months in Study CD303. Subjects were centrally randomized and enrollment was stratified according to three factors: disease status at Week 12 (remission versus no remission [i.e., a CDAI <150 or ≥ 150, respectively], use of oral corticosteroids at entry in Study CD301, and use of immunosuppressants at entry in Study CD301. Subjects were to return for their final treatment assessment approximately 1 month after their last study drug infusion (Month 15). Efficacy assessments and safety evaluations were scheduled to occur during monthly (every 4 weeks) clinic visits (Months 3 through 15). A total of 428 subjects (214 natalizumab and 214 placebo) were randomized and all received treatment. Subjects completing the treatment phase (i.e., up to Month 15) were eligible to enter an open-label, chronic treatment study (CD351) in which all subjects received natalizumab.

Trough serum concentrations of natalizumab were to be assessed at Months 3, 6, 9, 12, and 15, and at any Early Termination and Unscheduled visits. In addition, peak serum concentrations were to be assessed at Months 6 and 12. Immunogenicity was assessed at Months 3, 6, 9, 12, and 15, and at the Follow-Up Visit at Month 17. Data from all subjects who received at least one complete dose of natalizumab and provided evaluable serum natalizumab concentration data were used in this analysis.

CD305

Study CD305 was a Phase 2, multi-center, open-label, single-arm study designed to examine the safety, tolerability, and effectiveness of IV infusions of natalizumab (3.0 mg/kg) administered once a month for up to three months in adolescent subjects (12–17 years of age) with moderately to severely active CD (PCDAI >30). The treatment period spanned 12 weeks. Thirty-eight subjects received IV infusions of natalizumab (3.0 mg/kg) at Weeks 0, 4, and 8 and were assessed through Week 12. The follow-up phase

for this study comprised a visit at Week 20 and a telephone follow-up to assess adverse events (AEs) at Week 32. During the study subjects were allowed to remain on stable doses of oral 5-ASA compounds, oral corticosteroids, antibiotics, and specified immunosuppressants, as well as nasogastric/nasoenteric tube feeding and elemental/polymeric diets. Herbal preparations, rectal 5-ASA compounds, rectal corticosteroids, total parenteral nutrition (TPN), anti-tumor necrosis factor (TNF) therapy, and experimental agents were prohibited.

Blood samples for measurement of serum natalizumab concentrations were collected weekly from the 38 enrolled subjects (with the exception of Weeks 5, 6, and 7) during the 12-week treatment phase, including Week 12 and any Early Discontinuation visit, and then at Week 20. Subjects underwent additional, more intensive PK/PD sampling around the first (Week 0) and third infusions (Week 8) at pre-dose, and at 1, 2, and 24 hours, and at 1, 2, 3, and 4 weeks post-start of infusion. Immunogenicity was assessed at Week 0 (pre-infusion), Week 12, and Week 20 (or Early Discontinuation). Data from all subjects who received at least one complete dose of natalizumab and provided evaluable serum natalizumab concentration data will be used in this analysis.

CD306

Study CD306 was a Phase 2, multi-center, double blind, placebo-controlled pilot study of the safety, tolerability and efficacy of natalizumab (300 mg) in CD subjects concurrently receiving infliximab (Remicade®; 5 mg/kg IV) and not in remission (CDAI >150). The primary objective of this study was to evaluate the safety and tolerability of three monthly (Week 0, 4, and 8) IV infusions of natalizumab with concurrent infliximab administrations (at Week -2 and 6). Upon completion of the Week 10 visit of this study, subjects could elect to enroll in the open-label extension study, CD351. A total of 103 subjects were screened, of whom 52 were randomized to natalizumab and 27 to placebo at 17 sites. All 79 subjects randomized received at least one infusion of natalizumab or placebo.

Blood samples for measurement of serum levels of natalizumab were to have been collected from all subjects at Week 10, Week 20 and any Early Discontinuation Visit. Subjects participating in a PK/PD sub-study at selected sites only underwent more frequent blood sampling: Serum concentrations of natalizumab were evaluated around Dose 1 (Week 0) and Dose 3 (Week 8) at pre-dose, and at 1, 2, and 24 hours, and at 1, 2, 3 (Dose 1 only), and 4 (Dose 1 only) weeks post-start of infusion. Blood samples for screening natalizumab antibody measurement were collected from all subjects at Weeks 0, 20, and any Early Discontinuation visit. Additional samples for measuring anti-natalizumab antibodies were collected from any subject who developed an immune mediated AE leading to discontinuation of study drug (defined as anaphylaxis, angioedema, urticaria, clinical syndrome diagnostic of serum sickness, or biopsy-proven vasculitis). Data from all subjects who received at least one complete dose of natalizumab and provided evaluable serum natalizumab concentration data will be used in this analysis.

CD351

Study CD351 was a Phase 3, multi-center, open-label, long-term study in subjects who had participated in Study CD251, CD301, CD303, or CD306. Subjects received their first CD351 study drug infusion at Week 0 (the baseline visit) and returned to the clinic at monthly intervals (defined as a 4-week period) to receive natalizumab IV infusions and for assessments of safety and efficacy until the Month 24 Visit. All subjects were followed for safety for an additional 6 months, by a visit 3 months after the last infusion and a telephone call 6 months after the last infusion. Where possible, those subjects who withdrew from the study completed an Early Discontinuation Visit, and were followed for safety for an additional 6 months following their last infusion. Approximately 700 subjects were enrolled at the time of data assembly.

Blood samples for measurement of serum levels of natalizumab were to have been collected from all subjects at Week 0 and Months 3 and 12. Immunogenicity was assessed pre-infusion at Week 0 and Months 3, 6, 9, 12, 15, 18, 21, and 23. This is an ongoing study and the available data from all subjects who received at least one complete dose of natalizumab and provided evaluable serum natalizumab concentration data were used in this analysis.

CD352

Study CD352 was a Phase 2, multi-center, open-label, long-term study of the safety, tolerability, and efficacy of natalizumab in adolescent subjects who previously participated in Study CD305. At the Week 12 visit of Study CD305, subjects may have elected to continue natalizumab treatment every 4 weeks by enrolling in this open-label extension study. The primary object of this study was to evaluate the safety of 3.0 mg/kg natalizumab at monthly (every 4 weeks) intervals for up to 24 IV infusions. A total of 26 subjects were enrolled at the time of data assembly and all subjects had received two or more infusions.

Blood samples for measurement of serum levels of natalizumab were to have been collected from all subjects at Week 0 and Months 3 and 12. Immunogenicity was assessed pre-infusion at Week 0 and Months 3, 6, 9, 12, 15, 18, 21, and 23. This is an ongoing study and the available data from all subjects who received at least one complete dose of natalizumab and provided evaluable serum natalizumab concentration data were used in this analysis.

NONMEM Data Set

In general, any observation with missing dosing date/time or sampling date/time information was excluded. However, if only the time is missing, then an approach deemed appropriate was used to include these observations and suitably documented (e.g., imputing a time of 12:00, or setting the time to 1 hour before or after the start of dose administration depending upon the magnitude of the observed serum natalizumab concentration). Serum natalizumab concentration observations that were BLQ or any values that were otherwise missing were excluded from the analysis.

Extreme outliers and obvious data errors in the full data set were identified using appropriate diagnostic plots. Further, identification of extreme outlying observations was also aided by inspection of diagnostic plots created during the base and full model development phase.

The final assembled data set (natpoppk1.csv) contained 16445 records (dosing, observation, and other event records from 1194 patients), of which 5761 were observation records. Only 4194 of the observation records (from 1036 patients) were included in the analysis. The remaining 1567 observation records were excluded from the analysis, with 1495 (95.4%) of these being BLQ samples (i.e., low, but unknown concentrations). The 72 excluded non-BLQ observation records were apparent anomalous observed serum natalizumab concentration (DV) values, as determined by the scientific judgment of the study pharmacokineticist, inspection of diagnostic plots, or comparison to other DV values available for that patient.

Methods

Population PK Analysis

The population PK models evaluated in sponsor's analysis consisted of four basic model components:

1) A structural PK model, which describes the serum concentrations of natalizumab and defines the PK parameters (e.g., CL, V1, V2, and Q);
2) A covariate model, which describes the influence of fixed effects (e.g., demographic factors and other covariates) on the PK parameters;
3) A random inter-individual error model, which describes the inter-individual variability in the PK parameters after correction for individual specific fixed effects; and
4) A random residual error model, which describes random error resulting from intraindividual variability, measurement error, process error, and model misspecification.

Structural Models

One, two, and three compartment structural models with zero-order input and first-order elimination from the central compartment were evaluated in sponsor's analysis.

Time Varying Natalizumab Clearance

To account for potential time variance in CL, the inclusion of change functions on CL to account for increasing serum natalizumab trough concentrations upon repeated administration that was not due to accumulation were evaluated for addition to the structural model:

$$TVCL = \theta_n \cdot \prod_{1}^{p} \theta_{(n+p)}^{CCL_p}$$

where, *TVCL* is the typical value of CL, θ_n is the estimated parameter describing the *TVCL* value for an individual, CCL_p is a change function indicator value equal to either 0 or 1 depending upon the time after initiation of natalizumab treatment, and $\theta_{(n+p)}$ is the estimated parameter describing the magnitude of the change function-TVCL relationship.

According to the sponsor, the inclusion of the change function for the systemic clearance was considered appropriate since multi-compartment model fitting using an assumption of time-invariant PK would generate relatively large V_{ss} and terminal elimination $t_{½}$ estimates, and a biased (i.e., smaller) estimate of CL, to account for the higher than expected (based on single dosing) steady-state trough concentrations.

Covariate Models

A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for the population PK analysis. This notion is a simplification of the global model approach described by Burnham and Anderson. Covariate-parameter relationships were identified based on exploratory graphics, scientific interest, mechanistic plausibility, or prior knowledge, and a full model constructed with care to avoid correlation or co-linearity in predictors. Exploratory graphical analysis included inspection of plots of empirical maximum *a posteriori* probability (MAP) Bayes estimates of individual random effects (η_i) and/or weighted residual (WRES) from the base model vs. covariates. Population covariate coefficients were estimated for any effects revealing evidence of a relationship or deemed of potential clinical interest. Inferences about clinical relevance of covariates were then based on the resulting parameter estimates and measures of estimation precision (asymptotic standard errors, bootstrap 95% confidence intervals, or log-likelihood profile). No hypothesis testing was conducted. This approach directly addresses the question of clinical relevance of covariate effects and also provides some explanation for the apparent absence of a covariate effect (true lack of an effect vs. lack of information about that effect).

The full population PK model included the structural model definition, estimates of population mean and individual fixed effects parameters, and estimates of the inter-individual and residual random effects parameters. Lastly, a reduced model (i.e., more parsimonious model) was also developed for future use as a potential simulation tool, which included elements of the full model but with clinically unimportant covariate effects removed (e.g., 95% CI within ±20% change in typical value of parameter) and the remaining potentially clinically important parameters re-estimated.

The effects of continuous and categorical covariates were modeled using a normalized power model, i.e.

$$TVP = \theta_n \cdot \prod_{1}^{m} \left(\frac{Cov_{mi}}{ref_m} \right)^{\theta_{(m+n)}} \prod_{1}^{p} \theta_{(p+m+n)}^{COV_{pi}}$$

where, the typical value of a model parameter (*TVP*) will be described as a function of m individual continuous covariates (cov_{mi}) and p individual categorical (0-1) covariates (cov_{pi}) such that θ_n is an estimated parameter describing the typical PK parameter value for an individual with covariates equal to the reference covariate values ($cov_{mi} = ref_m$, $cov_{pi} = 0$); $\theta_{(m+n)}$ and $\theta_{(p+m+n)}$ are estimated parameters describing the magnitude of the covariate-parameter relationships.

Inter-Individual Variability

Unexplained random inter-individual variability of PK parameters was described by an exponential model:

$$P_j = TVP \cdot \exp(\eta_j)$$

where, P_j is the individual value for the PK parameter (e.g., CL) in the j^{th} individual and η_j is an independent random variable with a mean of zero and variance ω_P^2. This model assumes a log normal distribution for the difference between P_j and *TVP* (the model predicted PK parameter for the 'typical' individual). Estimates of inter-individual variance in P are presented as the square root of ω_P^2, which is an approximation of the coefficient of variation for a log-normally distributed quantity. A full block variance-covariance matrix for the inter-individual random effects was also explored, with any appropriate covariance terms retained in the base, full, and reduced models.

Intra-Individual Variability

A combined additive and proportional residual error model was used in this analysis:

$$Cs_{ij} = \hat{C}s_{ij} + \hat{C}s_{ij} \cdot \varepsilon_{ij1} + \cdot\varepsilon_{ij2}$$

where, Cs_{ij} is the i^{th} serum concentration measured in the j^{th} patient, $\hat{C}_{ij}$ is the corresponding model predicted serum concentration, and ε_{ij1} and ε_{ij2} are normally distributed error terms with means of zero and variances σ_1^2 and σ_2^2.

No covariance between residual variance terms was assumed (i.e., independence of residual variance terms). Examples of potential sources of residual variability may include intrasubject variability, assay error, incorrect model specification, and incorrect dose and/or sample records; however, procedural errors such as the latter two examples may also be reflected in ω^2.

Model Evaluation

The adequacy of the full model and parameter estimates was investigated with a posterior predictive check method. The basic premise being that a model and parameters derived from an observed data set should produce simulated data that are similar to the original observed data. Any problems evident in the simulations were investigated and further model development conducted as necessary.

Data Analysis

Data analyses were executed on (b) (4) using the nonlinear mixed effects modeling program NONMEM version 5, level 1.1. (b) (4) was used in concert with NONMEM. Base, full, and final model selection/development runs were typically implemented using a first-order estimation (FO) method for minimization of the objective function. However, first-order conditional estimation methods with interaction (FOCEI) and without interaction (FOCI) were also evaluated and used when considered appropriate or possible. Model parameters, including variances of the random effects and error terms, are more precisely estimated using FOCE and FOCEI compared to the first order (FO) method. However, successful minimization (i.e., convergence of model parameters to values that provide predicted concentrations that best fit the observed concentration data) and execution of the covariance step (to obtain the standard errors of

each parameter estimate, covariance matrix, and correlation matrix) using FOCE or FOCEI may not always be achievable, necessitating consideration of a simpler alternative estimation algorithm (i.e., FO).

A covariance step was required to be successfully executed in each NONMEM run for the run to be accepted. Three significant digits were required on all parameters for convergence.

The FO method was utilized for generating the time-variant base model parameter estimates, as attempts using FOCE or FOCEI failed to either converge or successfully execute the covariance step. The results obtained using the FO method were deemed to be acceptable based on the predictive check, the convergence difficulties with FOCE or FOCEI, and given that the likelihood ratio test was not used for covariate selection.

Results

Population PK Analysis

Base Model

The best time-invariant PK structural model was a two-compartment linear model. However, the PK parameter estimates from this model conflicted with the previously determined PK properties of natalizumab since the typical CL estimate of 0.0132 L/h, the typical V_{ss} estimate of 10.4 L (sum of V_1 and V_2), and a very long calculated terminal elimination half-life of 86 days are not consistent with previous observations of both single- and multiple-dose PK profiles for natalizumab and the observed nature of declining serum natalizumab concentrations after discontinuation of a repeated dose regimen (e.g., individual studies indicate that V_{ss} and $t_{½}$ values range only up to about 5.8 L and 12 days, respectively).

A two-compartment linear model incorporating CL change functions after administration of doses 3 and 4 was selected as a reasonable base model to carry forward into full model development. The sponsor's time-invariant and time-variant base PK model parameter estimates are shown in Table 1 and the goodness-of-fit graphs are illustrated in Figure 10-Figure 12.

Table 1 Sponsor's Time-Invariant and Time-Variant Base PK Model Parameter Estimates.

		Time-Invariant Model		Time-Variant Model	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate**	**%RSE**
Fixed-Effects Parameters					
CL	[L/hr]	0.0132	3.16	0.0177	3.11
CL reduction after 3rd dose	[-]	-	-	0.874	3.25
CL reduction after 4th dose	[-]	-	-	0.804	2.84
Q	[L/hr]	0.00305	11.1	0.290	34.1
V_1	[L]	3.14	2.22	2.72	3.82
V_2	[L]	7.22	34.9	1.56	15.1
Inter-Individual Variability					
ω_{CL}	[%CV]	32.6	6.41	30.7	7.51
ω_Q	[%CV]	80.2	15.4	-	-
ω_{V1}	[%CV]	30.1	13.6	37.8	23.8
ω_{V2}	[%CV]	125	10.1	66.0	31.0
$\omega_Q \omega_{V1}$	[-]	0.766	29.2	-	-
Intra-Individual Variability					
δ_1 (Prop residual error)	[%CV]	26.9	10.3	26.4	13.6
δ_2(Additive residual error)	[μg/mL]	1.90	23.7	2.53	19.6

Full and Final PK Model

The full model development utilized a covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing. Covariate relationships deemed of most interest were evaluated in this analysis, mainly based on prior knowledge or evidence of a correlation to model PK parameters, as well as scientific interest and mechanistic plausibility.

The full PK model equations are

$$CL = \theta_1 \times \theta_2^{CCL1} \times \theta_3^{CCL2} \times \left(\frac{TBW}{68}\right)^{\theta_4} \times (\theta_9)^{ANAC} \times (\theta_{13})^{INFL} \times (\theta_{16})^{RACE} \times (\theta_{17})^{AGE1} \times (\theta_{18})^{SEX} \times (\theta_{19})^{IMSU} \times (\theta_{20})^{STER1} \times (\theta_{20})^{CRCL} \times (\theta_{14})^{ALT} \times e^{\eta_1}$$

$$V_1 = \theta_4 \times \left(\frac{TBW}{68}\right)^{\theta_5} \times (\theta_{21})^{RACE} \times (\theta_{22})^{AGE1} \times (\theta_{15})^{SEX} \times e^{\eta_2}$$

$$V_2 = \theta_3 \times (\theta_{10})^{AGE1} \times e^{\eta_3}$$

$Q = \theta_6$ (fixed to base model value of 0.290 L/h)

$Y = F + F \times \varepsilon_1 + \varepsilon_2$ (proportional and additive residual error)

Only those covariate effects in the full model deemed of potential clinical relevance (either point estimate and/or 95% CIs are outside ±20% from population mean of the parameter) were included in the final model. Potentially clinically relevant effects included effects of total body weight (TBW) and RACE on both CL and V_1, an effect of AGE (categorized as adolescents vs. adults) on V_2, and an effect of anti natalizumab antibody category (ANAC) on CL. Further, most of the included covariates in the reduced model have been previously observed in the assessment of PK data from individual clinical studies. Of the covariate effects evaluated in this analysis, only TBW, ANAC, concomitant infliximab category (INFL), RACE, AGE, SEX, immunosuppressant category (IMSU), concomitant steroid category (STER), alanine aminotransferase category (ALT), and creatinine clearance category (CRCL) were included in the full model. Of these, only TBW, ANAC, AGE and RACE were significant covariate effects that could potentially produce a 20% or greater change in one or more PK parameters from that of the reference ('typical') patient.

Full and final PK model population parameter estimates are shown in Table 2 and the goodness-of-fit graphs are illustrated in Figure 13 - Figure 15.

Table 2 Sponsor's Full and Final PK Model Parameter Estimates.

		Full PK model		Final PK model	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate**	**%RSE**
Fixed-Effects Parameters					
CL	[L/hr]	0.0201	3.53	0.0191	2.97
CL reduction after 3rd dose	[-]	0.880	3.33	0.874	3.48
CL reduction after 4th dose	[-]	0.805	2.68	0.802	2.91
Q	[L/hr]	0.290 (fixed)	-	0.290 (fixed)	-
V_1	[L]	2.99	3.55	2.70	1.93
V_2	[L]	2.47	10.2	2.54	10.3
Covariate Relationships					
Exp. factor for TBW on CL	[-]	0.462	18.7	0.534	13.9
Exp. Factor for TBW on V_1	[-]	0.648	14.8	0.715	11.2
Scale factor for ANAC on CL	[-]	1.50	17.7	1.49	18.4
Scale factor for AGE1 on CL	[-]	1.01	8.73	-	-
Scale factor for AGE1 on V_1	[-]	0.989	7.72	-	-
Scale factor for AGE1 on V_2	[-]	0.217	27.1	0.222	22.0
Scale factor for SEX on CL	[-]	0.890	4.48	-	-
Scale factor for SEX on V_1	[-]	0.825	5.55	-	-
Scale factor for INFL on CL	[-]	1.02	4.61	-	-
Scale factor for RACE on CL	[-]	1.20	9.08	1.23	8.54
Scale factor for RACE on V_1	[-]	1.17	6.44	1.23	5.60
Scale factor for IMSU on CL	[-]	1.01	3.04	-	-
Scale factor for STER on CL	[-]	1.01	3.30	-	-
Scale factor for AGE2 on CL	[-]	1.02	5.82	-	-
Scale factor for CRCL on V_1	[-]	0.943	2.99	-	-
Scale factor for ALT on CL	[-]	1.03	4.15	-	-
Inter-Individual Variability					
ω_{CL}	[%CV]	30.3	6.28	30.6	6.39
ω_{V1}	[%CV]	25.8	33.0	27.2	35.7
ω_{V2}	[%CV]	36.3	40	38.6	38.2
Intra-Individual Variability					

δ_1 (Prop residual error)	[%CV]	27.6	12.4	27.7	13.3
δ_2(Additive residual error)	[µg/mL]	2.17	23.1	2.19	24.0

TBW is individual patient total body weight (kg), ANAC is anti-natalizumab antibody category (0 = antibody negative; 1 = antibody positive), INFL is concomitant infliximab category (0 = no; 1 = yes), RACE is race category (0 =Caucasian, Asian or Other; 1 = Black), AGE1 is an age category (0 = age >17 years; 1 = age ≤17 years), AGE2 is an age category (0 = age <60 years; 1 = age ≥60 years), IMSU is concomitant immunosuppressant category (0 = no; 1 = yes), STER is concomitant steroids category (0 = no; 1 = yes), ALT is alanine aminotransferase category (0 = ALT <64 U/L; 1 = ALT ≥64 U/L; where 64 U/L is approximately twice the upper normal range), CRCL is estimated serum creatinine clearance category (0 = CRCL >80 mL/min; 1 = CRCL ≤80 mL/min), SEX is subject gender (0 = male; 1 = female).

Posterior Predictive Check

As a predictive performance check, the full model was used to perform 500 simulations of the full data set. The simulated serum natalizumab concentrations at various time windows were compared to the observed data.

In general, all the various predictive check plots indicated reasonable predictive performance of the full model for 300 mg doses. Peak concentrations were very well predicted, with steady-state peak concentrations achieved by approximately doses 1–3. For the earlier doses, trough concentrations tended to be slightly over-predicted by the full model. Nonetheless, the full model well predicted the steady-state trough concentrations, which were achieved after approximately doses 4–6 (see Figure 16 - Figure 18 for posterior predictive check histograms for 300 mg doses only).

Covariate Effects on Population PK Model Parameters

Of the covariate effects evaluated in the analysis, only TBW, ANAC, INFL, RACE, AGE, SEX, IMSU, STER, ALT, and CRCL were included in the full model. Of these, only TBW, ANAC, AGE and RACE are significant covariate effects that could potentially produce a 20% or greater change in one or more PK parameters from that of the reference ('typical') patient.

Clearance (CL)

Evaluated covariate effects on CL included TBW, ANAC, INFL, RACE, AGE, SEX, IMSU, STER, ALT, and CRCL. However, covariate effects that could produce at least a 20% or greater change in the PK parameter from that of the reference ('typical') patient were limited to just TBW (population range evaluated 29–168 kg), ANAC (categorized as anti-natalizumab antibody negative vs. positive patients, *at the time of their serum natalizumab concentration assessment*), and RACE (categorized as black vs. all other races). These latter covariate effects were included in the final model. The effects of AGE (categorized as either adolescent vs. adult patients, or as patients ≥60 years vs. patients <60 years), INFL (categorized as coadministration with or without infliximab), IMSU (categorized as coadministration with or without immunosuppressants), STER (categorized as coadministration with or without steroids), ALT (categorized as alanine aminotransferase levels <64 U/L vs. ≥64 U/L), CRCL (categorized as estimated serum creatinine clearance >80 mL/min vs. ≤80 mL/min) and SEX (categorized as males vs.

females) on CL, appeared relatively small (i.e., very unlikely to be clinically relevant) or non-existent.

Based on the full population PK model developed, natalizumab serum CL (dose 1) would be predicted to increase with increasing TBW (estimated as 0.0174, 0.0204, and 0.0240 L/h in 50, 70, and 100 kg patients with otherwise similar characteristics to the reference patient in the full data set, respectively). Hence, for a 300 mg fixed dose, typical cumulative exposure (AUC_∞; where AUC_∞ = Dose/CL) would be expected to range from 17241 μg h/mL (50 kg patient) to 12500 μg h/mL (100 kg patient), and thus AUC_∞ would be expected to decrease by only approximately 28% for a doubling of TBW. Natalizumab serum CL at steady-state (>2184 hours after the first dose) would also be predicted to increase with increasing TBW (estimated as 0.0140, 0.0164, and 0.0193 L/h in 50, 70, and 100 kg patients with otherwise similar characteristics to the reference patient in the full data set, respectively). Hence, for a 300 mg fixed dose, typical cumulative exposure at steady-state (AUC_τ; where AUC_τ = Dose/CL) would be expected to range from 21429 μg h/mL (50 kg patient) to 15544 μg h/mL (100 kg patient), and thus AUC_τ would be expected to decrease by only approximately 28% for a doubling of TBW.

Serum natalizumab CL would also be predicted to be 20% higher in Blacks compared to other evaluated races, and be 50% higher in anti-natalizumab antibody positive compared to antibody negative patients. However, to further explore anti-natalizumab antibody effects, a supplementary analysis was conducted in which BLQ samples collected 672 ± 168 h post-dosing from all patients were set to a fixed value of LLOQ/2 (i.e., 0.125 μg/mL) in the assembled data set. This supplementary analysis resulted in natalizumab serum CL predicted to be typically 114% higher in anti-natalizumab antibody positive compared to antibody negative patients. Addition of the evaluated covariates to the equation for CL in the full model reduced the inter-individual variability estimate (%CV) for CL from 30.7% to 30.3%.

Central Volume of Distribution (V_1)
Evaluated covariate effects on V_1 included TBW, RACE (categorized as black vs. all other races), AGE (categorized as adolescent vs. adult patients), and SEX (categorized as males vs. females). However, covariate effects that could produce at least a 20% or greater change in the PK parameter from that of the reference ('typical') patient were limited to just TBW (population range evaluated 29–168 kg). RACE was also estimated to produce up to a 32% change in V_1 (based on the upper bound of the 95% confidence interval). Hence, both TBW and RACE were included in the reduced model. The effects of AGE, and SEX on V_1, appeared relatively small (i.e., very unlikely to be clinically relevant) or non-existent.

Based on the full population PK model developed, V_1 would be predicted to increase with increasing TBW (estimated as 2.45, 3.05, and 3.84 L in 50, 70, and 100 kg patients, respectively, who had otherwise similar characteristics to the reference patient in the full data set). Typically, V_1 would be predicted to be 17% higher in Blacks compared to other evaluated races. Addition of the evaluated covariates to the equation for V_1 in the full model reduced the inter-individual variability estimate (%CV) for V_1 from 37.8% to 25.8%.

Peripheral Volume of Distribution (V_2)
Evaluated covariate effects on V2 only included AGE. A model incorporating both AGE and TBW was also evaluated, but the added inclusion of TBW was not found necessary. AGE was observed to produce at least a 20% or greater change in the PK parameter from that of the reference ('typical') patient, and thus was included in the reduced model. Based on the full population PK model developed, V_2 would be predicted to be lower in the typical adolescent CD patient (0.54 L) compared to the typical adult CD patient (2.47 L). Addition of AGE to the equation for V_2 in the full model reduced the inter-individual variability estimate (%CV) for V_2 from 66.0% to 36.3%.

Covariate Effects on Derived Individual PK Model Parameter Estimates
Selected 'significant' covariate influences (i.e., TBW, RACE, and AGE) on derived individual patient natalizumab $t_{½\beta}$ and serum exposure measures (AUC, C_{max}, and C_{trough}; assuming 300 mg fixed dose) are presented below, for both a single dose and at steady-state. For this assessment, TBW was categorized into four groups: TBW ≤50 kg, 50 kg<TBW≤75 kg, 75 kg<TBW≤100 kg, TBW >100 kg. Further, race was categorized into two groups: non-Black and Black, and age were categorized into two groups: AGE >17 years and AGE ≤17 years.

The influence of immunogenicity (anti-natalizumab antibodies), as defined in the full model, on derived individual patient PK parameters was not practical to assess here given that immunogenicity status could change in a patient during the course of treatment. Further, the effect of immunogenicity on serum CL is likely underestimated in this analysis.

Of main clinical interest was to characterize the effects of TBW, AGE (categorized as adolescent vs. adult age groups), RACE (categorized as black vs. other races) and anti-natalizumab antibody status (categorized as negative vs. positive) on natalizumab PK:

Total Body Weight
Predicted serum natalizumab exposure measures (single dose or steady-state AUC, C_{max}, and C_{trough}) were shown to decrease with increasing TBW. However, the relatively modest magnitude of this effect (e.g., only a 28% decrease in AUC_{∞} is expected over a doubling of TBW for a 300 mg fixed dose) generally supports the selection of a fixed-dose regimen (300 mg every 28 days) during Phase 3 testing in adult CD patients, especially considering the efficacy and safety profiles of this compound. Even for patients >100 kg, typical $C_{ss,trough}$ values using a 300 mg fixed dose regimen would still be anticipated to exceed the range of 1–5 μg/mL, which is expected to maintain α4 integrin receptor percent saturation ≥70% and corresponding approximately two-fold mean elevation of peripheral lymphocyte counts above baseline levels. Generally comparable mean and median $t_{½\beta}$ values were also observed between the various TBW categories evaluated.

Age and Race
Only a limited number of adolescent (n = 38; 3.2%) or black (n = 36; 3.0%) patients were included in this analysis, precluding a definitive assessment of the effects of AGE

(adolescent vs. adult patients) and RACE (black vs. other races). Thus, some caution should be applied to any interpretation of these effects. The limited data available suggest that adolescent patients typically have about a 78% lower V_2 and a 43% shorter mean $t_{½\beta}$ than adult patients. Mean $C_{ss,max}$ and $C_{ss,trough}$ values are predicted to be about 22% higher and 55% lower, respectively, for a 300 mg fixed dose regimen when compared to adult patients. Corresponding predicted mean AUC_τ values are predicted to be about 14% higher in adolescent compared to adult patients, which mainly reflects the estimated modest TBW effect on CL. With respect to RACE effects, the limited data available suggest that black patients typically have 20% higher serum CL of natalizumab, 17% higher V_1, and about a 14% shorter mean $t_{½\beta}$ than patients of other races, with corresponding 17%, 14%, and 34% lower predicted mean AUC_τ, $C_{ss,max}$, and $C_{ss,trough}$ values, respectively. These observations are likely of no or limited clinical relevance as, for both adolescent and black patients, mean $C_{ss,trough}$ values for a 300 mg fixed dose regimen would still be anticipated to be either within or exceed the range of 1–5 μg/mL, which is expected to typically maintain α4 integrin receptor percent saturation ≥70% and corresponding approximate two-fold elevation of peripheral lymphocyte counts above baseline levels. However, in adolescent patients, C_{trough} values from the first few 300 mg natalizumab doses are predicted to be at or near the lower end of this target concentration range.

Anti-Natalizumab Antibody Status

Although 132 (11.1%) patients with transient or persistent anti-natalizumab antibodies were included in the assembled data set, many such patients only had immediately predose (trough) serum level assessments during natalizumab treatment, which were almost always BLQ. Hence, evaluation of anti-natalizumab antibody status effect was limited in this analysis by the relatively small number of observations with quantifiable serum natalizumab concentrations in antibody positive patients (i.e., only 34 out of 361 available observation records [from 30 patients] with a corresponding positive anti-natalizumab antibody measurement) and assessments at earlier time points after dosing were often not available in many anti-natalizumab antibody positive patients. Natalizumab serum CL was predicted in this analysis to be 50% higher (and thus serum exposure would be correspondingly lower) in anti-natalizumab antibody positive compared to antibody negative patients, though it should be recognized that this is likely an underestimate of the true effect. Using an alternative approach to further explore the effect of immunogenicity on natalizumab PK, an additional supplementary analysis was conducted with an assembled NONMEM data set in which any BLQ samples collected 672 ± 168 h post-dosing from all patients were set to a fixed value of LLOQ/2 (i.e., 0.125 μg/mL). Though this approach will still result in a biased effect estimate (i.e., from fixing BLQ trough values), it nonetheless provided a larger number of antibody positive observations (120 observations from 81 patients) for the analysis. This supplementary analysis resulted in natalizumab serum CL predicted to be typically 114% higher in anti-natalizumab antibody positive compared to antibody negative patients, though again this is likely an underestimate of the true effect.

Sponsor's Population PK Conclusions

- The developed full population PK model reasonably predicted the observed serum natalizumab concentrations included in this analysis from CD subjects participating in Phase 2 or 3 clinical studies.
- Upon repeat dosing (300 mg every 28 days), there was a relatively small increase in mean Cmax, but an approximate 2-fold increase in mean C_{trough}. Approximate (≥90%) steady-state Cmax and C_{trough} values were observed by approximately doses 1–3 and after doses 4–6, respectively.
- In the full model, only TBW, age (categorized as adolescent vs. adult age groups), race (categorized as black vs. other races), and anti-natalizumab antibody status (categorized as negative vs. positive) appeared to affect natalizumab PK parameters. Although serum natalizumab exposure decreased with increasing TBW, the effect was modest and not of sufficient magnitude to warrant dose adjustment based on body weight. Since only limited data are available for adolescent and black subjects, caution needs to be applied in the interpretation of any results for these subpopulations.
- A 300 mg fixed dose of natalizumab given every 28 days should typically provide, in all evaluated patient subpopulations (with the likely exception of anti-natalizumab antibody-positive subjects), predicted $C_{ss,trough}$ values that fall within or exceed the range of 1–5 μg/mL, which is generally required to maintain mean α4 integrin receptor percent saturation ≥70% and maintain approximately 2-fold elevation of mean peripheral lymphocyte counts. This dose regimen was determined through consideration of pharmacokinetic, pharmacodynamic, and clinical response (safety and efficacy) data observed within the natalizumab CD clinical program as follows:
    - Clinical efficacy investigations initially focused on 3–6 mg/kg monthly regimens based on PK and pharmacodynamic (PD) considerations.
    - Results from a Phase 2 dose-ranging study (CD202) showed that both the 3.0 and 6.0 mg/kg doses administered twice, one month apart, were efficacious and well tolerated in subjects with moderate-to-severe CD. Safety and efficacy profiles were similar, with no statistically significant differences observed between the two doses.
    - These two doses (3 and 6 mg/kg) provided serum natalizumab concentrations that were associated with a sufficient degree of α4 integrin saturation (i.e. ≥70%) throughout most or all of a monthly dose interval.
    - A 300 mg fixed dose (approximately 4.3 mg/kg; 70 kg subject) was selected for Phase 3 studies based on the following:
        - 3 mg/kg dose was efficacious, with the 99th percentile weight in the Phase 2 studies being 100 kg and there was no apparent added clinical benefit of the 6 mg/kg dose over the 3 mg/kg dose;
        - PK modeling and simulations predicted that a 300 mg fixed-dose would produce a range of natalizumab serum exposures in subjects that overlap and generally fall within those observed with the 3 and 6 mg/kg dose regimens;
        - Natalizumab clearance appears to be largely independent of body weight over the body weight range of approximately 40–100 kg, such that a fixed dose is feasible.

Reviewer's Comments on Sponsor's Population PK Analysis

- A total of 72 observations above BLQ were excluded in sponsor's analysis. A rerun including these samples did not change the mean population PK parameter estimates but the intra-individual variability parameters increased.
- The data from study CD307 (CRP elevated study) was not included in the population PK analysis. It is noted that the study report for CD307 was finalized after the population PK analysis report but it would have been preferred to include the data since the population the sponsor is seeking approval in this special population.
- The inter-compartmental clearance Q was fixed to 0.29 L/hr in the final model based on the base model's parameter estimate. When attempting to estimate Q, the estimate was close to zero and statistically non-significant when using the FOCE method with interaction. A one-compartment model seems more appropriate and should have been further explored.
- A one-compartment model also seems to calculate $t_{1/2}$ and V_{ss} values closer to the non-compartmental analysis.
- The sponsor based their covariate analysis on statistics rather than physiological understanding of data. Several statistical significant covariates with minor clinical significance were therefore identified.

The identified deficiencies in sponsor's analysis are addressed in the reviewer's analysis.

Reviewer's ANALYSIS

Studies

See section 0 under Sponsor's analysis. The following changes from sponsor's population PK analysis were made:

- The studies in adolescents (CD305 and CD352) were removed from the reviewer's analysis since the volume of distribution seemed markedly different from adults and it was not possible to correct this by including body weight or other physiologically meaningful covariates. The sponsor is not seeking an indication in this age group and therefore not deemed necessary for the analysis even though it would have been preferred to use all data.

Methods

Population PK Analysis

The methods used for the population PK analysis are similar to sponsor's methods.

Mixed-Model Repeated Measures Analysis

When considerable data are missing, especially mostly due to symptom worsening, it is important to analyze the data in multiple ways to arrive at sound inferences about effectiveness.

Last observation carried forward (LOCF) for missing data can be an inappropriate imputation technique for these types of data when the dropouts are not missing completely at random (MCAR) but rather due to lack of effectiveness.

An alternative method has therefore been investigated, i.e. mixed-model repeated measures (MMRM) analyses which are briefly described in the following.

Mixed-model repeated measures analysis was performed to utilize all the collected data to investigate the time course of effectiveness. The MMRM analysis was implemented via PROC MIXED in SAS 9.1 by fitting all the data collected during the open-label and double blind phases (no imputation). The model was fitted to baseline corrected CDAI score as a dependent variable and baseline, treatment, visit and treatment-by-visit interaction as independent variables. An unstructured (co)variance matrix was used to model the within subject errors. Parameters were estimated using maximum likelihood method.

Results and Discussion

Population PK Analysis

Base Model

The most adequate base PK model was a one-compartment model with first-order elimination. This model was chosen based on goodness-of-fit graphs and supported by PK data from a subset of patients (at selected US sites only) in study CD301 with more intense PK sampling (see Figure 2) as well as PK data from studies C-1805 and C-1806 showing a linear decline in log concentration over time from 0 hr up to 42 days post-infusion as well (see Figure 11.2-2 in study reports C-1805 and C-1806 on page 54).

The natalizumab clearance was found by the sponsor to decrease after multiple dosing. This change in clearance over time was confirmed by the reviewer (see Figure 3) and modeled the same way as the sponsor by changing the clearance after 3rd and 4th dose.

(b) (4)

The reduction in clearance with multiple dosing results in accumulation not expected based on the half-life of natalizumab ($t_{1/2}$ = 6 days) as illustrated in Figure 4 showing a box plot of the trough natalizumab concentrations from study CD-301 and CD-303.

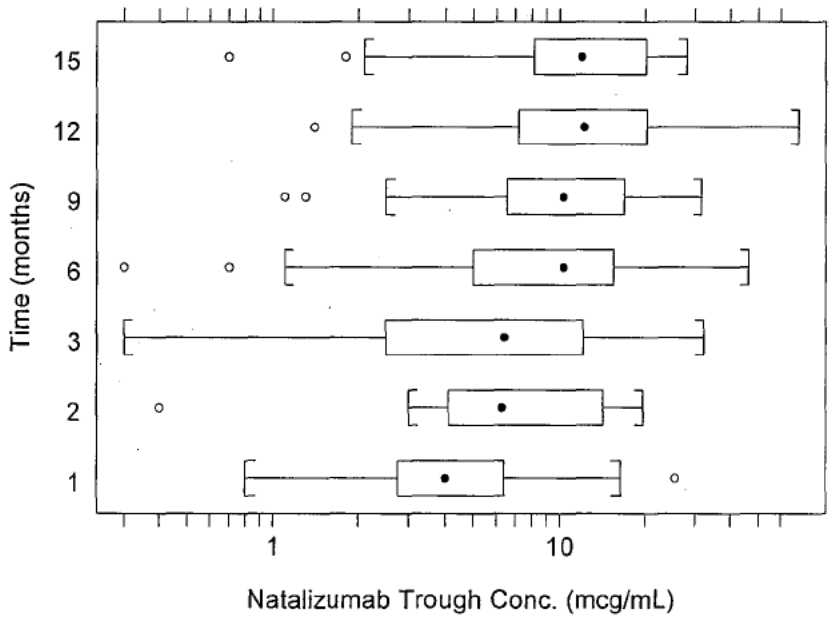

Figure 4 Box-plot of natalizumab trough concentrations from study CD-301 and CD-303.

The sponsor used a combined additive plus proportional residual error model in their population PK analysis. This was found to increase the bias at the lower concentration and therefore not used in this analysis. Instead, an additive residual error model on the log scale which is equivalent to a constant coefficient of variation (CV) residual error model on the normal scale was used.

Inter-individual variability was estimated for the clearance and volume parameters using an exponential model.

The model parameters were estimated using the FOCE method unlike the sponsor who used the simpler FO method for the estimation of model parameters.

The population PK parameter estimates for the reviewer's base PK model are shown in Table 3.

Covariate Model
Graphical analysis of covariate-PK parameter relationships showed that anti-natalizumab antibody status is the only significant covariate influencing natalizumab clearance.

From study CD303, the steady-state clearance was calculated using the formula

$$CL = \frac{Dose}{C_{ss} \cdot \tau}$$

where Dose is the administered dose, C_{ss} is the steady-state concentration, and τ is the dosing interval. The lack of an apparent trend in Figure 5 illustrating the relationship between CL_{ss} and body weight indicates that body weight is not a significant covariate for clearance but perhaps a slight tendency towards higher clearance for high body weight patients.

Therefore, only antibody status was included in the final PK model while body weight, age, creatinine clearance, steroid usage, prior infliximab usage, immuno suppressant usage, sex, and race were not since they did not significantly influence the natalizumab PK (see Figure 20-Figure 21).

Final Model
The parameter estimates for the final PK model are shown in Table 3. The goodness-of-fit graphs and covariate–PK relationships for the final PK model are shown in Figure 22 - Figure 24**Error! Reference source not found.**.

Table 3 Reviewer's Base and Final PK Model Parameter Estimates.

		Base PK model		**Final PK model**	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate**	**%RSE**
OFV	[-]	624	-	588	-
Fixed-Effects Parameters					
CL	[L/hr]	0.0181	2.34	0.0180	2.43
CL reduction after 3rd dose	[-]	0.845	2.65	0.848	2.72
CL reduction after 4th dose	[-]	0.771	2.32	0.773	2.37
V	[L]	3.56	2.19	3.56	2.22
Covariate Relationships					
Scale factor for antibody effect on CL	[-]	-	-	1.42	13.8
Inter-Individual Variability					
ω_{CL}	[%CV]	30.4	6.41	29.9	6.47
ω_V	[%CV]	16.6	28.7	17.2	26.0
Intra-Individual Variability					
σ(Prop residual error)	[%CV]	48.4	3.99	48.1	3.91

Dropout Analysis

Analysis of the baseline corrected CDAI score in the induction and maintenance studies are complicated by a significant dropout due to the lack of effectiveness, i.e. see Figure 6, where the percentage of patients remaining in the trial is plotted against time stratified on the baseline corrected CDAI score at final visit.

Patients are dropping out of the studies due to worsening of symptoms. The dropouts are not missing completely at random (MCAR), rather they are correlated with the ΔCDAI score. In particular, almost all patients with ΔCDAI > 96 drop out by Week 60 in study CD303, whereas only 20% of those patients with ΔCDAI score < -30 drop out of the study by Week 60.

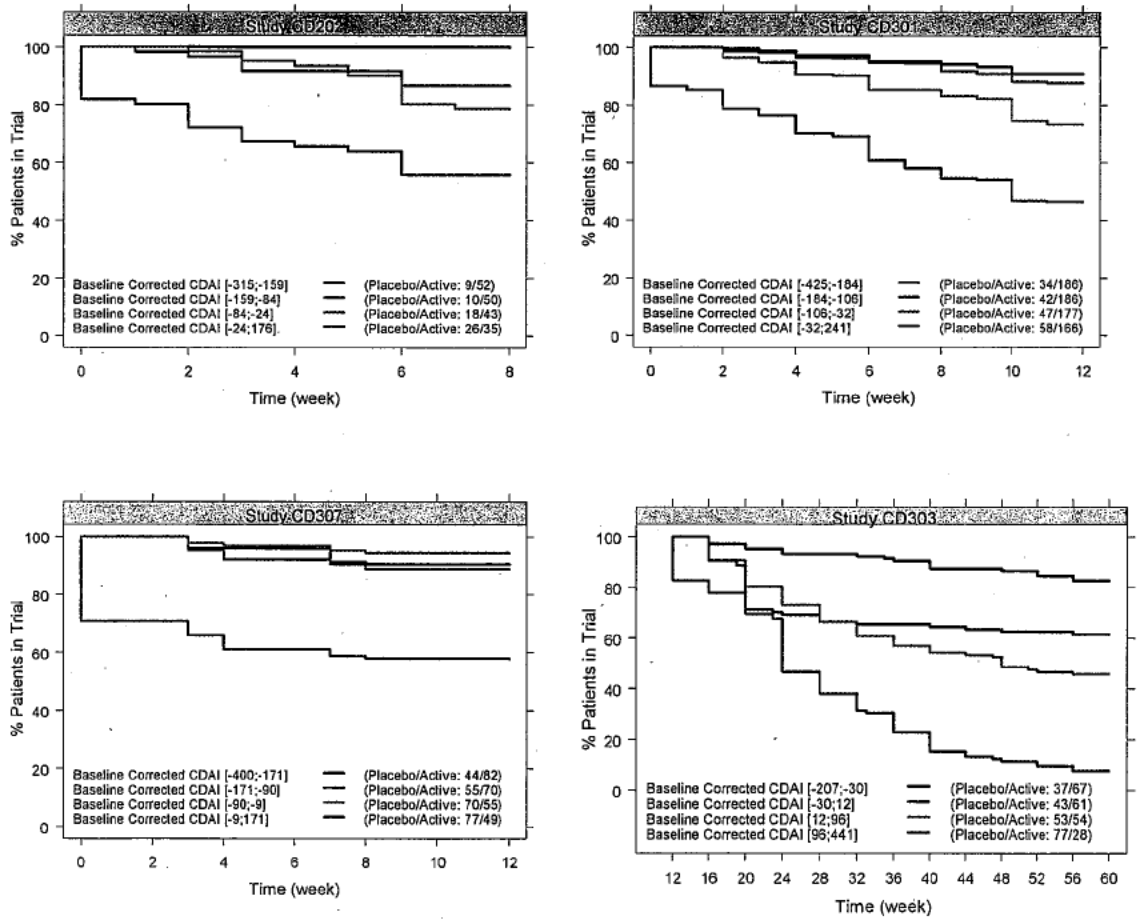

Figure 6 Dropouts in induction and maintenance studies stratified on last CDAI score.

Mixed Model Repeated Measures (MMRM) Analysis

The developed mixed-model repeated measures (MMRM) model is described by:

$$\Delta CDAI = ß_0 + ß_1 Visit\ ß_2 Treatment + ß_3 Base\ CDAI + ß_4 Visit*Treatment$$

where $ß_0$, $ß_1$, $ß_2$, $ß_3$, $ß_4$ refer to the intercept, slope in placebo group, symptomatic effect, baseline CDAI covariate effect, and slope differences between the treatment and placebo groups.

The least-squares mean predicted baseline corrected CDAI scores are shown in Figure 7 for induction studies CD202, CD301, and CD307 and maintenance study CD303. The active treatment groups are clearly separated from placebo in all studies except for study CD202 at week 12 where the highest dose group of 6+6 mg/kg is similar to placebo.

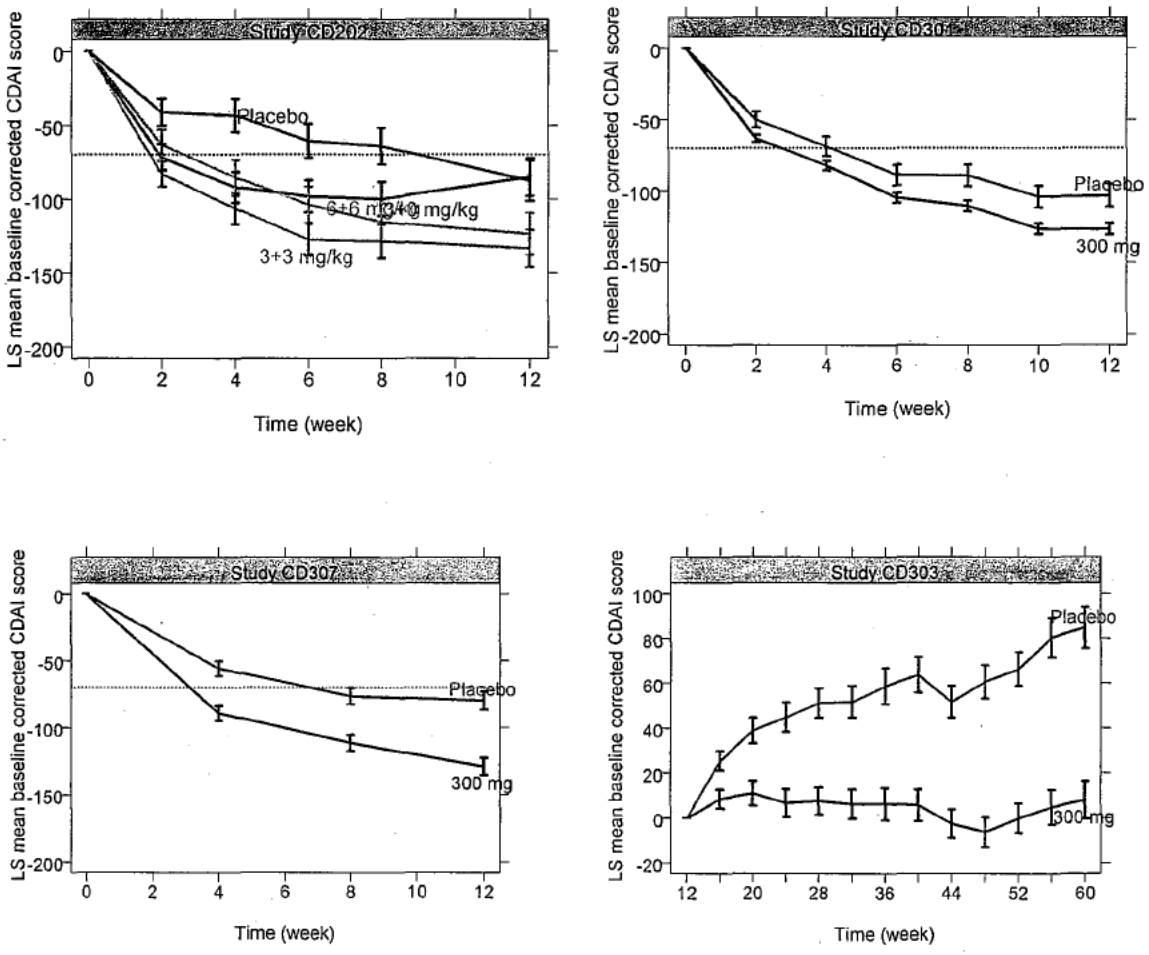

Figure 7 Least-squares mean predicted (±SE) baseline corrected CDAI scores.

Exposure-Response Analysis

The dose finding study CD202 revealed that monthly dosing of 3 mg/kg resulted in the highest clinical response rate (defined as ΔCDAI <-70) of approx. 70% compared to the highest dose of 6 mg/kg which had 50% response rate (see left graph in Figure 8).

The probability of clinical response in study CD202 was further explored by logistic regression where the natalizumab AUC_{τ} was identified to be a significant covariate for response.

The placebo response rate was approx. 40% and increases to approx. 80% for subjects with $AUC_{0\text{-}6\ weeks}$ around 20 mg*hr/mL whereas the upper concentration quartile of patients with $AUC_{0\text{-}6\ weeks}$ above 30 mg*hr/mL exhibited response rates of approx. 60% as illustrated right graph in Figure 8 where the mid-quartile $AUC_{0\text{-}6\ weeks}$ are shown with the corresponding response rate and the $AUC_{0\text{-}6\ weeks}$ ranges for the different doses tested shown as horizontal colored bars. The reason for observing a U-shaped exposure-response relationship for natalizumab was not identified.

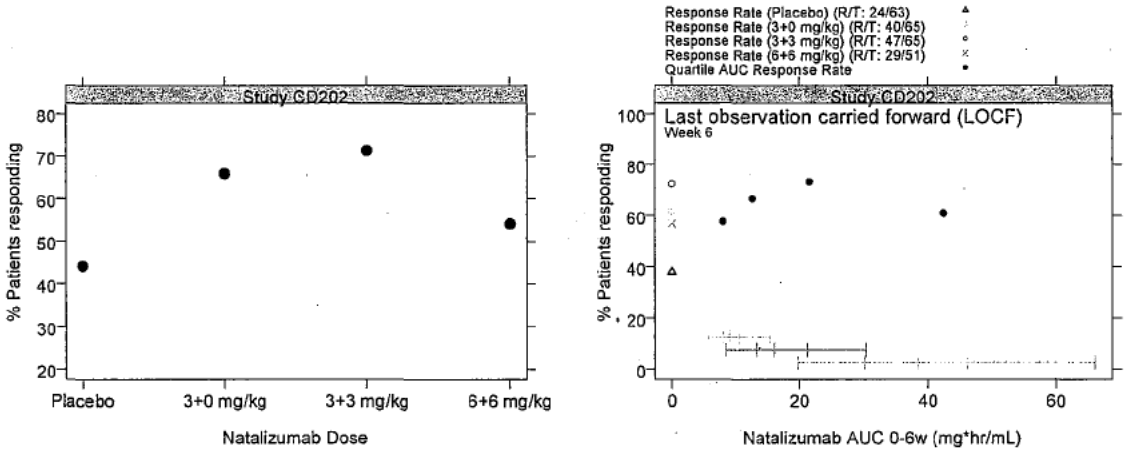

Figure 8. Exposure-response relationship for natalizumab. Percentage patients responding vs. (**Left**) natalizumab dose and (**Right**) natalizumab $AUC_{0\text{-}6\ weeks}$.

Exposure-Safety Analysis

The relationship between natalizumab exposure and serious infections, serious adverse events, urinary infections, and herpes simplex was investigated with only having a trend towards higher incidents of herpes simplex with higher exposure.

The overall percentage of patients with herpes simplex was 2.8% (N=14) and 4.4% (N=27) in the placebo and active treatment groups, respectively, across all studies.

The mid-quartile natalizumab AUC_{ss} vs. the percentage patients with herpes simplex indicates that patients with AUC_{ss} above 20 mg*hr/mL has a higher probability of getting herpes simplex compared to patients with lower AUC_{ss} (see Figure 9).

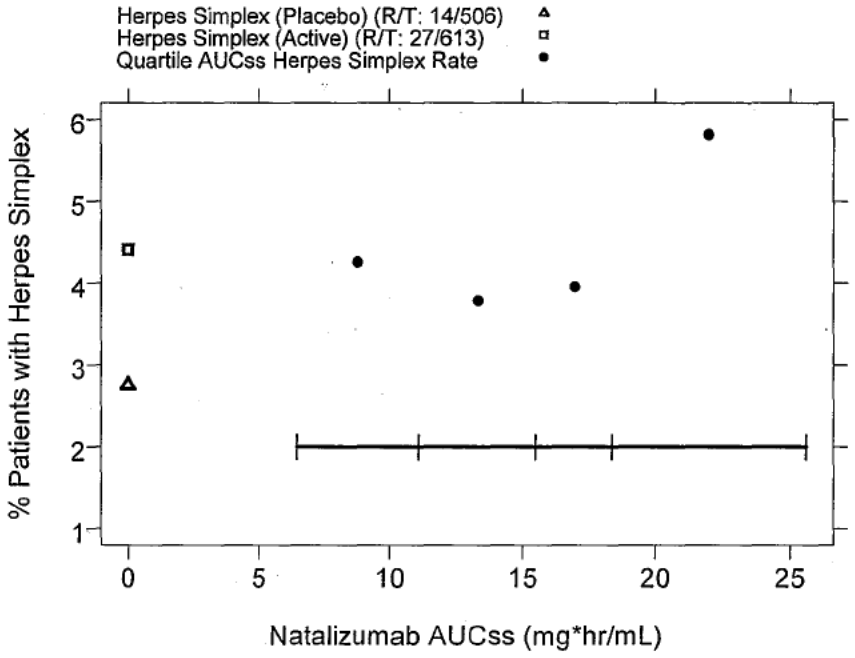

Figure 9. Exposure-herpes simplex relationship for natalizumab.

Pharmacometric Review Conclusions

The overall conclusions for the Pharmacometric review are:

- A one-compartment pharmacokinetic model with first-order absorption and elimination described the time-course of the observed serum natalizumab concentrations from 1156 Crohn's disease subjects participating in the 1 Phase II and 3 phase III clinical studies.

- An (unexplained) time dependency of CL was found to reduce CL by 25% with repeated administration. This results in a relative small increase in mean C_{max} but an approximate 2-fold increase in mean C_{trough}.

- In the final PK model, only anti-natalizumab antibody status (categorized as negative vs. positive) occurring in approx. 10% of the patients was found to affect natalizumab CL with an increase of 42% in CL for positive patients. This is likely to an underestimate of the true effect due to many antibody positive subjects had PK trough samples below LOQ.

- Body weight, age, race, ALT, AST, bilirubin, and creatinine clearance had no clinically relevant influence on the PK of natalizumab.

- A fixed dose of 300 mg q4w proposed by the sponsor is acceptable based on the following findings:
  - 3 mg/kg dose was efficacious, with the 99th percentile weight in the Phase 2 studies being 100 kg and there was no apparent added clinical benefit of the 6 mg/kg dose over the 3 mg/kg dose.
  - 6 mg/kg resulted in no dose-limiting toxicities.
  - Natalizumab clearance appears to be largely independent of body weight over the body weight range of approximately 40–100 kg, such that a fixed dose is feasible.
  - The probability of clinical response defined as a decrease in CDAI score of more than 70 points was found to be correlated with natalizumab exposure ($AUC_{.\tau}$in the dose-finding study CD202. However, an inverse U-shaped dose- and exposure-response relationship was found with the highest dose group of 6 mg/kg q4w having lower response rate compared to 3 mg/kg q4w. The reason for observing an inverse U-shaped relationship for natalizumab was not identified.

- The percentage of patients with herpes simplex in the natalizumab treated subjects was double that of placebo patients, i.e. 2.8% (N=14) for placebo and 4.4% (N=27) for natalizumab treated patients across all studies. The probability of herpes simplex appeared to increase for patients with natalizumab AUC_{ss} above 20 mcg*hr/mL.

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Posterior Predictive Check of Sponsor's Full Model

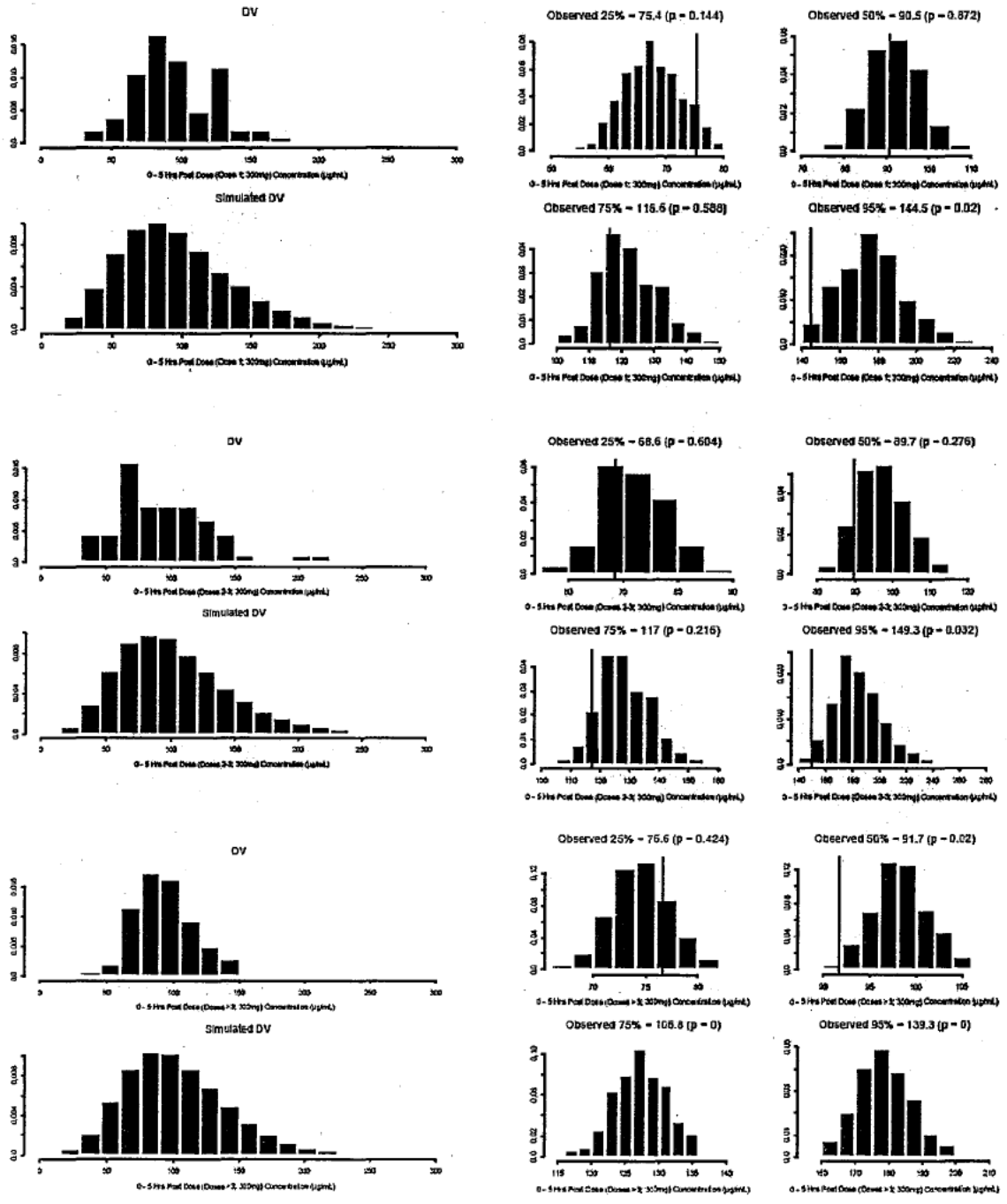


Figure 16 Comparison of the 0-5 hours post-dose concentrations for the 1st dose (top), 2nd and 3rd dose (middle), and >3rd dose (bottom) for 300 mg doses only.

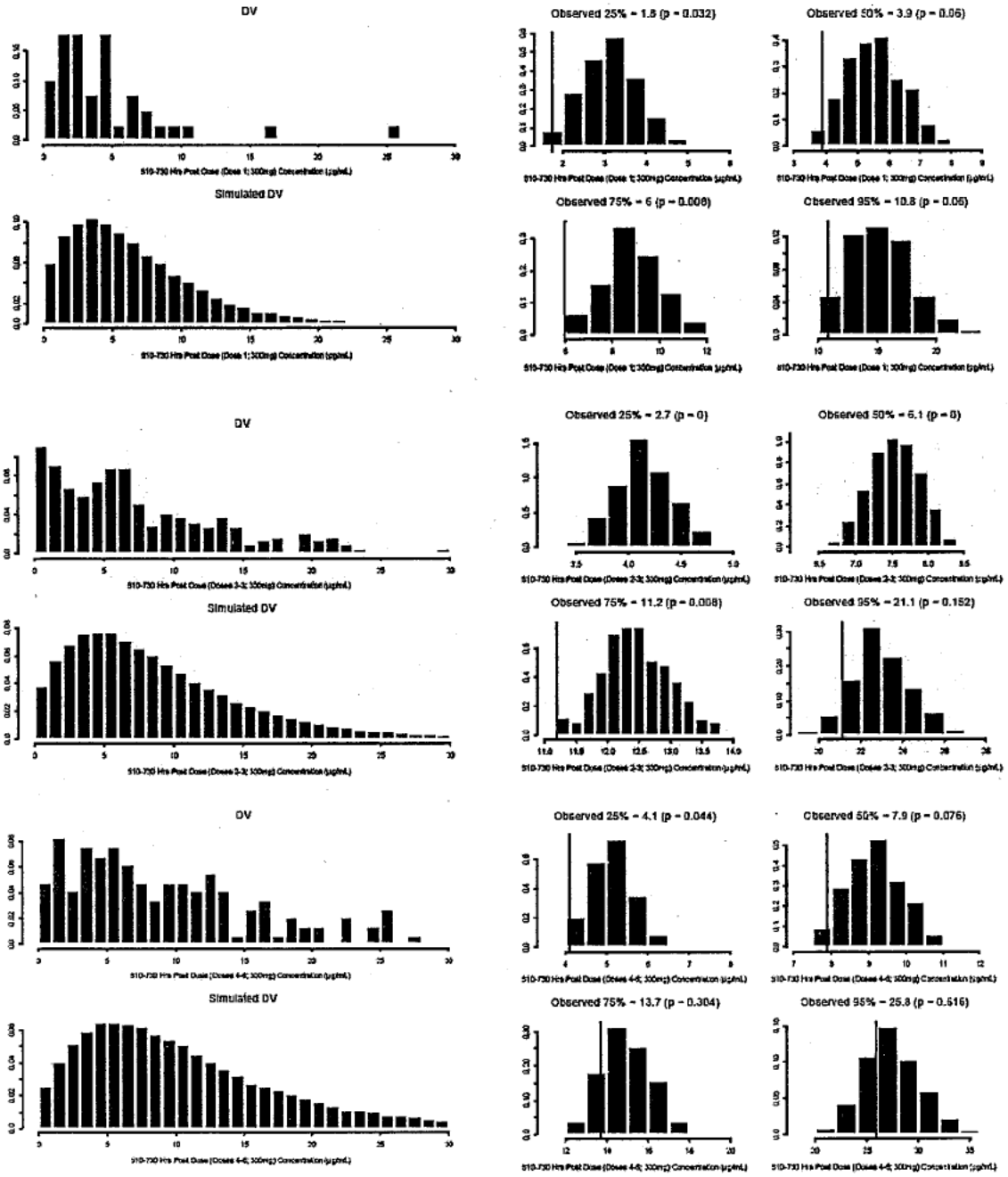


Figure 17 Comparison of 610-730 hours post-dose concentrations for the 1st dose (top), 2nd and 3rd dose (middle), and 4-6th dose (bottom) for 300 mg doses only. DV=observed concentration, Simulated DV = simulated concentration.

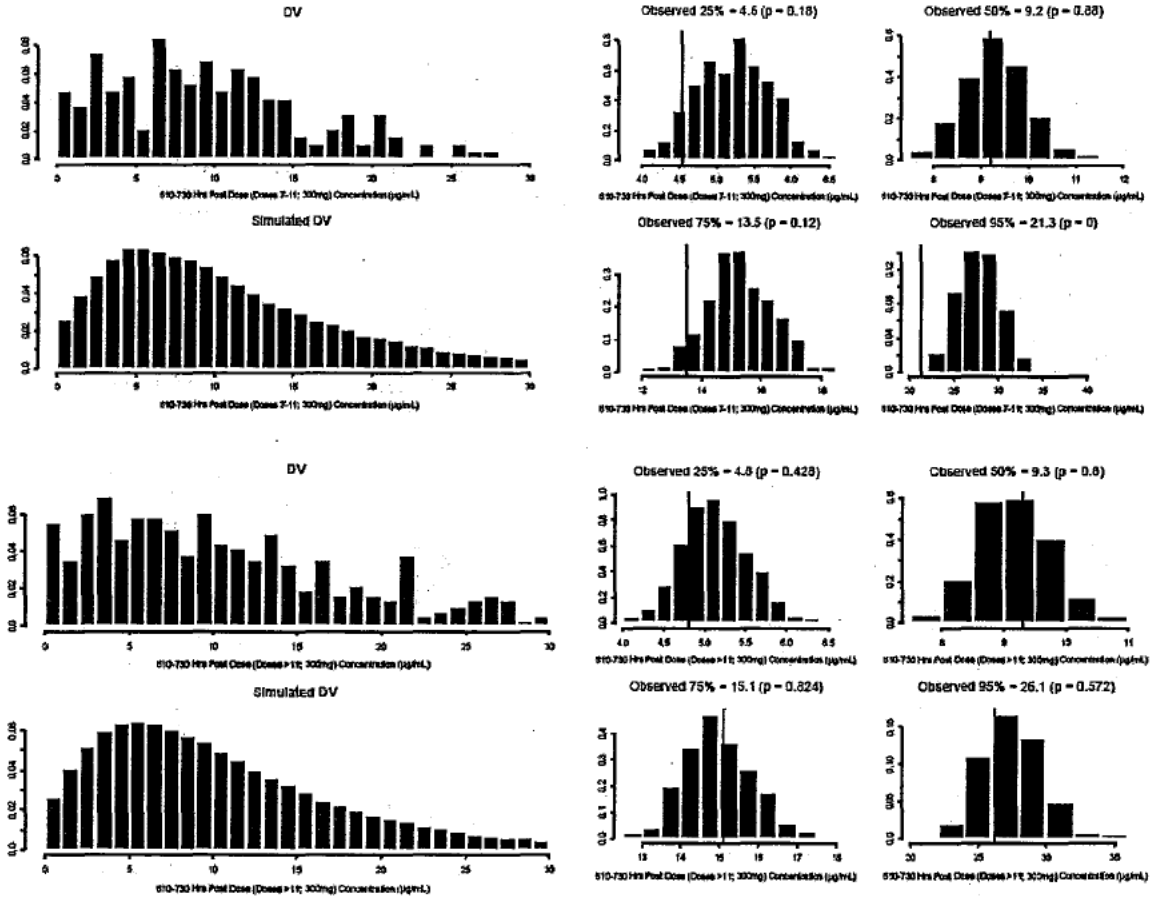


Figure 18 Comparison of 610-730 hours post-dose concentrations for the 7-11th dose (top) and >11th dose (bottom) for 300 mg doses only. DV=observed concentration, Simulated DV = simulated concentration.

Goodness-Of-Fit Graphs for Reviewer's Base PK Model

(b) (4)

(b) (4)

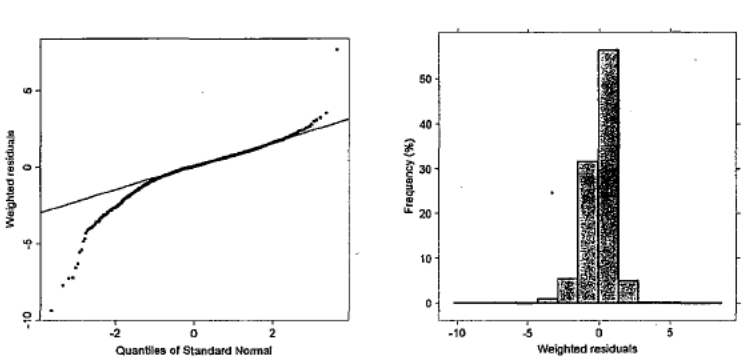


Figure 19 Goodness-of-fit graphs for reviewer's base PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the solid red line is a smoothing regression line.

Covariate-PK Parameter Relationships for Base PK Model

(b) (4)

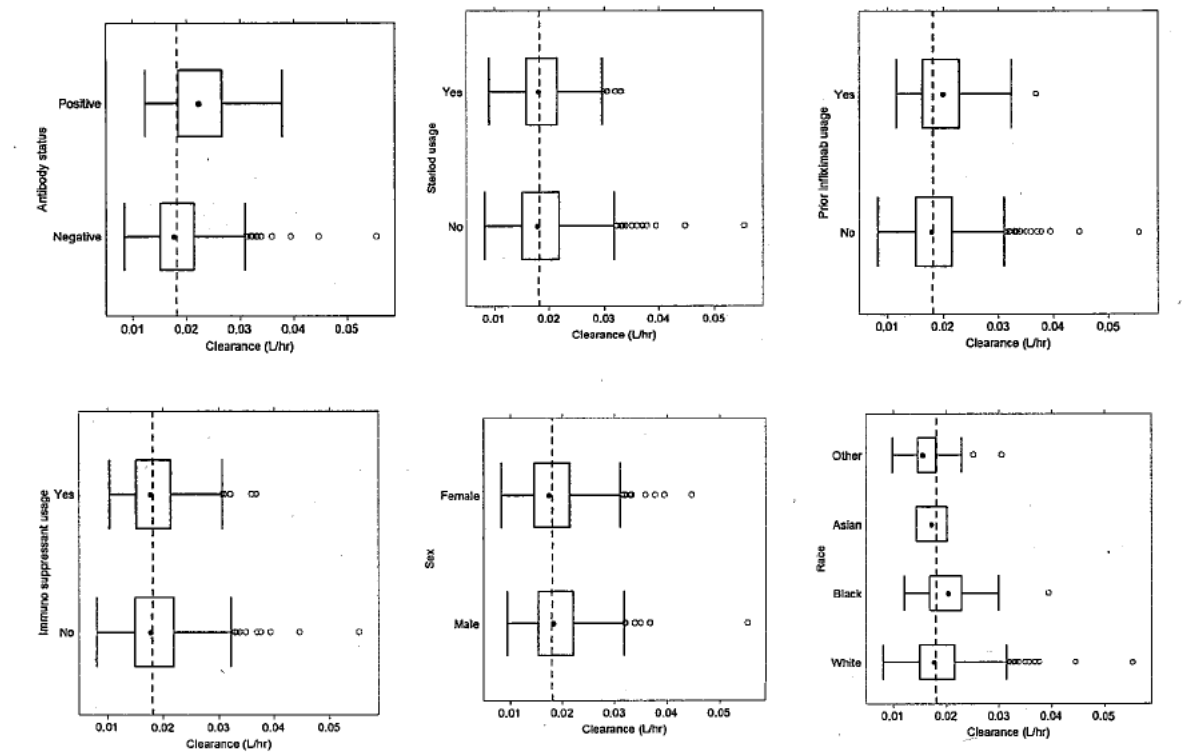


Figure 20 Graphical analyses of clearance-covariate relationships from base PK model. Individual clearance estimates vs. body weight (top left), age (top center), creatinine clearance (top right), antibody status (middle left), steroid usage (middle center), prior infliximab usage (middle right), immuno suppressant usage (bottom left), sex (bottom center), and race (bottom right). The dotted black lines are the population estimate of 0.0181 L/hr.

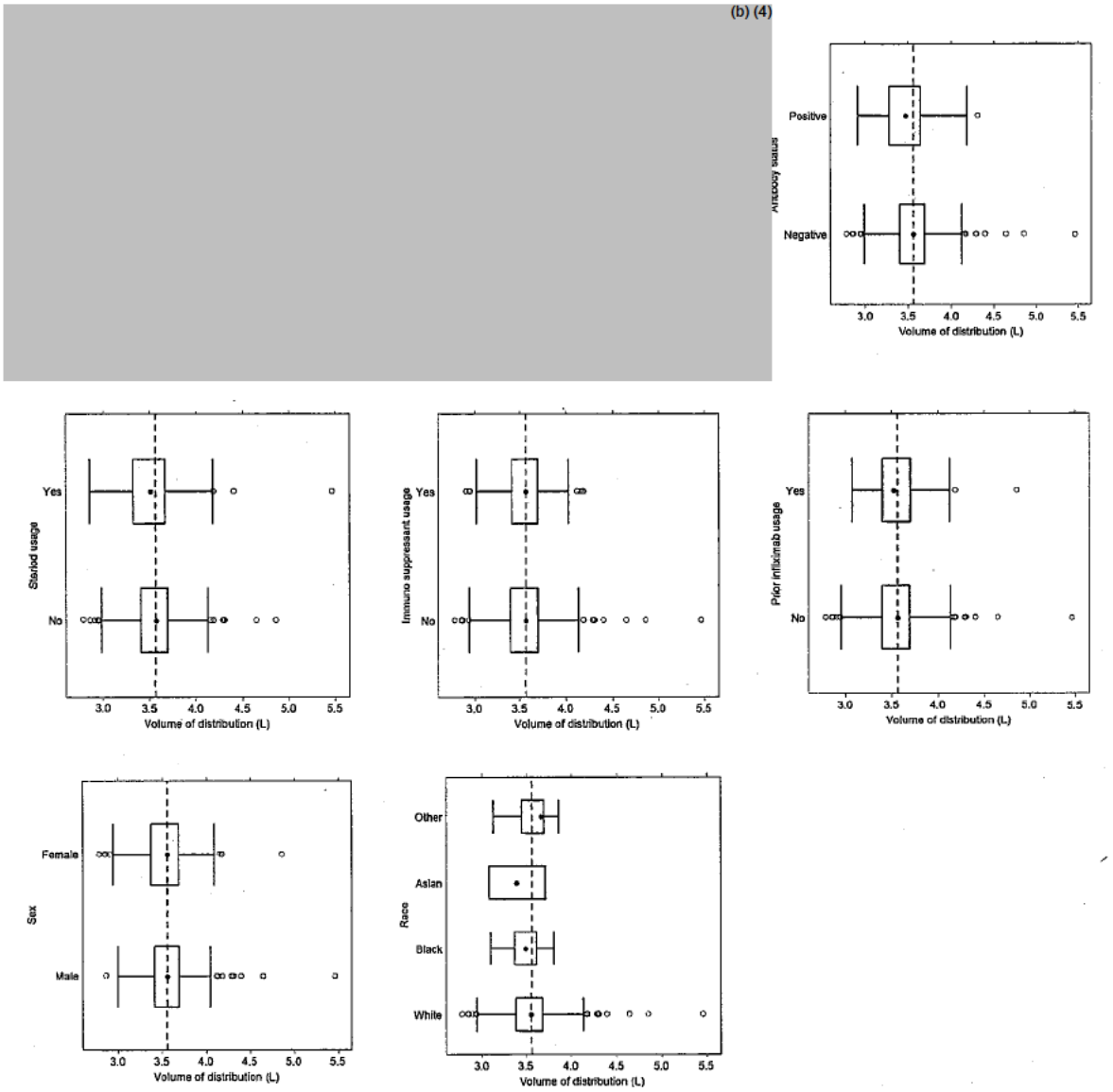


Figure 21 Graphical analyses of volume of distribution-covariate relationships from base PK model. Individual volume of distribution estimates body weight (top left), age (top center), antibody status (top right), steroid usage (middle left), immuno suppressant usage (middle center), prior infliximab usage (middle right), sex (bottom left), and race (bottom center). The dotted black lines are the population estimate of 3.56 L.

Goodness-Of-Fit Graphs for Reviewer's Final PK Model

(b) (4)

(b) (4)

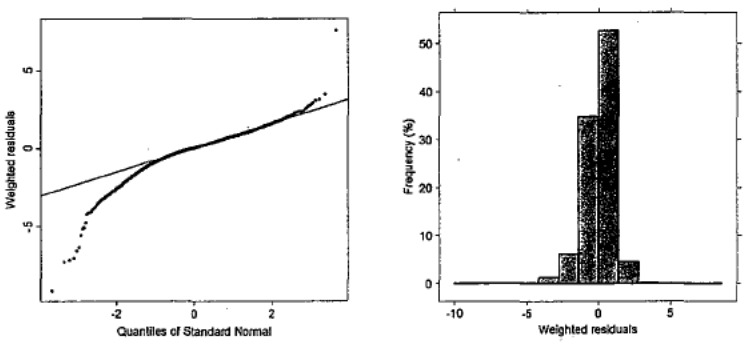


Figure 22 Goodness-of-fit graphs for reviewer's final PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the solid red line is a smoothing regression line.

Covariate-PK Parameter Relationships For Final PK Model

(b) (4)

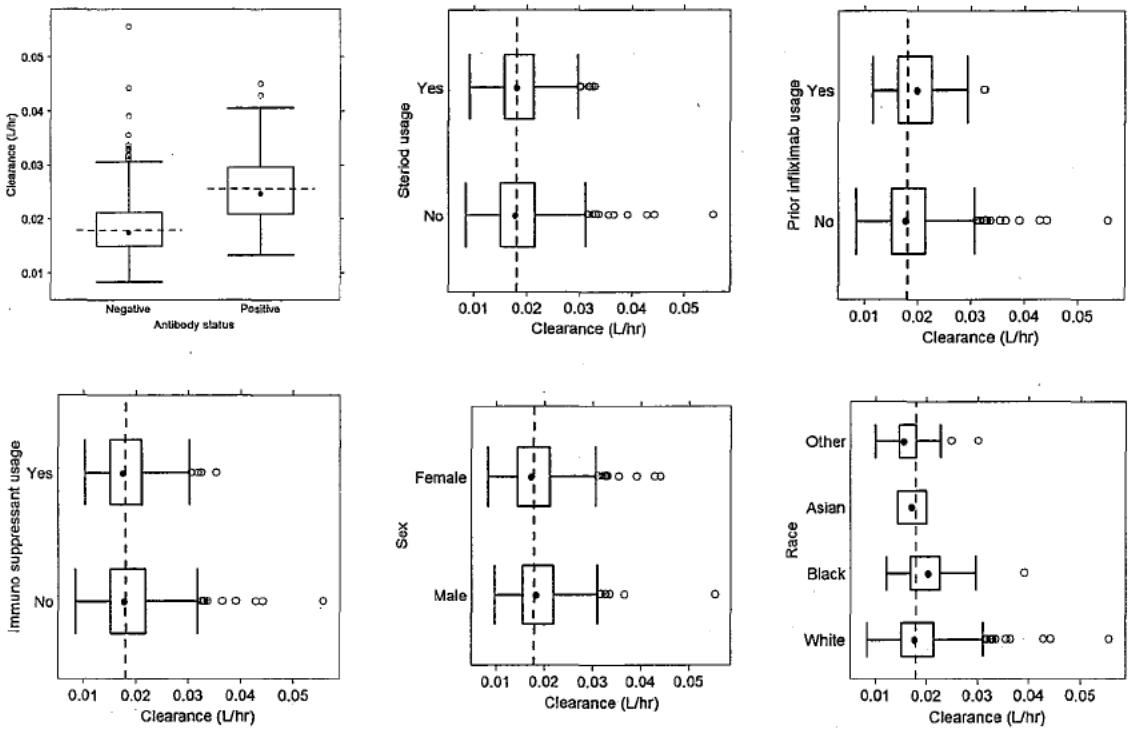


Figure 23 Graphical analyses of clearance-covariate relationships from base PK model. Individual clearance estimates vs. body weight (top left), age (top center), creatinine clearance (top right), antibody status (middle left), steroid usage (middle center), prior infliximab usage (middle right), immuno suppressant usage (bottom left), sex (bottom center), and race (bottom right). The dotted black lines are the population estimate of 0.018 L/hr.

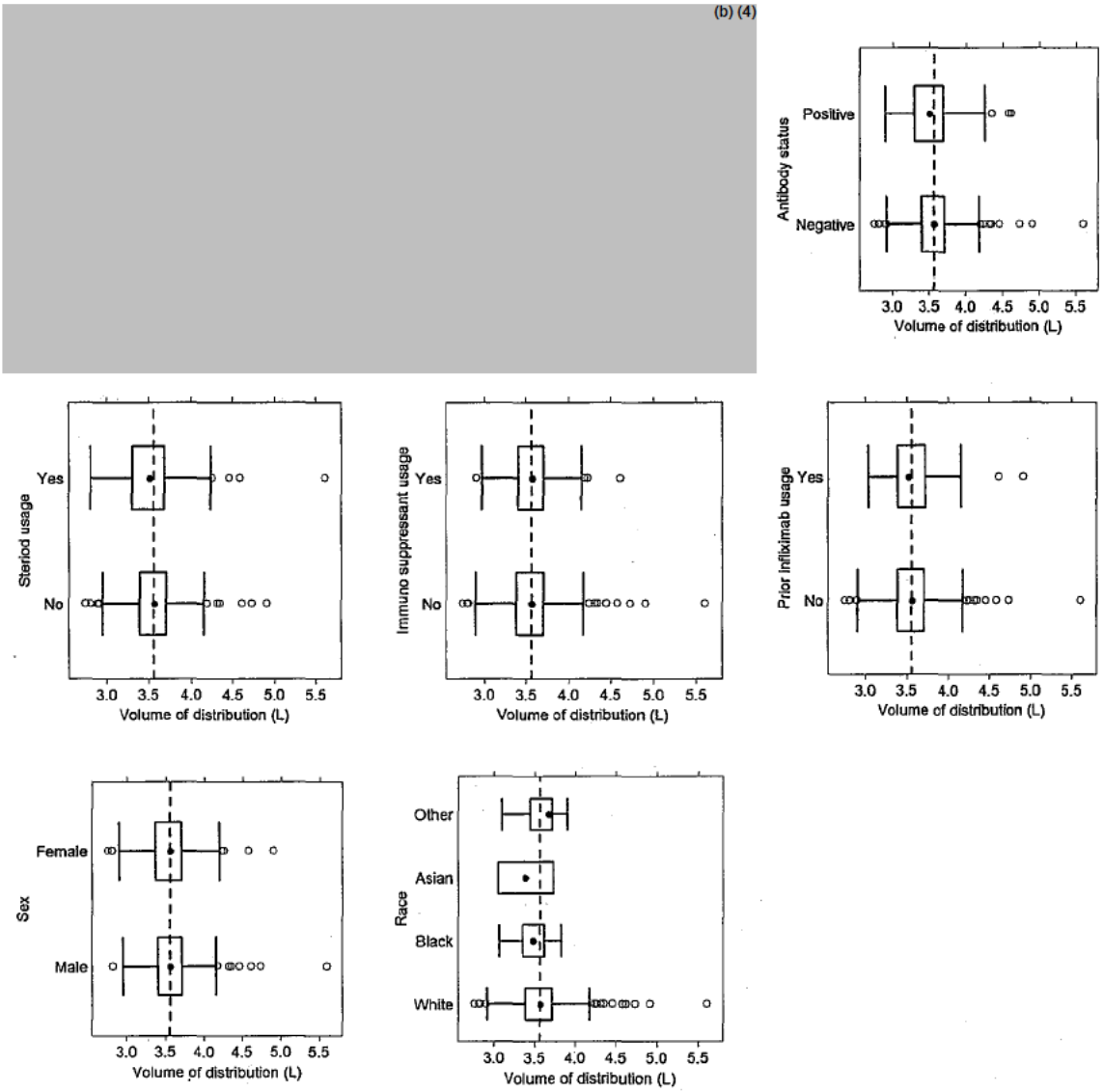


Figure 24 Graphical analyses of volume of distribution-covariate relationships from base PK model. Individual volume of distribution estimates body weight (top left), age (top center), antibody status (top right), steroid usage (middle left), immuno suppressant usage (middle center), prior infliximab usage (middle right), sex (bottom left), and race (bottom center). The dotted black lines are the population estimate of 3.56 L.

4.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

Biological License Application Filing and Review Form

General Information about the Submission

	Information		Information
BLA Number	125104/33	**Brand Name**	Tysabri
OCPB Division (I, II, III)	DCP3	**Generic Name**	Natalizumab
Medical Division	OND 540	**Drug Class**	Monoclonal Antibody
OCPB Reviewer	Abimbola Adebowale	**Indication(s)**	Treatment of Crohn's disease
OCPB Team Leader	Sue Chih-Lee	**Dosage Form**	IV Infusion
Letter Date	December 14th, 2006	**Dosing Regimen**	300 mg intravenously every 4 weeks.
Stamp Date	December 14th, 2006	**Route of Administration**	IV
Estimated Due Date of OCPB Review	08/15/07	**Sponsor**	Biogen Idec, Cambridge, MA
PDUFA Due Date	10/15/07	**Priority Classification**	Standard
Division Due Date	09/07/07	**BB IND Number**	006895

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	Not reviwed because it was already reviewed with the MS application	HV-101
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	6	6	CD201, CD202, CD251 (not TBMF dose), CD 305, CD306, CD352
Phase 3 clinical trial:	X	5	5	CD301, CD303,CD307, CD 351, CD354 (PK data was combined with CD351)
Population Analyses -				
Data rich:	X		1A	ELN100220-CD901
Data sparse:	X		1A	ELN100220CD901
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference (IR):				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	Not reviwed because it was already reviewed with the MS application	C-1805 and C-1806
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**14**	**14**	**11**	
Filability and QBR comments				

Types and #'s of studies and supplementary information (literature review) are adequate to conduct a review	"X" if yes X	Comments Filing Meeting on 01/31/07. Possibility of going to AC was discussed. Further information will be provided in Mid-March.
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Do we need a PM consult? Yes Do we need a Pharmacogenetics consult? NO	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale 01/30/07**	
Secondary reviewer Signature and Date		

CC: BLA 125104/33, HFD-850 (P.Lee), HFD-180 (M. Swider), DCP 3 (D. Bashaw, S. Lee)

1.1A.B

CLINICAL REVIEW

Application Type	Supplemental BLA
Submission Number	STN 125104 / 33
Letter Date	December 14, 2006
Stamp Date	December 15, 2006
PDUFA Goal Date	January 14, 2008
Reviewer Name	Anil Rajpal, M.D.
Review Completion Date	January 8, 2008
Established Name	Natalizumab
(Proposed) Trade Name	Tysabri(R)
Therapeutic Class	Monoclonal Antibody
Applicant	Biogen-Idec, Inc.
Priority Designation	S (Standard)
Formulation	Concentrated solution for dilution prior to infusion
Dosing Regimen	300 mg IV Q 4 weeks
Indication	Crohn's Disease (CD)
Intended Population	Moderately to severely active Crohn's disease patients who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-alpha

1/8/08

John E Hyde 1-8-08

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approving the efficacy supplement with revisions to the proposed labeling and to the proposed risk management program. The information in this supplement provides substantial evidence to support the proposed additional indication, and there are data to provide adequate directions for use.

This reviewer recommends that the population be adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and an inhibitor of TNF-α.

This reviewer recommends that the indication state that concomitant immunosuppressants or inhibitors of TNF-α should not be taken with natalizumab, and that prolonged steroid therapy should be discouraged.

This reviewer recommends that natalizumab should be discontinued by three months as proposed by the Applicant if the CD patient has not experienced therapeutic benefit.

This reviewer recommends that there be continued, intensive post-marketing surveillance and continued restricted distribution. In addition, this reviewer recommends that baseline neurological exams by a neurologist, baseline MRIs, and baseline JC virus assay of body fluids should not be required at baseline but should be performed in patients with newly emerging neurologic symptoms.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant has modified the current Risk Minimization Action Plan (RiskMAP) called the TOUCH (Tysabri Outreach: Unified Commitment to Health) Prescribing Program. The proposed RiskMAP has been extensively reviewed by the Office of Surveillance and Epidemiology Reviewer (Dr. Claudia Karwoski). Based on that review, the objectives and the main features of the two versions (CD-TOUCH and MS-TOUCH) are the same; however, each version differs in how forms and educational materials are customized to patients, their prescribers, and infusion site staff. There are two principal differences between CD-TOUCH and MS-TOUCH:

(1) Under CD-TOUCH, prescribers are to evaluate the patient at (b) (4) of Tysabri treatment to determine if the patient has experienced a therapeutic benefit, and are encouraged to

discontinue Tysabri in those patients that have not benefited. (This (b) (4) evaluation for therapeutic benefit is not required under the MS-TOUCH program.)

(2) Although concomitant therapy with systemic steroids will be permissible in the CD population (in contrast to the monotherapy indication for MS), the prescribing physician is encouraged to begin tapering systemic steroids and to discontinue Tysabri treatment in those patients that cannot be discontinued from systemic steroids within six months of initiating Tysabri. Similar to MS-TOUCH, concomitant treatment with other immunomodulatory and immunosuppressive medications is also discouraged.

To further assess the risks of Tysabri, the Applicant has proposed to conduct a prospective, observational cohort study of CD patients (Tysabri Global Observational Program in Safety; TYGRIS-CD). The primary objective of the study is to determine the incidence and pattern of serious infections, malignancies, and other serious adverse events (SAEs) with longer-term use of Tysabri in CD. The Agency and the Applicant have agreed on the sample size (see Review by Dr. Mark Levenson, Quantitative Safety and Pharmacoepidemiology Group). This study will be outlined in the approval letter as a postmarketing commitment.

In addition to the RiskMAP, natalizumab labeling has a description of what is known about the potential risk of PML and other adverse effects, including atypical and opportunistic infections; the existing labeling has a black BOXED WARNING for the risk of PML and general information about the RiskMAP.

1.2.2 Required Phase 4 Commitments

1. To conduct a prospective, observational study in subjects with Crohn's disease who are receiving natalizumab, by completing the protocol, "TYGRIS-CD: TYSABRI Observational Program in Safety in CD (Crohn's Disease)". (The number of patients and the duration of follow-up is pending. This will be provided in the review from Dr. Claudia Karwoski and Dr. Mary Willy.)

1.2.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

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 ordinarily 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 Applicant also categorized subjects by proportion with inadequate response to prior medications. However, the Applicant 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.

The current submission addresses the benefit of TYSABRI® therapy both in inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to, or inability to tolerate, conventional CD therapies and inhibitors of TNF-α. In support of this goal, Elan conducted two Phase 3 induction studies and one Phase 3 maintenance study that enrolled responders from the first Phase 3 induction study. A total of 1414 patients were enrolled in the Phase 3 studies.

A joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was convened largely 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 appropriate CD population in which to be indicated based on severity of disease and response to prior medications, requirements for concomitant medications, and requirements of and modifications to the proposed TOUCH program for the CD population.

The Advisory Committee voted 12 in favor, three opposed, and two abstentions for the approval of Tysabri for the treatment of Crohn's disease assuming that an effective risk management program is in place. Advisory Committee recommendations pertaining to efficacy and safety are summarized in the respective sections below.

1.3.2 Efficacy

In October 2003, Elan met with the Agency in order to finalize the natalizumab clinical development plan for Crohn's disease given results from the first Phase 3 induction study. In that study, natalizumab appeared to have a higher clinical response rate than placebo, but statistical significance was not reached. Elan conducted a post-hoc analysis in the elevated C-reactive protein (CRP) subpopulation, and found that the treatment effect was higher in that population. Elan proposed conducting a second induction study that would prospectively enroll

patients with elevated CRP, and a single maintenance study that enrolls responders from the first induction study. The Agency advised Elan that if both the proposed induction study and the proposed maintenance study were positive, that this could support a BLA submission.

Two Phase 3 induction studies and one Phase 3 maintenance study in CD 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).

The Applicant 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.

The 2007 Advisory Committee generally agreed that it would be best to restrict use of this product to patients who have had an inadequate response to all available therapies specifically including immunosuppressants, steroids and TNF-alpha inhibitors, or who are intolerant to these therapies.

1.3.3 Safety

The submission contains safety 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, which 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)

Subgroup analyses may help to determine if the risk of infections including serious infections is increased based on concurrent or prior immunosuppressant use, and help identify a population

which may have a more favorable benefit to risk ratio. No clear pattern has emerged. The 2007 Advisory Committee found no evidence for lesser efficacy of monotherapy and therefore agreed that concomitant immunosuppressant or prolonged steroid therapy should be discouraged.

The Advisory Committee's general consensus was that there is a need for continued, intensive post-marketing surveillance and continued restricted distribution. Specific recommendations from the Advisory Committee were that baseline general physical exams, including full neurological exams (with cognitive testing) would be most appropriate, and that baseline MRIs and JC virus assay of body fluids were not considered helpful, although these studies should be performed in patients with newly emerging neurologic symptoms.

1.3.4 Dosing Regimen and Administration

This reviewer recommends that the dose of natalizumab for Crohn's disease is 300 mg intravenous (IV) infusion every four weeks. Natalizumab should not be used with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, or methotrexate) or concomitant inhibitors of TNF-α. Aminosalicylates may be continued during treatment with natalizumab.

If the patient has not experienced therapeutic benefit by 12 weeks of therapy, the patient should stop natalizumab. Patients that start natalizumab while on chronic corticosteroids should commence steroid withdrawal as soon as a therapeutic benefit has occurred; if the patient cannot discontinue systemic corticosteroids within six months, natalizumab should be stopped.

1.3.5 Drug-Drug Interactions

Because of the potential for increased risk of PML and other infections, Crohn's disease patients receiving natalizumab should not be treated with concomitant immunosuppressants (e.g., azathioprine, 6-mercaptopurine, or methotrexate) or inhibitors of TNF-α, and corticosteroids should be tapered in those patients with Crohn's disease who are taking corticosteroids when they start natalizumab therapy. Ordinarily, MS patients receiving chronic immunosuppressant or immunomodulatory therapy should not be treated with natalizumab.

The Applicant submitted a population PK analysis which suggested that infliximab, steroids and immunosuppressants do not influence the pharmacokinetics of natalizumab on co-administration. The FDA has reviewed the data (see Clinical Pharmacology Review) and agrees with the Applicant's conclusion.

The Applicant also submitted results of Study CD306 in which CD patients concurrently received infliximab. The Applicant stated that the mean serum natalizumab PK parameters from CD306 for subjects receiving concomitant therapy with infliximab appeared to be generally comparable to those obtained in CD301 in which anti-TNF therapy was prohibited, indicating little or no readily apparent effect of infliximab on natalizumab PK. The clinical pharmacology reviewer (Dr. Abimbola Adebowale) commented that the results of the population PK analysis supported the Applicant's conclusions, but added that, due to the extrapolation of data following the third dose, AUC and half-life from Study CD306 were not truly comparable to those in Study CD301. (See Clinical Pharmacology Review.)

At the time of the original approval, the PK data suggested that multiple dosing with Interferon β-1a (Avonex® 30 μg IM once weekly) reduced the clearance of natalizumab by 30% (see original Clinical Review by Dr. Wilson Bryan). A population PK analysis however suggested that Avonex® does not influence the pharmacokinetics of natalizumab (see Clinical Review by Drs. Alice Hughes and Susan McDermott).

1.3.6 Special Populations

Natalizumab has not been studied in enough patients with renal insufficiency, hepatic insufficiency, age ≥ 65, age < 18, or in women who are pregnant or nursing to assess safety and efficacy in these populations. Natalizumab should be used during pregnancy only if clearly needed. For the MS indication, the Applicant was granted a pediatric waiver pursuant to 21 CFR 601.27(c) prior to the original approval.

The Applicant has requested: (1) a partial waiver excluding subjects (b) (4) from enrollment in future pediatric CD studies with natalizumab; and (2) a deferral in the pediatric CD population until the safety profile of natalizumab is better understood. Based on the information submitted, this reviewer recommends that the Applicant be granted both.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Natalizumab 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 MS, 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 MS may be secondary to blockade of the molecular interaction of α4β1-integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells.

In CD, the interaction of the α4β7 integrin with the endothelial receptor MadCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease. MadCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to gut lymph tissue found in Peyer's patches. MAdCAM-1 expression has been found to be increased at active sites of inflammation in patients with CD, which

suggests it may play a role in the recruitment of leukocytes to the mucosa and contribute to the inflammatory response characteristic of CD. The clinical effect of natalizumab in CD may therefore be secondary to blockade of the molecular interaction of the α4ß7-integrin receptor with MAdCAM-1 expressed on the venular endothelium at inflammatory foci. Although VCAM-1 expression has been found to be upregulated on colonic endothelial cells in a mouse model of IBD and appears to play a role in leukocyte recruitment to sites of inflammation, the role of VCAM-1 in CD is not clear.

2.2 Currently Available Treatment for Indications

Currently approved products for the treatment of Crohn's disease include: (1) systemic steroids (2) budesonide (Entocort EC®), (3) infliximab (Remicade®), and (4) adalimumab (Humira®).

Budesonide is a poorly absorbed oral steroid indicated for the treatment of mild to moderate Crohn's disease involving the ileum and/or the ascending colon and the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months.

Infliximab is an intravenously administered TNFα blocking agent indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. It is also indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

Adalimumab is a subcutaneously administered TNFα blocking agent indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. It is also indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have lost response to or are intolerant to infliximab.

2.3 Availability of Proposed Active Ingredient in the United States

Recombinant humanized IgG4 antibody to α4-integrin is not approved in any other form than natalizumab, and thus the active ingredient is not otherwise available on the market.

Natalizumab is currently licensed and marketed in the United States. Natalizumab is currently available through the TOUCH (TYSABRI Outreach: Unified Commitment to Health) Prescribing Program. This program has several features including a controlled distribution system for natalizumab and mandatory enrollment of prescribing physicians, patients, pharmacies, and infusion centers. The program is also designed to systematically track all natalizumab-treated patients, and includes special assessments for PML and other serious opportunistic or atypical infections. (See Sections 2.5.6 and 8.7)

2.4 Important Issues With Pharmacologically Related Products

Other than natalizumab, there are no other approved α4-integrin antagonists available on the world market at this time. A small number of other products that interfere with integrin interactions are under development for CD. Experience to date has been limited and no additional important issues have been identified.

2.5 Presubmission Regulatory Activity

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
7/31/07	Joint Gastrointestinal Drugs / Drug Safety and Risk Management Advisory Committee

2.5.1 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.

2.5.2 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 [redacted] (b) (4), approximately 7000 patients received up to three doses of natalizumab.

2.5.3 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[4]).

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 was diagnosed with astrocytoma and died; 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.

2.5.4 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.

The committee consensus was that Biogen has demonstrated natalizumab's efficacy in MS 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.

The committee consensus was that hypersensitivity reactions and development of antibodies were important considerations in making a risk-benefit assessment, and there is some concern of serious viral infections.

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

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."

The committee came to a consensus that natalizumab should not be taken as "add-on" therapy by MS patients who were receiving Avonex, Betaseron, Copaxone, Rebif, or Novantrone, and that a washout period would be needed if switching from one of those medications to natalizumab.

Committee members chose the option of evaluating concurrent use of interferon beta in clinical trials only after the risk of PML or other infections in monotherapy is better quantified.

2.5.5 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. The population to receive natalizumab 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)]

2.5.6 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.

2.5.7 Current Submission for CD

The current submission for CD was received on December 15, 2006 (FDA stamp date). 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 (proposed by Applicant to be re-named MS-TOUCH), with one new proposal as follows. For patients on steroids at initiation, these patients are to taper steroids after response to Tysabri. They must be tapered off of steroids by six months from the time of starting Tysabri; otherwise, they must discontinue Tysabri.

An Advisory Committee meeting was held July 31, 2007, to discuss the application. (See Section 8.5)

The Applicant subsequently submitted a major amendment on September 10, 2007, which resulted in a three-month extension of the review clock. The current PDUFA date is January 14, 2007.

2.6 Other Relevant Background Information

Other than natalizumab, there are no other approved α4-integrin antagonists available on the world market at this time.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Tysabri is an approved product. There are no significant issues with CMC or product microbiology in this submission.

3.2 Animal Pharmacology/Toxicology

No animal pharmacology/toxicology data was submitted as part of this BLA efficacy supplement.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on data from clinical trials conducted by the applicant and input from the 2007 Advisory Committee. In addition, the previous review for the MS indication was used to guide the review of safety issues. Submissions reviewed are summarized in the table below.

Table 2. Significant Submissions Reviewed

STN Numbers*	Description	FDA Received Date*
STN 125104/33/0	Efficacy Supplement	15-Dec-2006
STN 125104/33/1	Additional biostatistical data for CD303 and amendment to study report for CD307	15-Dec-2006
STN 125104/33/2	Response to Day 60/74 Information Request Letter	20-Mar-2007
STN 125104/44/0	Periodic Safety Update Report for 11/24/06 to 2/23/07	23-Mar-2007
STN 125104/33/3	Day 74 Information Request Letter Correction	26-Apr-2007
STN 125104/33/4	Revised redlined draft labeling (from a Changes Being Effected Special Labeling Supplement that was submitted to DNP)	16-May-2007
STN 125104/33/5	Confirmation of lots used in the phase 3 clinical trials.	21-May-2007
STN 125104/51/0	Periodic Safety Update Report for 11/24/06 to 5/23/07	25-Jun-2007
STN 125104/33/6	First response to selected items in Information Request Letter dated June 14, 2007.	13-Jul-2007
STN 125104/33/7	Materials that were reviewed in meeting with Agency held on June 27, 2007	16-Jul-2007
STN 125104/33/8	Second response to selected items in Information Request Letter dated June 14, 2007	19-Jul-2007
STN 125104/33/9	Third response to selected items in Information Request Letter dated June 14, 2007	25-Jul-2007
STN 125104/33/10	Redlined draft labeling and data tables supporting revisions	30-Aug-2007
STN 125104/33/11	Redlined and annotated draft labeling	04-Sep-2007
STN 125104/33/12	Redlined and annotated draft labeling	05-Sep-2007
STN 125104/33/13	Major amendment including Revision to the RiskMAP and TOUCH Program	10-Sep-2007
STN 125104/33/14	Revised draft labeling in SPL format	11-Sep-2007
STN 125104/33/15	Revised Medication Guide	12-Sep-2007
STN 125104/33/16	Clarification of "absolute" in pharmacodynamics section of label in phrase "absolute number of circulating neutrophils"	13-Sep-2007
STN 125104/33/17	Revised CD RiskMAP forms	17-Sep-2007
STN 125104/33/18	PMC Study - Protocol Concept	28-Sep-07
STN 125104/33/19	Revised Prescription Information and data tables	1-Oct-07
STN 125104/33/20	Response to RiskMAP questions and forms	4-Oct-07
STN 125104/33/21	Clinical site information	4-Oct-07
STN 125104/33/22	PMC Study Protocol concept and response to questions	16-Oct-07
STN 125104/33/23	Revised Prescription Information and annotated document	24-Oct-07
STN 125104/33/24	Statistics for CD 303, responses to the IR Letter received by	31-Oct-07

	firm on October 1, 2007 and data tables	
STN 125104/33/25	Discussion of rationale to not require baseline neurological examinations and MRI scans for the CD indication.	16-Nov-07
STN 125104/33/26	Response to questions regarding calculation of AEs in tables for Adverse Reactions section of labeling.	21-Nov-07
STN 125104/33/27	Correction to response received 21-Nov-07.	27-Nov-07
STN 125104/33/28	Revised draft full prescribing information	11-Dec-07
STN 125104/33/29	Response to comments about patient-reported outcomes.	14-Dec-07
STN 125104/33/30	Response to questions regarding RiskMAP questionnaires.	17-Dec-07
STN 125104/33/31	Analysis of hepatic events and supporting data.	20-Dec-07
STN 125104/33/32	Response to statistical comments and comments about AE information, and	20-Dec-07
STN 125104/33/33	Updated RiskMAP for CD	31-Dec-07
STN 125104/33/34	Carton and container labels	31-Dec-07
STN 125104/33/35	Revised draft full prescribing information	31-Dec-07

*. Based on RMS/BLA

4.2 Tables of Clinical Studies

The table below summarizes the clinical trials conducted as part of the development for the CD indication. The clinical trials in CD form the primary basis for this review.

Table 3. Clinical Development in Crohn's Disease

Study	Description	Design	Dose	# Doses	N
Phase 1					
CD201	Treatment of Active Disease (Single Dose)	R, DB, PC	3 mg/kg	1	30
Phase 2					
CD202	Treatment of Active Disease (Dose-Finding)	R, DB, PC	3 & 6 mg/kg	2	248
CD305	Adolescent Safety and PK (Active Disease)	OL	3 mg/kg	3	38
CD352	Adolescent Open-Label Extension (Chronic Re-Treatment)	OL	3 mg/kg	≤48	26
CD251	Open-label Intermittent Re-Treatment (Treatment Continuation of CD201, CD202)	OL	6 mg/kg	≤24	96
CD306	Safety in Subjects Receiving Infliximab with Disease Not in Remission (2:1 Randomization)	R, DB, PC	300 mg	3	79
Phase 3					
CD301	Treatment of Active Disease (4:1 Randomization)	R, DB, PC	300 mg	3	905
CD307	Treatment of Active Disease with Elevated CRP	R, DB, PC	300 mg	3	510
CD303	Maintenance of Response and Remission (Treatment Continuation of CD301)	R, DB, PC	300 mg	12	428
CD351	Open-label Extension Chronic Re-Treatment (Treatment Continuation of CD301, CD303, CD251, CD306, CD307)	OL	300 mg	≤24	1100
CD354	Open-label Extension Long-term Re-Treatment (Continuation of CD351)	OL	300 mg	≤24	39

R = randomized; DB = double-blind; PC = placebo-controlled; OL = open-label; PK = pharmacokinetics
(Table above is summarized from the Applicant's 5.2 Tabular Listing of All Clinical Studies.)

Clinical trials in patients with MS, ulcerative colitis (UC), and rheumatoid arthritis (RA) are briefly described in the table below; however, they did not contribute materially to the evidence of effectiveness for natalizumab in patients with CD and the data were considered primarily in terms of assessment of serious safety events.

Table 4. Clinical Development in Multiple Sclerosis, Ulcerative Colitis, and Rheumatoid Arthritis

Study	Description	Design	Dose	# Doses	N
Phase 1					
MS101	Safety and tolerability in normal male volunteers (dose escalation)	R, DB, PC	0.03-3.0 mg/kg	1	35
MS200	Safety and tolerability in RRMS and SPMS (dose escalation)	RD, DB, PC	0.03-3.0 mg/kg	1	28
MS224	Safety and PK in MS; on β-INF	OL	3 and 6 mg/kg	1	38
MS221	PK and PD in RRMS and SPMS	R, PC	1, 3, and 6 mg/kg	1	39
MS1805	PK, comparability, and comparison of formulations in normal volunteers	Crossover	300 mg	2	89
MS1806	PK, comparability, and comparison of formulations in normal volunteers	Crossover	300 mg	2	86
Phase 2					
MS201	Preliminary efficacy (MRI) in RRMS and SPMS	R, DB, PC	3 mg/kg	2	72
MS202	Preliminary efficacy (EDSS, MRI) in RRMS, SPMS, and AEX	R, DB, PC	1 and 3 mg/kg	1	180
MS231	Preliminary efficacy (MRI, EDSS, RR) in RRMS and SPMS (dose escalation)	R, DB, PC	3 and 6 mg/kg	6	213
MS1803	PK and drug interaction in RRMS; on GA	R, DB, PC	300 mg	6	110
MS1804	Emergency use in 5 y.o., refractory MS	OL	3 - 6 mg/kg	10	1
UC201	Preliminary safety and efficacy in UC patients	OL	3 mg/kg	1	10
RA201	Safety, tolerability and efficacy in RA patients receiving methotrexate	DB, PC	300 mg	6	299
RA251	Safety and tolerability in RA patients	OL	300 mg	≤ 12	200
Phase 3					
MS1801	Efficacy and safety (RR and EDSS) in RRMS	R, DB, PC	300 mg	30	939
MS1802	Efficacy and safety (RR and EDSS) in RRMS; on β-INF	R, DB, PC	300 mg	30	1171
MS1808	Extension safety and efficacy (from 1801, 1802, 1803[1])	OL	300 mg	≤24	1615
MS322	Safety, tolerability, and dose re-initiation[2] in RRMS	OL	300 mg	≤ 12	≤700
MS321	Safety, tolerability, and dose re-initiation[2] in RRMS	OL	300 mg	≤ 12	≤900

R = randomized; DB = double-blind; PC = placebo-controlled; OL = open-label; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; β-INF = β-interferon; PK = pharmacokinetics; PD = pharmacodynamics; MRI= magnetic resonance imaging; EDSS = Expanded Disability Status Scale; RR = relapses; AEX = acute exacerbation; GA = glatiramer acetate; 1 = Study 1808 included only subjects who completed previous trials; 2 = study is ongoing;
[Table above is modified from the Tabular Listing of All Clinical Studies and the Review by Drs. Susan McDermott and Alice Hughes for Natalizumab in MS (5/18/06)]

4.3 Review Strategy

Clinical review of the efficacy data, the safety data, and the proposed labeling of this efficacy supplement was done by this reviewer, Dr. Anil Rajpal. Dr. Lisa Kammerman reviewed the statistical aspects of the efficacy supplement. In addition, the proposed Risk Management Plan was reviewed by reviewers from the Office of Surveillance and Epidemiology, which included Dr. Mary Willy and Dr. Claudia Karwoski. Clinical pharmacology results were reviewed by Dr. Abimbola Adebowale and Dr. Christoffer Tornoe from the Office of Clinical Pharmacology. Product issues were reviewed by the Reviewer from the Office of Biotechnology Products, Dr. Barbara Rellahan.

The primary focus of the efficacy review is the three Phase 3 studies in CD, Studies CD301, CD303, and CD307. Studies CD301 and CD307 are placebo-controlled studies of the efficacy of natalizumab for induction of clinical response and clinical remission at the proposed recommended dose in the proposed target population. Study CD303 is a placebo-controlled study of the efficacy of natalizumab for maintenance of clinical response and clinical remission at the proposed recommended dose in the proposed target population.

The safety review is based primarily on the placebo-controlled studies in active CD and the previous placebo-controlled studies in MS. Although the studies in active CD were controlled, these were limited by short duration of exposure. Long-term studies in subjects with CD were reviewed for safety signals, but the information gained was limited with regard to product safety as most of these studies were uncontrolled. One long-term study, CD303, was controlled and included 428 patients randomized 1:1 to natalizumab or placebo; the duration of treatment in the study was 12 months following 3 months of treatment in a short-term induction study (CD301). The other long-term studies were uncontrolled. These were CD351 (n=1100), CD352 (n=26), and CD354 (n=39). (See Section 7.2.1.3.2.)

Information about the three cases of natalizumab-associated PML and the potential risk of PML came from a variety of sources, including the case reports, the Dose Suspension MS Safety Assessment Report, and the Dose Suspension CD/RA Safety Assessment Report.

Because subgroups for who the risks might be more acceptable might include those with prior medication use or those with inadequate response to prior therapies (i.e., these patients would likely be more severe and/or refractory than other patients), information was requested on how each of these subgroups were defined, and how the clinical response rates in each of these subgroups compared to the overall clinical response rate.

Information also was requested in an effort to identify characteristics that may predict the development of PML as there were only three cases. The Applicant was requested to analyze the incidence of infections (in particular opportunistic infections were used as a surrogate for PML risk) across categories of concomitant medication use (monotherapy versus steroids and/or immunosuppressants) in an effort to determine if there is a relation of infections to concomitant therapies.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) performed four clinical site audits for this application. Sites were selected for inspection based on higher number of patients enrolled and higher proportion meeting the primary endpoint than other sites. Sites selected for inspection are shown in the table below.

Table 5. Sites Selected for Inspection

Investigator	Site No.	Study (n at site)
Dr. Douglas Wolf	558	CD307 (n=10)
Dr. Jeffrey Breiter	509	CD301 (n=9); CD303 (n=9)
Dr. Robert Enns	521	CD301 (n=35); CD303 (n=12)
Dr. Jens Dahlerup	037	CD301 (n=14); CD303 (n=8)

DSI recommended that efficacy data from one site (Site No. 509, Dr. Jeffrey Breiter) be excluded in data analysis of Study CD301 primarily because of lack of source documents for primary endpoint data. DSI recommended that the other three sites appeared acceptable in support of the indication. (See DSI Clinical Inspection Summary dated December 21, 2007.)

Dr. Lisa Kammerman, the statistics reviewer, re-analyzed the efficacy data for Studies CD301 and CD303 with data for Site No. 509 (Dr. Jeffrey Breiter) excluded. Based on that re-analysis, the conclusions have not changed for either Study CD301 or Study CD303. (See Statistics Review by Dr. Lisa Kammerman.)

4.5 Compliance with Good Clinical Practices

The Applicant stated that Studies CD301, CD303, and CD307 were each carried out in accordance with International Conference on Harmonization (ICH) / Good Clinical Practice (GCP) guidelines. In addition, other CD studies (CD201, CD202, CD305, CD306, CD251, CD351, CD352, and CD354) were each also carried out in accordance with ICH/GCP guidelines.

4.6 Financial Disclosures

Financial disclosures were included in the submission, and notable findings include the following:

1. (b) (4): Studies (b) (4) Sub-Investigator at Site # (b) (4) owned Elan stock with estimated value of greater than $50,000.00 at the start of the study, but no longer held any significant equity interest in Elan stock by the end of the study; all previously acquired stock was sold prior to his end of study date.
2. (b) (4) Studies (b) (4) Sub-Investigator at Site # (b) (4)) owned 1,000 shares of Elan stock with estimated value not exceeding $50,000.00 at the

start of the study, and increased amount of Elan stock to 10,000 shares with estimated value exceeding $50,000.00 by the end of the study. He no longer holds any significant equity interest in Elan stock as all previously acquired stock was sold as of November 15, 2004.

3. (b) (4): Studies (b) (4) Principal Investigator and Scientific Consultant/Medical Advisor at Site # (b) (4)) received payments (honoraria, consulting fees) totaling $32,901.00 at the start of the study, and received payments (honoraria, consulting fees) totaling $98,501.00 at the end of the study.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology data have been extensively reviewed by the Clinical Pharmacology Reviewers (Abimbola Adebowale and Christoffer Tornoe); please see the Clinical Pharmacology Review. A summary of the Clinical Pharmacology Reviewers' findings is presented below.

5.1 Pharmacokinetics

Non-Compartmental Analysis:

Following single (first) and repeat (third) dosing of 300 mg of natalizumab to CD patients (N=19) in study CD301, the mean maximum observed serum concentrations (Cmax) were 102 ± 31 and 101 ± 34 mcg/mL for the first and third doses, respectively. The Cmax was observed at approximately 1 to 3 hours after the start of drug infusion, followed by a somewhat rapid drop within the first 24 hours after infusion, with a slower decline thereafter over the 4 week dosing interval. The mean "trough" serum concentrations were 5.3 ± 6.3 and 8.0 ± 6.1 mcg/mL four weeks following the first and third doses, respectively. The mean half-life, volume of distribution, and clearance (CL) of natalizumab following the third dose were 231 ± 173 hrs (= 9.6 ± 7.2 days), 5.2 ± 2.8 L and 22 ± 22 ml/hr, respectively. In Study CD306, patients received concurrent infliximab 5.0 mg/kg every 8 weeks (including one dose each at Week -2 and Week 6). PK parameters for natalizumab were generally comparable to those observed in Study CD301.

The results of the dose-ranging study CD202 indicated that natalizumab's systemic exposure was approximately dose proportional over the dose range of 3.0 to 6.0 mg/kg. Inter-subject variability for Cmax and AUC typically ranged from 30 to 60% for a 300 mg fixed monthly natalizumab dose.

Population PK Analyses:

The findings of the population PK in CD patients (N=1156) from three Phase 2 studies (two studies #305 and #352 conducted in the adolescent population were excluded) and three Phase 3 studies were similar to those obtained for MS patients, i.e.,

- In both patient populations, an (unexplained) time dependency of CL was found to reduce CL by 25% with repeated administration.

- Anti-natalizumab antibodies occurring in approximately 10% of the patients were found to increase CL by approximately 40%. This is likely to be an underestimate of the true effect due to many antibody positive subjects having PK trough samples below LOQ.
- Body weight, age, race (categorized as black vs. other races), ALT, AST, bilirubin, and creatinine clearance had no clinically relevant influence on the PK of natalizumab suggesting that a fixed dosing regimen is appropriate.

5.2 Pharmacodynamics

Pharmacodynamic (PD) markers that were consistent with the mechanism of action of natalizumab were collected throughout clinical development. These markers included both flow cytometric determination of α4 integrin receptor occupancy (% saturation) on peripheral blood mononuclear cells (PBMCs) and also elevated peripheral lymphocyte counts. Both markers were assessed from the time of natalizumab administration to the end of the monthly dosing interval and beyond the discontinuation of natalizumab therapy. In general, these measures did not show a consistent correlation with clinical outcome, and should be considered as exploratory at this time.

5.3 Exposure-Response Relationships

Efficacy: Exposure-response relationships for efficacy were evaluated in a dose-finding study CD 202, where CD patients received two IV doses (placebo+placebo; 3+0 mg/kg; 3+3 mg/kg; or 6+6 mg/kg) separated by 4 weeks. The results of this study indicated that the probability of a clinical response defined as a decrease in CDAI score of more than 70 points was found to be correlated with natalizumab exposure (AUC_τ). However, an inverse U-shaped dose- and exposure-response relationship was observed, with the highest dose group of 6 mg/kg every 4 weeks having a lower response rate compared to the 3 mg/kg every 4 weeks. The reason for observing an inverse U-shaped relationship for natalizumab was not identified.

Safety: The relationship between natalizumab exposure and serious infections, serious adverse events, urinary infections, and herpes simplex was investigated. However, only a trend towards higher incidents of herpes simplex with higher exposure was observed. Serious infections (other than PML), urinary infections, serious adverse events were not found to be correlated with natalizumab exposure.

Immunogenicity: Generally, the presence of anti-natalizumab antibodies, particularly in persistent antibody–positive subjects (i.e., positive antibodies at two or more time points separated by at least 42 days), was observed to be associated with reduced serum natalizumab concentrations in the individual studies. In the population PK analysis, the presence of anti-natalizumab antibodies occurring in approximately 10 % of the CD patients was found to increase CL by approximately 40 %.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In the "Indications and Usage" section, the Applicant proposed (b) (4)

Following the Advisory Committee and discussions with FDA, the Applicant proposed (b) (4)

6.1.1 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.

6.1.2 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 Section 10.1). 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 Applicant 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 Applicant 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.

6.1.3 Study Design

6.1.3.1 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.

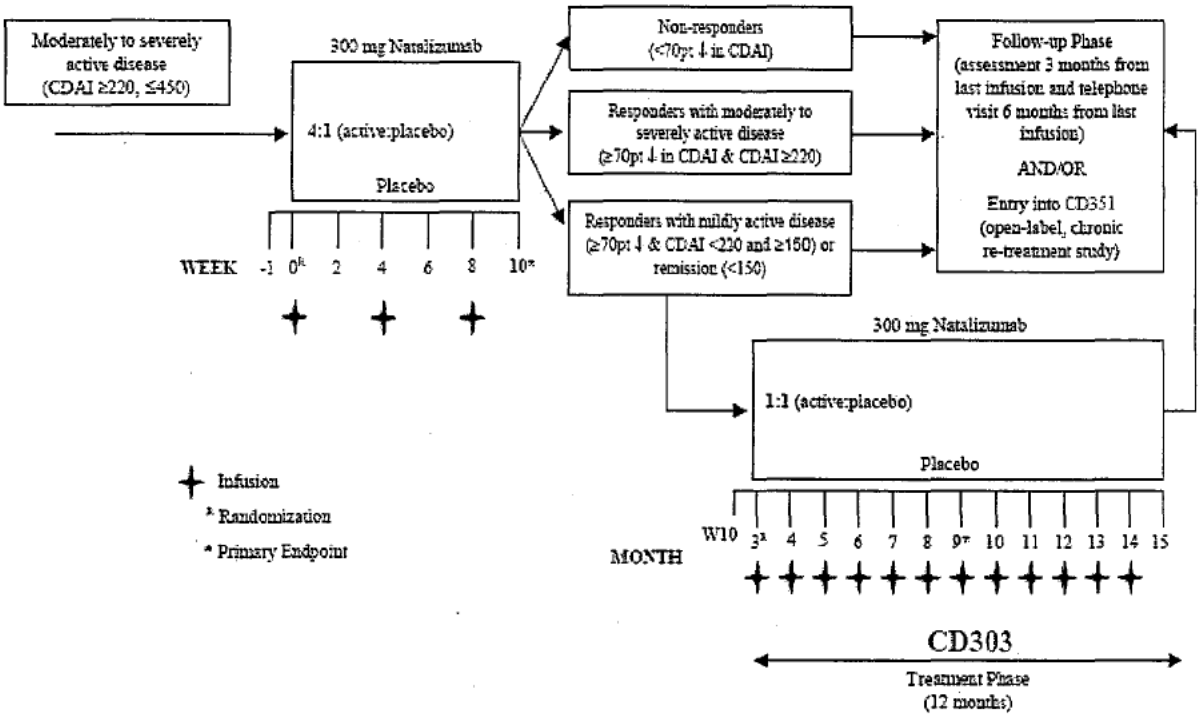
Subjects were screened for eligibility and randomized 7 to 14 days later at the baseline (Week 0) Visit to one of two treatment groups: natalizumab 300 mg or placebo at Weeks 0, 4, and 8 (4:1 in favor of treatment with natalizumab). Randomization was stratified based on baseline CDAI score and concomitant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

6.1.3.2 ENACT-2 (Study CD303)

This was a Phase 3, 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 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 Section 10.3.) 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 four 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 six 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.

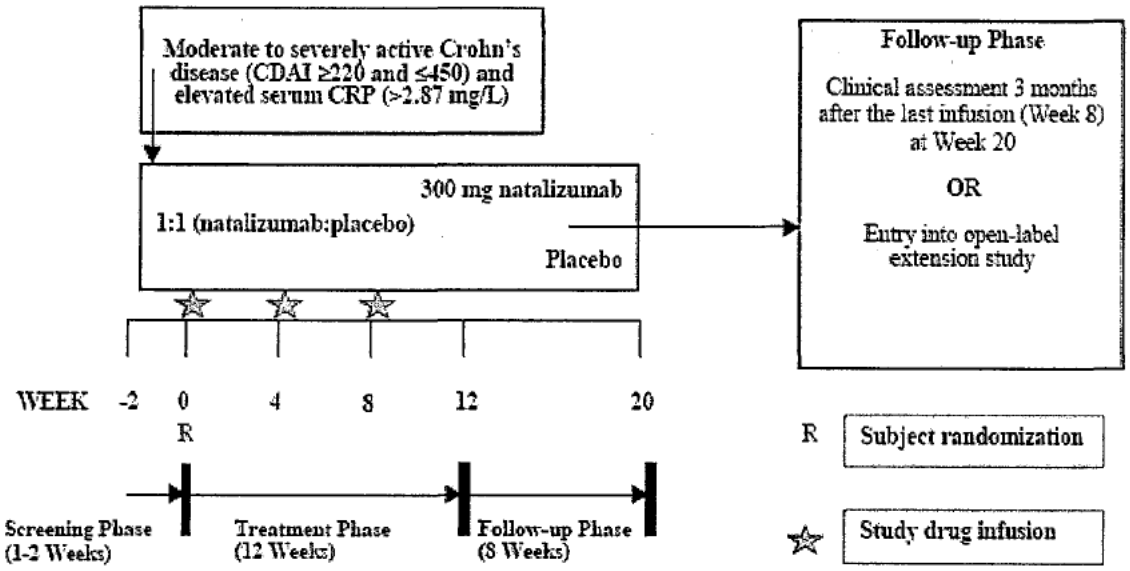
6.1.3.3 ENCORE (Study CD307)

ENCORE (Study CD307) was a Phase 3, 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 four-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)

6.1.3.4 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)

6.1.3.5 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.

6.1.3.6 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 Stable dose ≥2 wks	Steroid Taper Algorithm#	Prior use ≥6 wks Stable dose ≥4 wks
Azathioprine, 6-MP (if used)	Prior use ≥4 mo Stable dose ≥2 mo	No criteria	Prior use ≥4 mo Stable dose ≥2 mo
Methotrexate (if used)	Prior use ≥4 mo Stable dose ≥2 mo	No criteria	Prior use ≥4 mo 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 Section 10.3 for Steroid Taper Algorithm
(Table above is adapted from Page 27 of Summary of Clinical Efficacy.)

6.1.4 Efficacy Findings

6.1.4.1 Demographics and Baseline 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.

6.1.4.1.1 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 6. Demographic Characteristics - Intent-to-Treat Population (Study CD301)

Variable Statistic or Category	Placebo (n=181)	Natalizumab (n=724)	Overall (n=905)
Age (yr)			
Mean	39.4	38.0	38.3
S.D.	13.6	12.4	12.7
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.	17.6	17.8	17.8
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.	9.5	9.4	9.4
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.	5.3	5.7	5.6
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 7. Baseline Characteristics – Intent-to-Treat Population (Study CD301)

Variable Statistic or Category	Placebo (n=181)	Natalizumab (n=724)	Overall (n=905)
Baseline CDAI Score			
N	181	721	902
Mean	303.4	301.8	302.1
S.D.	65.2	60.2	61.2
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.	26.2	31.0	30.1
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.	5.3	5.6	5.5
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.	93.2	98.4	97.4
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.

6.1.4.1.2 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 was well balanced. There were 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 8. Demographic Characteristics (Study CD303)

Variable Statistic	Placebo (n=214)	Natalizumab (n=214)	Overall (n=428)
Age (yr)			
Mean	38.4	37.4	37.9
s.d.	13.3	12.5	12.9
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.	16.4	17.5	17.0
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 9. Baseline Disease Characteristics* (Study CD303)

Variable Statistic	Placebo (n=214)	Natalizumab (n=214)	Overall (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.	56.5	59.7	58.1
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.	15.6	15.6	15.6
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.	31.8	26.7	29.3
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.	89.3	92.8	91.0
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.

6.1.4.1.3 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 10. Demography Characteristics - Intent-to-Treat Population (Study CD307)

Variable Statistic or Category	Placebo (n=250)	Natalizumab (n=259)	Overall (n=509)
Age (yr)			
N	250	259	509
Mean	37.7	38.1	37.9
S.D.	12.8	12.7	12.8
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.	19.3	19.0	19.2
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.	9.2	9.6	9.4
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.	6.7	5.8	6.3
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 11. Baseline Disease Characteristics – Intent-to-Treat Population (Study CD307)

Variable Statistic or Category	Placebo (n=250)	Natalizumab (n=259)	Overall (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%)
Duration of Disease (months) (a)			
Mean	120.3	121.4	120.9
S.D.	108.8	98.4	103.6
Median	84.0	92.5	89.5
Min., Max.	4, 550	6, 487	4, 550
Site of Disease N (%)			
Ileum	65 (26%)	56 (22%)	121 (24%)
Colonic	65 (26%)	69 (27%)	134 (26%)
Ileocolonic	120 (48%)	134 (52%)	254 (50%)

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

6.1.4.2 Prior and/or Concomitant Medications

6.1.4.2.1 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 12. 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 13. 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 Unresponsive or Intolerant to Previous Medication Use	96/148 (65%)	437/634 (69%)	533/782 (68%)
Previous Immunosuppressants Use Unresponsive or Intolerant to Previous Medication Use	83/121 (69%)	335/484 (69%)	418/605 (69%)
Previous Steroids Use Unresponsive or Intolerant to or Dependent on Previous Medication Use	102/158 (65%)	455/643 (71%)	557/801 (70%)
Previous Anti-TNF Use Unresponsive or Intolerant to Previous Medication Use	46/69 (67%)	196/291 (67%)	242/360 (67%)
Previous Antibiotics Use 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 Section 10.1.2.

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 14. 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)

6.1.4.2.2 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 15. 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 16. 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 Unresponsive or Intolerant to Previous Medication Use	125/185 (68%)	123/183 (67%)
Previous Immunosuppressants Use Unresponsive or Intolerant to Previous Medication Use	97/139 (70%)	95/149 (64%)
Previous Steroids Use Unresponsive or Intolerant to or Dependent on Previous Medication Use	134/191 (70%)	124/190 (65%)
Previous Anti-TNF Use Unresponsive or Intolerant to Previous Medication Use	46/ 78 (59%)	46/ 74 (62%)
Previous Antibiotics Use 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 17. 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.)

6.1.4.2.3 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 18. 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 19. 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 20. 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 21. 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.)

6.1.4.3 Subject Disposition

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

6.1.4.3.1 ENACT-1 (Study CD301)

Table 22. 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 23. 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.)

6.1.4.3.2 ENACT-2 (Study CD303)

Table 24. 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.	4.1	4.0	4.2
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 25. 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.)

6.1.4.3.3 ENCORE (Study CD307)

Table 26. 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%)
Applicant'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%)
Applicant'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 27. 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. 2: Missing responses or responses of N/A (not applicable) are not counted.		

(Table above taken from page 107 of CSR CD307)

The Applicant 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 $\geq$220 and $\leq$450 window qualified for the per protocol population based on recalculated CDAI scores using the hematocrit value from the baseline visit.

Table 28. 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.)

6.1.4.4 Efficacy Results

6.1.4.4.1 ENACT-1 (Study CD301)

6.1.4.4.1.1 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 29. 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 30. 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.)

6.1.4.4.1.2 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 31. 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 32. 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.)

6.1.4.4.1.3 Additional Post-Hoc Analyses

6.1.4.4.1.3.1 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 Section 6.1.3.6). 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 33. 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.)

6.1.4.4.1.3.2 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 34. 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.)

6.1.4.4.1.3.3 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 35. 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.

(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 138 of the Study Report for Study CD301.)

6.1.4.4.1.4 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.

6.1.4.4.2 ENACT-2 (Study CD303)

6.1.4.4.2.1 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; $p \leq 0.001$ 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 36. 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.)

6.1.4.4.2.2 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 37. 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.)

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

6.1.4.4.2.3.1 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 38. 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.)

6.1.4.4.2.3.2 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 39. 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.)

6.1.4.4.2.4 Additional Post-Hoc Analyses

6.1.4.4.2.4.1 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 40. 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 41. 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.)

6.1.4.4.2.4.2 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 42. 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 43. 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.)

6.1.4.4.2.5 Steroid Withdrawal Results

6.1.4.4.2.5.1 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 44. 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.)

6.1.4.4.2.5.2 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 45. 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.)

6.1.4.4.2.6 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).

6.1.4.4.3 ENCORE (Study CD307)

6.1.4.4.3.1 ITT Population

6.1.4.4.3.1.1 Clinical Response (≥70-point Decrease in CDAI from Baseline) 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 46. 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).

6.1.4.4.3.1.2 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 47. 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.

6.1.4.4.3.2 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.

6.1.4.4.3.2.1 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 48. 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)

6.1.4.4.3.2.2 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 49. 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)

6.1.4.4.3.2.3 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 50. 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).

6.1.4.4.3.3 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.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

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 Applicant'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.

7 INTEGRATED REVIEW OF SAFETY

In addition to a discussion of deaths and serious adverse events (SAEs) and the cases of PML, some areas of focus in this review are 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.

There were a number of information requests sent to the Applicant. Many of these information requests were related to assessment of AEs with concomitant medication use. No additional safety concerns have been raised from the review.

7.1 Methods and Findings

The safety data for each of the mentioned studies are reviewed in this safety section by reviewing all pertinent safety events that occurred in each study.

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 51. 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 Applicant'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.

In tabulating common adverse events, selected preferred terms were grouped (see Section 7.1.5.2) for each of the placebo-controlled studies CD301, CD307, and CD303. For the induction studies (CD301 and CD307), preferred terms or grouped preferred terms that occurred at an incidence of at least 1% higher in the natalizumab-treated patients than placebo-treated patients, were tabulated by treatment group. For the maintenance study (CD303), preferred terms or grouped preferred terms that occurred at an incidence of at least 2% higher in the natalizumab-treated patients than placebo-treated patients, were tabulated by treatment group. In addition, if an adverse event could only possibly occur in one gender, then the denominator in the calculation of incidence was only the number of patients of that gender in each treatment group.

7.1.1 Deaths

7.1.1.1 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.

7.1.1.1.1 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 four 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 RA201, 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 52. 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.

7.1.1.1.2 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. (See Section 7.1.3.3.1.)
(2) PML: 60 year old male (CD351) died of PML after receiving eight natalizumab infusions. (See Section 7.1.3.3.1.)
(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. He had a history of malignant melanoma excised from the left shoulder approximately four years prior.

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 25th natalizumab infusion.

(2) Suicide: 27 year old male (MS Study 1808) committed suicide 23 weeks after his 31st 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 22nd 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.

7.1.1.2 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 have received natalizumab between its approval (November 23, 2004) and market suspension (February 28, 2005).

7.1.1.2.1 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+ year old 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)

7.1.1.3 Summary of Deaths

The 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 hemicolectomy, 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 unlikely in each of the cases although there is a possibility of one of the cases having a worse progression due to natalizumab. 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. 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, and this patient had a history of excised malignant melanoma. However, while this may have been a pre-existing condition, in view of natalizumab's mechanism, there is a possibility that the melanoma may have had a worse progression due to natalizumab.

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.

7.1.2 Other Serious Adverse Events

7.1.2.1 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 Section 10.5.)

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

Table 53. 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 Applicant'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 Section 10.5.

7.1.2.1.1 Concomitant Medications

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

Table 54. 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 55. 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)

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 with concomitant immunosuppressants (13.7% [28/205] versus 6.7% [6/89]). The reason for this difference is not clear.

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.

7.1.2.2 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.

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.

7.1.2.3 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 Section 10.4.)

Table 56. SAEs in Placebo-controlled Studies of MS with ≥1% Incidence in Natalizumab group

Serious Adverse Event	Placebo (n=1135) N (%)	Natalizumab (n=1617) % (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.)

7.1.2.4 Post-marketing Reports

The following serious adverse events have been reported in the post-marketing setting:

- Serious infections (33 cases; discussed in Section 7.1.3.3.2.5)
- Malignancies (4 cases; discussed in Section 7.1.11.5)
- Hypersensitivity reactions (15 cases)
- Hepatic dysfunction (3 cases)
- Hematologic events (2 cases of pancytopenia and one case of leukopenia)
- Cardiovascular events (12 cases)
- Neurological events (9 cases)
- Psychiatric disorders or depression (2 cases of suicidal ideation, 2 cases of depression, 1 completed suicide)

7.1.2.5 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.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The numbers of subjects who terminated from each of the studies in the Crohn's disease development program are displayed in Section 6.1.4.3.

7.1.3.2 Adverse events associated with dropouts

7.1.3.2.1 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.

7.1.3.2.2 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.

7.1.3.3 Other significant adverse events

Other significant adverse events are discussed below and in other sections of this review. These include the following sections:

- Progressive Multifocal Leukoencephalopathy (PML) (7.1.3.3.1);
- Infections Other Than PML ();
- Hypersensitivity (7.1.3.3.3);
- Immunogenicity (7.1.10);
- Human Carcinogenicity (7.1.11)

The three confirmed PML cases and 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.

Each of the issues below will be discussed.

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

7.1.3.3.1 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[1], Langer-Gould 2005[2], and Van Assche 2005[3]); 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[4]). 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[1])

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 February 2005. She died later that month. An autopsy was conducted, which confirmed PML.

PML Case 2 (reported by Langer-Gould[2])

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[3])

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 December 2003. The Applicant 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 Applicant 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 Applicant 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[4]) 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.

7.1.3.3.2 Infections Other Than PML

7.1.3.3.2.1 Short-term Placebo-Controlled CD Studies

7.1.3.3.2.1.1 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 57. 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 58. 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 59. 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 60. 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.)

7.1.3.3.2.1.2 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 61. 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%)
Bacteremia	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.)

7.1.3.3.2.2 Concomitant Medications

Overall infections and serious infections were summarized by category of concomitant medication use for the short-term placebo-controlled CD population.

7.1.3.3.2.2.1 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.

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.

7.1.3.3.2.2.2 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).

Table 62. 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 63. 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
Bacteremia	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.)

7.1.3.3.2.3 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 were provided in the Clinical

Briefing Document by Drs. Alice Hughes and Susan S. McDermott for the 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 Section 7.1.3.3.2.1.) 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.

7.1.3.3.2.4 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 64.)

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 65). One opportunistic infection was reported; this was a cryptosporidial gastroenteritis in a 31 year old male that had received 16 infusions of natalizumab.

Table 64. 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 65. 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)

7.1.3.3.2.5 Post-Marketing

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

Table 66. 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
Of the four "Cases Mentioning PML" (suspect cases of PML), none were confirmed as PML by the Independent Adjudication Committee.

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 2006 Advisory Committee.)

7.1.3.3.2.6 Summary of Infections other than PML

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.

7.1.3.3.3 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.

7.1.4 Other Search Strategies

No other search strategies were performed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

An adverse event was defined as any undesirable event that occurred to a participant during the course of the study (or a reasonable time after study termination), whether or not that event was considered study drug related.

All adverse events, whether or not related to the study drug, and whether non-serious or unexpected must have been fully and completely documented on the Adverse Event page of the CRF and in the patient's medical chart. The following attributes must have been assigned: description, dates of onset and resolution, severity, assessment of relatedness to study drug (either related or not related), serious criteria if applicable, and action taken. The Investigator may have been asked to provide follow-up information.

Also, in the event that a subject was withdrawn from the study because of an adverse event, it had to be recorded on the CRF as such. The Investigator had to report all directly observed adverse events and all spontaneously reported adverse events.

The severity of each adverse event should have been characterized and then classified into one of three clearly defined categories as follows:

- Mild: The adverse event does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance;
- Moderate: The adverse event produces some impairment of functioning, but is not hazardous to health. It is uncomfortable or an embarrassment;
- Severe: The adverse event produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

These three categories were based on the Investigator's clinical judgment, which in turn depended on consideration of various factors such as the subject's reports, the physician's observations, and the physician's prior experience.

An adverse event was considered "not related" to the use of the product if any of the following tests were met:

- An unreasonable temporal relationship between administration of the product and the onset of the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product related;
- A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident);
- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event). Individual adverse event reports will be considered "related" to the use of the product if the "not related" criteria are not met. "Related" to the use of the product means that there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

In addition to the severity rating, each adverse event was to be classified by the Investigator as "serious" or "not serious". The evaluation of seriousness is distinguished from the evaluation of severity. The seriousness of an event is defined according to the applicable regulations, and generally refers to the outcome of an event. A serious adverse event (SAE) is one that:

- Is fatal;
- Is immediately life threatening;
- Is permanently (or significantly) disabling;
- Requires hospitalization (A hospitalization is considered admittance for 24 hours or greater);
- Prolongs existing hospitalization;
- Is a congenital anomaly or birth defect (in an offspring).

In Study CD301, subjects had pre-infusion and post-infusion adverse event assessments at Weeks 0 and 4. The post-infusion assessment was 120 minutes after the start of each infusion and by telephone follow-up 24 hours after the start of each infusion; at the 24 hour call, concomitant medications were also assessed. In addition, adverse events were assessed at Week 2, Week 6, and at Week 10 (or at an early discontinuation at any point prior to Week 10).

In Study CD307, subjects had pre-infusion and post-infusion adverse event assessments at Weeks 0, 4, and 8. The post-infusion assessment was 120 minutes after the start of each infusion and by telephone follow-up 24 hours after the start of each infusion; at the 24 hour call, concomitant medications were also assessed. In addition, adverse events were assessed at Week 12 (or at an early discontinuation at any point prior to Week 12) and at Week 20 (or at an early discontinuation occurring between Weeks 12 and 20).

In Study CD303, subjects had pre-infusion and post-infusion adverse event assessments at each month for Months 3 through 14. The post-infusion assessment was 120 minutes after the start of each infusion and by telephone follow-up 24 hours after the start of each infusion; at the 24 hour call, concomitant medications were also assessed. Adverse events were also assessed at Month 15 (or at an early discontinuation at any point prior to Month 15). In addition, a follow-up assessment of adverse events occurred at Month 17, and a telephone follow-up assessment of adverse events occurred at Month 20.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse events recorded on subjects' case report forms (CRFs) were coded using the Medical Dictionary of Regulatory Activities (MedDRA), Version 6.0. In all cases, tables show the incidence of events using preferred terms (PTs). Within MedDRA, the PT level represents distinct medical concepts. However, due to the granularity of the dictionary, a single medical concept can have distinct PTs. For example, urinary tract infection NOS and cystitis NOS are unique PTs with different mappings. Confronted with these challenges, attempts were made to assess any imbalance between the natalizumab-treated and placebo-treated subjects by examining multiple levels of the dictionary classification from the System Organ Class (SOC) to

high-level term (HLT) through to the PT level. When appropriate, some PTs are combined for an overall incidence as in Section 7.1.3.3.2.1.1.

In tabulating adverse events for common adverse event tables, selected preferred terms were grouped for each of the placebo-controlled studies CD301, CD307, and CD303. The table below shows the definitions of grouped preferred terms.

Table 67. Definitions of Grouped Preferred Terms

Grouped preferred term	Preferred terms
Headache	Headache NOS, Sinus headache, Post-traumatic headache, Tension headache
Fatigue	Lethargy, Muscle fatigue, Fatigue
Rash	Rash erythematous, Rash pruritic, Genital rash, Rash generalized, Rash macular, Rash maculo-papular, rash pustular, Heat rash, Rash scaly, Rash popular, Rash NOS
Hypersensitivity	Urticaria papular, hypersensitivity NOS, urticaria NOS, drug hypersensitivity
Vaginal infections	Vaginosis fungal NOS, Vaginal candidiasis, Vaginitis, Vaginitis bacterial NOS, Vulvovaginitis NOS, Vaginal abscess, Vaginal infection NOS
Dysmenorrhea	Dysmenorrhea, Menstrual disorder NOS
Sinusitis	Sinusitis NOS, sinusitis acute NOS, viral sinusitis
Upper respiratory tract infection	Laryngitis NOS, Laryngitis viral NOS, Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Pharyngitis viral NOS, Pharyngotonsillitis, Rhinolaryngitis, Tonsillitis NOS, Upper respiratory tract infection NOS, Upper respiratory tract infection viral NOS

7.1.5.3 Incidence of common adverse events

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.

7.1.5.4 Common adverse event tables

7.1.5.4.1 Controlled Studies of Active CD

The incidence of adverse events by preferred term (or grouped preferred term) that occurred in Studies CD301 and CD307 at an incidence of at least 1% higher in Tysabri-treated patients than placebo-treated patients are presented in the table below. The methods used in generating the table and the definitions of grouped preferred terms are provided in Sections 7.1 and 7.1.5.2.

Table 68. Adverse Reactions in Studies CD301 and CD307

Adverse Reactions*	TYSABRI n=983 Percentage	Placebo n=431 Percentage
General		
Headache	32%	23%
Fatigue	10%	8%
Arthralgia	8%	6%
Influenza-like illness	5%	4%
Acute hypersensitivity reactions	2%	<1%
Tremor	1%	<1%
Infection		
Upper respiratory tract infection	22%	16%
Vaginal infections#	4%	2%
Viral infection	3%	2%
Urinary tract infection	3%	1%
Respiratory		
Pharyngolaryngeal pain	6%	4%
Cough	3%	<1%
Gastrointestinal		
Nausea	17%	15%
Dyspepsia	5%	3%
Constipation	4%	2%
Flatulence	3%	2%
Aphthous stomatitis	2%	<1%
Skin		
Rash	6%	4%
Dry skin	1%	0%
Menstrual Disorder		
Dysmenorrhea#	2%	<1%

* Occurred at an incidence of at least 1% higher in TYSABRI-treated patients than placebo-treated patients.
# Percentage based on female patients only.

7.1.5.4.2 Controlled Maintenance Study in CD

The incidence of adverse events by preferred term (or grouped preferred term) that occurred in Study CD303 at an incidence of at least 2% higher in Tysabri-treated patients than placebo-treated patients are presented in the table below. The methods used in generating the table and the definition of grouped preferred terms are provided in Sections 7.1 and 7.1.5.2 .

Table 69. Adverse Reactions in Study CD303

Adverse Reactions* (Preferred Term)	TYSABRI n=214 Percentage	Placebo n=214 Percentage
General		
Headache	37%	31%
Influenza-like illness	11%	6%
Toothache	4%	<1%
Peripheral edema	6%	3%
Infection		
Influenza	12%	5%
Sinusitis	8%	4%
Viral infection	7%	3%
Vaginal infections#	8%	<1%
Respiratory		
Cough	7%	5%
Gastrointestinal		
Lower abdominal pain	4%	2%
Musculoskeletal and Connective Tissue		
Back pain	12%	8%
Menstrual disorder		
Dysmenorrhea#	6%	3%

* Occurred at an incidence of at least 2% higher in TYSABRI-treated patients than placebo-treated patients.
# Percentage based on female patients only.

7.1.5.5 Identifying common and drug-related adverse events

Adverse events that occurred more frequently in natalizumab-treated patients compared to placebo-treated patients in the induction studies (CD301 and CD307) and in the maintenance study (CD303) are more likely to be drug-related than those adverse events that did not demonstrate such a pattern. Thus, the table in Section 7.1.5.4.1 that displays adverse reactions in the induction studies, and the table in Section 7.1.5.4.2 that displays adverse reactions in the maintenance study should each be added to the Adverse Reactions section of the labeling.

7.1.5.6 Additional analyses and explorations

For explorations of the effect of concomitant medications on incidence of infections, see Section 7.1.3.3.2.2. For explorations of the effect of concomitant medications on incidence of malignancies, see Section 7.1.11.4.

7.1.6 Less Common Adverse Events

Review of uncommon adverse events in the entire safety database did not identify additional safety concerns not addressed elsewhere in the review. Less common but clinically significant adverse events are discussed in Section 7.1.2 (Other Serious Adverse Events) of this review.

7.1.7 Laboratory Findings

An increase in circulating leukocytes, except neutrophils, is a known pharmacodynamic effect of natalizumab. Thus, increases are found in all of the following: lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Such an increase was seen in subjects taking natalizumab; this appears to be reversible with stopping of the medication.

The Applicant 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. Subjects with nucleated red blood cells appeared to have a higher incidence of anemia when compared to both placebo-treated and natalizumab-treated subjects.

With regard to platelet counts or prothrombin, no significant associated safety signals were identified.

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.

See also original Clinical Review by Dr. Wilson Bryan and Clinical Review by Drs. Alice Hughes and Susan McDermott.

7.1.7.1 Overview of laboratory testing in the development program

Urinalysis was obtained in each study as follows:

Study	Urinalysis
CD301	▪ Screening (Day -7 to -14) ▪ Week 10 (or early discontinuation)
CD307	▪ Screening (Day -7 to -14) ▪ Week 12 (or early discontinuation)
CD303	▪ Months 3, 6, 9, & 12 (pre-infusion) ▪ Month 15 (or early discontinuation)

(Above was summarized by this reviewer using final protocol version for each of the studies.)

Hematology evaluations (white blood cells, lymphocytes, neutrophils, monocytes, esoinophils, basophils, red blood cells, hemoglobin, hematocrit, mean corpuscular volume [MCV], and platelets) were obtained by study as follows:

Study	Hematology evaluations
CD301	▪ Screening (Day -7 to -14) ▪ Weeks 0 (pre-infusion), 2, 4 (pre-infusion), 6, & 8 (pre-infusion), ▪ Week 10 (or early discontinuation)
CD307	▪ Screening (Day -7 to -14) ▪ Weeks 0 (pre-infusion), 2, 4 (pre-infusion), & 8 (pre-infusion), ▪ Weeks 12 (or early discontinuation prior to Week 12), & 20 (or early discontinuation between Weeks 12 and 20)
CD303	▪ Months 3 through 14 (pre-infusion) ▪ Month 15 (or early discontinuation) ▪ Month 17 (follow-up)

(Above was summarized by this reviewer using final protocol version for each of the studies.)

Chemistries (sodium, potassium, chloride, creatinine, BUN, and bicarbonate) and liver function tests (total bilirubin, albumin, AST, ALT, alkaline phosphatase, GGT) were obtained by study as follows:

Study	Chemistries and Liver Function Tests
CD301	▪ Screening (Day -7 to -14) ▪ Week 4 (pre-infusion) & Week 8 (pre-infusion) ▪ Week 10 (or early discontinuation)
CD307	▪ Screening (Day -7 to -14) ▪ Week 4 (pre-infusion) & Week 8 (pre-infusion) ▪ Week 12 (or early discontinuation prior to Week 12) & Week 20 (or early discontinuation between Weeks 12 and 20)
CD303	▪ Month 3 (pre-infusion), Month 4 (pre-infusion), Month 5 (pre-infusion), Month 6 (pre-infusion), Month 9 (pre-infusion), and Month 12 (pre-infusion) ▪ Month 15 (or early discontinuation)

(Above was summarized by this reviewer using final protocol version for each of the studies.)

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The results of the short-term placebo-controlled studies of active CD are described.

7.1.7.3 Standard analyses and explorations of laboratory data

Shift tables summarize hematology, liver function tests, kidney function tests, electrolytes, other blood chemistry tests, urinalysis, and anti-nuclear antibodies. Each subject's laboratory values have been classified as "low" (below the lower limit of normal [LLN]), "normal" (within the normal range), or "high" (above the upper limit of normal [ULN]). If a subject was missing a baseline value but had a post-baseline value, then the baseline assessment has been labeled as "unknown." Likewise, if a subject had a baseline value but had no post-baseline values then the minimum and maximum have been labeled as "unknown."

The primary analyses of data include:

- Examining the shifts (relative to the normal range) from baseline to minimum and maximum post-baseline values. Should a treatment affect a laboratory parameter, that parameter could be affected at different times for different subjects. Therefore, these analyses present the most extreme values for each subject. For many laboratory parameters, the effect could be in either direction (i.e., an increase or a decrease), therefore, both the maximum and minimum values have been analyzed. Shifts for short-term placebo-controlled treatment studies of active CD are presented.
- Examining the shifts (relative to the normal range) from baseline to low and from baseline to high. For each parameter, the incidence of shift to low has been summarized using the minimum post-baseline values. Shift to low includes subjects with a normal, high or unknown baseline value and at least one post-baseline value of the given test. Similarly, the incidence of shift to high has been summarized using the maximum post-baseline values. Shift to high includes subjects with a low, normal or unknown baseline value and at least one post-baseline value.

7.1.7.3.1.1 Hematology

The table below shows a summary of shifts from baseline for hematology laboratory parameters in short-term placebo-controlled studies of active CD.

Table 70. Summary of Shifts from Baseline for Hematology (Short-Term Placebo-Controlled Studies of Active CD)

Laboratory Parameters	Shift to (a)	Placebo	Natalizumab
WBC	Low	19/496 (4%)	25/1145 (2%)
	High	101/388 (26%)	372/897 (41%)
Lymphocytes	Low	74/408 (18%)	50/964 (5%)
	High	15/495 (3%)	345/1155 (30%)
Neutrophils	Low	9/499 (2%)	28/1161 (2%)
	High	113/340 (33%)	248/789 (31%)
Monocytes	Low	26/491 (5%)	46/1142 (4%)
	High	28/493 (6%)	157/1138 (14%)
Eosinophils	Low	0/503	0/1171
	High	18/487 (4%)	205/1145 (18%)
Basophils	Low	0/503	0/1171
	High	14/499 (3%)	105/1165 (9%)
Red Blood Cells (RBC)	Low	83/399 (21%)	227/904 (25%)
	High	0/502	6/1170 (<1%)
Hemoglobin	Low	77/376 (20%)	217/867 (25%)
	High	0/503	5/1169 (<1%)
Hematocrit	Low	71/403 (18%)	229/949 (24%)
	High	2/502 (<1%)	9/1170 (<1%)
Mean Corpuscular Volume (MCV)	Low	37/445 (8%)	70/1050 (7%)
	High	37/462 (8%)	74/1075 (7%)
Platelets	Low	4/501 (<1%)	14/1167 (1%)
	High	64/340 (19%)	137/810 (17%)

NOTE: Entries are number low (or high)/number at risk(%). Number at risk for shift to low is the number of subjects whose baseline value was not low and who had at least one post-baseline value; number at risk for analyses of shift to high is the number of subjects whose baseline value was not high and who had at least one post-baseline value.

(a) Shift to low includes normal to low, high to low and unknown to low. Shift to high includes normal to high, low to high and unknown to high.

(Values in the table above are taken from Page 308 of the Applicant's Summary of Clinical Safety.)

Consistent with the expression of α4-integrins on all leukocytes, each of these lineages increased in the peripheral blood in the natalizumab-treated subjects. However, the absolute increase in number of lymphocytes was greater than all of the other cell types. As neutrophils do not express α4 under normal conditions, a similar pattern of increased numbers on therapy was not seen.

There are some differences in the hematology results between MS and CD. In the CD experience, shifts to high neutrophils were observed in approximately one-third of both placebo and natalizumab-treated subjects compared to 18% and 19% in the placebo and natalizumab groups of the MS population (see Clinical Review by Drs. Alice Hughes and Susan McDermott). Natalizumab-treated subjects had lower mean hemoglobin levels than placebo-treated subjects in MS, but not in CD. In both MS and CD, the proportion of subjects with laboratory shifts to low hemoglobin was higher in the natalizumab-treated group compared to the placebo-treated group.

While there were few MS subjects (<8%) with elevated platelet counts, 17% of natalizumab-treated and 19% of placebo-treated CD subjects had shifts to high platelet count. Elevated platelets and anemia are both associated with active CD. All of the serious anemias in CD were related either to CD worsening or to bleeding from an ulcer. There were no events suggesting hemolysis.

In both MS and CD, nucleated RBCs (nRBCs) were detected in a minority of subjects. In placebo-controlled studies of active CD, the presence of nRBCs was noted in 121 (10%) of natalizumab-treated subjects and in 3 (0.6%) of placebo-treated subjects. In the MS experience, the detection of nRBCs was transient and was not associated with anemia. By contrast, 46% of CD subjects with nRBCs had anemia, but in 61% of these subjects, the anemia was present at baseline. Circulating nRBCs have no physiologic or pathologic consequences but represent a minor alteration in distribution of hematologic progenitor cells.

7.1.7.3.1.2 Liver Function Tests

The table below shows a summary of shifts from baseline for liver function tests in short-term placebo-controlled studies of active CD.

Table 71. Summary of Shifts from Baseline for Liver Function Tests (Short-Term Placebo-Controlled Treatment Studies of Active CD)

Laboratory Parameters	Shift to (a)	Placebo	Natalizumab
Total Bilirubin	Low	103/432 (24%)	130/1017 (13%)
	High	9/495 (2%)	43/1149 (4%)
Albumin	Low	67/418 (16%)	76/968 (8%)
	High	5/499 (1%)	11/1161 (<1%)
ALT/SGPT	Low	19/494 (4%)	27/1151 (2%)
	High	50/470 (11%)	91/1074 (8%)
AST/SGOT	Low	32/489 (7%)	29/1126 (3%)
	High	34/484 (7%)	69/1102 (6%)
Alkaline Phosphatase	Low	3/500 (<1%)	10/1160 (<1%)
	High	30/445 (7%)	60/1068 (6%)
GGT	Low	7/249 (3%)	20/889 (2%)
	High	16/220 (7%)	38/824 (5%)

NOTE: Entries are number low (or high)/number at risk(%). Number at risk for shift to low is the number of subjects whose baseline value was not low and who had at least one post-baseline value; number at risk for analyses of shift to high is the number of subjects whose baseline value was not high and who had at least one post-baseline value.

(a) Shift to low includes normal to low, high to low and unknown to low. Shift to high includes normal to high, low to high and unknown to high.

(Values in the table above are taken from Page 322 of the Applicant's Summary of Clinical Safety.)

The rate of shift to high was similar between natalizumab-treated subjects and those who received placebo for all liver enzymes and bilirubin.

The shift to low in albumin in 16% of the placebo-treated subjects compared to 8% of the natalizumab-treated subjects may indicate more active CD or protein loss from the inflamed intestine. No subject in the CD studies had an AST or ALT $\geq$ 3 x ULN on at least 2 post-dosing time points accompanied by an elevated bilirubin.

Shift tables from baseline to the expanded limits of high are shown in the tables below; the first table displays results for ALT, and the second displays results for AST.

Table 72. Summary of Shifts from Baseline ALT to High Post-Baseline ALT (Short-Term Placebo-Controlled Treatment Studies of Active CD)

Post-baseline						
	Placebo (N = 501)			Natalizumab (N = 1162)		
Baseline	>1-3 X ULN	≥ 3-5 X ULN	≥5 X ULN	>1-3 X ULN	≥ 3-5 X ULN	≥ 5 X ULN
Unknown	1 (<1%)	0	0	0	0	0
LLN	0	0	0	0	1 (<1%)	0
Within	46 (9%)	0	3 (<1%)	87 (7%)	3 (<1%)	0
>1-3 X ULN	18 (4%)	0	1(<1%)	50 (4%)	5 (<1%)	0
≥3-5 X ULN	0	0	0	1 (<1%)	1 (<1%)	1(<1%)
≥5 X ULN	0	0	0	0	0	0

Numbers in parentheses are percentages. The denominator for the percentages is the total number of subjects who had at least one post-baseline value.
(Table above is taken from Page 324 of the Applicant's Summary of Clinical Safety.)

Table 73. Summary of Shifts from Baseline AST to High Post-Baseline AST (Short-Term Placebo-Controlled Treatment Studies of Active CD)

Post-baseline						
	Placebo (N = 501)			Natalizumab (N = 1162)		
Baseline	>1-3 X ULN	≥ 3-5 X ULN	≥5 X ULN	>1-3 X ULN	≥ 3-5 X ULN	≥ 5 X ULN
Unknown	2 (<1%)	0	0	0	0	0
LLN	0	0	0	2 (<1%)	0	0
Within	32 (6%)	0	0	66 (6%)	1 (<1%)	0
>1-3 X ULN	7 (1%)	0	1(<1%)	26 (2%)	3 (<1%)	0
≥3-5 X ULN	0	0	0	0	0	0
≥5 X ULN	0	0	0	0	0	0

Numbers in parentheses are percentages. The denominator for the percentages is the total number of subjects who had at least one post-baseline value.
(Table above is taken from Page 325 of the Applicant's Summary of Clinical Safety.)

The majority of the natalizumab-treated subjects that had shifts to high in AST and ALT were within 3 X ULN. For ALT, one natalizumab-treated subject had a value greater than 5 X ULN, in contrast to 4 placebo-treated subjects; for AST, one placebo-treated subject had a value >5 X ULN. Of the 11 natalizumab-treated subjects with an ALT ≥ 3 X ULN, 7 were elevated at screening.

In both MS and CD studies, liver function test abnormalities were similar between placebo- and natalizumab-treated subjects. (See also Clinical Review by Drs. Alice Hughes and Susan McDermott.) When subjects experienced elevations in liver function tests, these were usually mild and transient. Many subjects also had elevated liver function tests at screening and baseline. Elevated bilirubin levels rarely accompanied elevations in transaminase levels. The liver related SAEs in the natalizumab-treated subjects were attributable to other proximate causes such as cholelithiasis or other medications including interferon beta. The majority of subjects were not hospitalized, although the laboratory findings were considered medically significant.

7.1.7.3.1.3 Kidney Function Tests and Electrolytes

The table below shows a summary of shifts from baseline for kidney function tests in short-term placebo-controlled studies of active CD.

Table 74. Summary of Shifts from Baseline for Kidney Function Tests and Electrolytes (Short-Term Placebo-Controlled Studies of Active CD)

Laboratory Parameters	Shift to (a)	Placebo	Natalizumab
Creatinine	Low	4/500 (<1%)	3/1163 (<1%)
	High	7/491 (1%)	17/1154 (1%)
BUN/Urea	Low	7/498 (1%)	11/1155 (<1%)
	High	6/499 (1%)	12/1160 (1%)
Sodium	Low	5/500 (1%)	10/1162 (<1%)
	High	27/496 (5%)	61/1153 (5%)
Potassium	Low	28/494 (6%)	35/1140 (3%)
	High	3/496 (<1%)	15/1158 (1%)
Chloride	Low	3/498 (<1%)	3/1161 (<1%)
	High	17/494 (3%)	35/1147 (3%)

NOTE: Entries are number low (or high)/number at risk(%). Number at risk for shift to low is the number of subjects whose baseline value was not low and who had at least one post-baseline value; number at risk for analyses of shift to high is the number of subjects whose baseline value was not high and who had at least one post-baseline value.

(a) Shift to low includes normal to low, high to low and unknown to low. Shift to high includes normal to high, low to high and unknown to high.

(Values in the table above are taken from Page 328 of the Applicant's Summary of Clinical Safety.)

The results showed no indication of renal impairment related to natalizumab.

7.1.7.3.1.4 Other Blood Chemistry Tests

The table below shows a summary of shifts from baseline for other blood chemistry tests in short-term placebo-controlled studies of active CD.

Table 75. Summary of Shifts from Baseline for Other Blood Chemistry Tests (Short-Term Placebo-Controlled Treatment Studies of Active CD)

Laboratory Parameters	Shift to (a)	Placebo	Natalizumab
Calcium	Low	29/493 (6%)	73/1133 (6%)
	High	11/499 (2%)	26/1145 (2%)
Phosphorus	Low	23/496 (5%)	41/1144 (4%)
	High	19/493 (4%)	41/1155 (4%)
Protein	Low	35/486 (7%)	76/1109 (7%)
	High	10/491 (2%)	26/1149 (2%)
Glucose	Low	31/482 (6%)	113/1132 (10%)
	High	100/446 (22%)	224/1061 (21%)

NOTE: Entries are number low (or high)/number at risk(%). Number at risk for shift to low is the number of subjects whose baseline value was not low and who had at least one post-baseline value; number at risk for analyses of shift to high is the number of subjects whose baseline value was not high and who had at least one post-baseline value.

(a) Shift to low includes normal to low, high to low and unknown to low. Shift to high includes normal to high, low to high and unknown to high.

(Values in the table above are taken from Page 330 of the Applicant's Summary of Clinical Safety.)

The rate of shifts to low and shifts to high were comparable between the natalizumab and placebo groups.

7.1.7.3.1.5 Urinalysis

The table below shows a summary of shifts from baseline for urinalysis tests in short-term placebo-controlled studies of active CD.

Table 76. Summary of Shifts from Baseline for Urinalysis Tests (Short-Term Placebo-Controlled Treatment Studies of Active CD:

Laboratory Parameters	Shift to	Placebo	Natalizumab
Occult Blood	Non-negative	55/366 (15%)	120/843 (14%)
Glucose	Non-negative	21/448 (5%)	31/1033 (3%)
Ketones	Non-negative	25/433 (6%)	62/1006 (6%)
Protein	Non-negative	57/391 (15%)	122/905 (13%)
RBC	Non-negative	0	0
WBC	Non-negative	0	0

NOTE: Entries are number nonnegative/number at risk(%). Number at risk for shift to nonnegative is the number of subjects whose baseline value was negative or unknown and who had at least one post-baseline value. Shift to nonnegative includes negative to nonnegative, and unknown to nonnegative.
(Values in the table above are taken from Page 332 of the Applicant's Summary of Clinical Safety.)

Although there were some shifts to non-negative for occult blood, glucose, ketones, and protein, the incidence in the natalizumab group was either the same or lower than that of placebo.

7.1.7.4 Additional analyses and explorations

No additional analyses and explorations are indicated.

7.1.7.5 Special assessments

The data provided in this submission do not provide evidence that natalizumab increases the risk of hepatotoxicity (see Section 7.1.7.3.1.2). However, there is evidence that natalizumab increases the risk of hepatotoxicity from four Tysabri-associated serious hepatic injury cases selected from the AERS database by the safety evaluator, Charlene M. Flowers, R.Ph. These cases were selected from AERS searches conducted on July 7, 2007, and September 21, 2007. (These cases are discussed in Section 7.1.17.2; see also the safety evaluator review by Charlene M. Flowers, R.Ph.)

7.1.8 Vital Signs

No clear association was appreciated between treatment with natalizumab and incidence of abnormalities in vital signs. (See Section 7.1.8.2.)

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured before and after each natalizumab infusion in the placebo-controlled active CD studies.

7.1.8.2 Standard analyses and explorations of vital signs data

The table below shows a summary of the incidence of abnormalities in vital signs for short-term placebo-controlled studies of active CD.

Table 77. Incidence of Abnormalities in Vital Signs (Short-Term Placebo-Controlled Studies of Active CD)

Vital Sign	Criteria For Abnormality	Placebo	Natalizumab
Temperature (C)	>38 C and increase from pre-infusion >=1 C	0/ 431	1/ 980 (<1)
Pulse (/min.)	>120 /min. and increase from pre-infusion >20/min.	0/ 505	2/1181 (<1)
	<50 /min. and decrease from pre-infusion >20/min.	1/ 505 (<1)	1/1181 (<1)
Systolic Blood Pressure (mmHg)	>180 mmHg and increase from pre-infusion >40 mmHg	0/ 505	0/1181
	<90 mmHg and decrease from pre-infusion >30 mmHg	0/ 505	3/1181 (<1)
Diastolic Blood Pressure (mmHg)	>105 mmHg and increase from pre-infusion >30 mmHg	0/ 505	0/1181
	<50 mmHg and decrease from pre-infusion >20 mmHg	0/ 505	1/1181 (<1)
Respiration (/min.)	<10 or >24 /min. at post-infusion	10/ 502 (2)	25/1173 (2)

NOTE: Entries are number of subjects meeting criterion / number of subjects being evaluated (%) at infusion visits.
(Values in the table above are taken from Page 338 of the Applicant's Summary of Clinical Safety.)

No clinically significant differences were evident in the incidence of abnormalities in vital signs between the placebo and natalizumab groups. Treatment with natalizumab did not have a significant effect on vital sign findings.

7.1.8.3 Additional analyses and explorations

No additional analyses and explorations were performed or are indicated.

7.1.9 Electrocardiograms (ECGs)

Additional ECG data were not submitted as part of the efficacy supplement. An overview of ECG testing in the development program is described in Dr. Bryan's review of the original BLA submission.

7.1.10 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.

7.1.10.1 CD Studies

The Applicant 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.

7.1.10.1.1 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 78. 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 79. 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).

7.1.10.1.2 Adverse Events by Antibody Development

The Applicant 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.

7.1.10.2 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 Applicant 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%) .

7.1.10.3 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.

7.1.11 Human 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.

Malignancies that were fatal are discussed in Sections 7.1.1.1.2 and 7.1.1.2.1.

7.1.11.1 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 80. 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.

7.1.11.2 MS Studies

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

Table 81. 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.

7.1.11.3 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 82. 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.

7.1.11.4 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.

7.1.11.5 Post-marketing

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

Table 83. 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 Section 7.1.1; 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.

7.1.11.6 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.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Subjects who discontinued treatment with natalizumab after participation in Study CD301 did not experience pronounced increase in CDAI score. In addition, the majority of natalizumab-treated subjects from CD301 re-randomized to placebo in CD303 did not experience severe disease by CDAI score, or show rebound to above baseline CDAI scores. (See tables below.)

These analyses suggest that subjects who discontinue natalizumab treatment are not at increased risk for pronounced exacerbation of CD; however, interpretation of the data is limited by the small number of patients in each treatment group. In addition, patients who discontinue treatment early may not be doing well on treatment, and thus may not be representative of the larger group of natalizumab-treated patients.

Table 84. CD303: Natalizumab Responders Who Experienced Significant Worsening of CDAI Scores Relative to CD301 Baseline Scores (Natalizumab Responder Population)

	Increase from CD301 baseline score:					
	25% or greater		50% or greater		75% or greater	
	Placebo	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab
Number of subjects who lost response at any time	134	75	134	75	134	75
Month 4	2 (1)	0	1 (1)	0	0	0
Month 5	3 (2)	3 (4)	0	2 (3)	1 (1)	0
Month 6	1 (1)	0	1 (1)	0	1 (1)	0
Month 7	1 (1)	0	0	0	0	0
Month 8	1 (1)	0	1 (1)	0	0	0
Month 9	2 (1)	2 (3)	2 (1)	1 (1)	0	0
Total number of subjects	10 (7)	5 (7)	5 (4)	3 (4)	2 (1)	0

NOTE: 1. Numbers in parentheses are percentages. The denominator used was the number of subjects who lost response at any time during the study.

2. A subject was counted only once within each category of percentage increase in baseline CDAI.

3. A subject was counted only once at the first month that the observed CDAI score was 25% or higher than the CD301 baseline CDAI score.

(Table above was taken from Page 470 of the Applicant's Summary of Clinical Safety.)

Table 85. CD303: incidence of SAEs related to Crohn's disease by number of days since last natalizumab infusion (natalizumab responder population)

	Time interval			
	>30 to 60 days		≥60 to 90 days	
	Placebo	Natalizumab	Placebo	Natalizumab
Number of subjects randomised in CD303	171 (100)	168 (100)	171 (100)	168 (100)
Number of subjects with a serious adverse event related to CD	1 (0.6)	1 (0.6)	2 (1.2)	0
Crohn's disease	0	1 (0.6)	2 (1.2)	0
Small intestinal obstruction	1 (0.6)	1 (0.6)	0	0

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

(Table above was taken from Page 471 of the Applicant's Summary of Clinical Safety.)

The effects of natalizumab discontinuation on hematological parameters are discussed in Dr. Bryan's review of the original BLA submission and in Section 7.1.7 (Laboratory Findings) of this review.

The effects of natalizumab discontinuation on MS relapses were discussed in both the review of the original BLA submission by Dr. Bryan, and the review by Drs. Hughes and McDermott that was completed in June of 2006.

The Applicant did not specifically study natalizumab's potential for abuse. Natalizumab has no known effects that would make such study warranted.

7.1.14 Human Reproduction and Pregnancy Data

Strict precautions are enforced in all clinical trials to ensure women of childbearing potential are not pregnant or nursing at the time of dosing and are using effective contraception (e.g., oral contraception, depot contraceptives or intrauterine device) throughout the study. Despite these precautions, 78 pregnancies have been identified in the MS and CD clinical development program to date. These data have been extracted from the Applicant's safety database. Fifty-six pregnancies occurred while subjects were receiving or had recently received varying exposures of natalizumab, while 22 pregnancies occurred in placebo-treated subjects. The results are summarized by indication in the table below.

Table 86. Pregnancy Outcomes

	MS studies		CD studies		
	Placebo	Natalizumab	Placebo	Natalizumab	Total
Number of pregnant subjects	15	33	7	23	78
Pregnancy outcome					
Spontaneous abortion	5	3	2	5	15
Elective termination	4	12	1	6	23
Live birth	6	15	4	12	37
Pregnancy ongoing	0	0	0	0	0
Unknown / missing	0	3	0	0	3

NOTE: Pregnancy data through 18 July 2006
(The table above is taken from Page 463 of the Applicant's Summary of Clinical Safety.)

There were a total of 37 live births of which 27 have occurred with exposure to natalizumab. Of these 27 neonates, one infant experienced seizures attributed to hypoxia secondary to meconium aspiration, and the other live births were unremarkable. There were a total of 23 elective pregnancy terminations. Eighteen pregnancies were terminated in subjects exposed to natalizumab. Fifteen spontaneous abortions were recorded, 8 of 56 (14.3%) pregnant subjects exposed to natalizumab and 7 of 22 (31.8%) receiving placebo.

The rate of spontaneous abortion in those exposed to natalizumab including early pregnancy losses does not exceed the expected rate within the general population of 12 to 22% (based on Garcia-Enguidnaos et al, 2002[5]).

The Applicant recommends that women of childbearing potential use birth control while receiving natalizumab.

7.1.15 Assessment of Effect on Growth

Natalizumab's effect on growth has not been studied. Natalizumab exposure in patients younger than 18 to date has been negligible. The Applicant conducted two open-label trials (CD305 and CD352) that included adolescents (11-17 years old) with CD, enrolling a total of 64 patients. Natalizumab's effects on growth were not assessed in those studies.

7.1.16 Overdose Experience

The highest dose used in the clinical development programs was 6 mg/kg when administered to the heaviest subjects. No differences in safety profiles were appreciated between this dose and 3 mg/kg in Phase 2 studies.

7.1.17 Postmarketing Experience

7.1.17.1 Deaths

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). (See Section 7.1.1.2.)

7.1.17.2 Other Serious Adverse Events

See Section 7.1.2.4 also.
The following serious adverse events 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):

- Serious infections (33 cases; discussed in Section 7.1.3.3.2.2.2)
- Malignancies (4 cases; discussed in Section 7.1.11.5)
- Hypersensitivity reactions (15 cases)
- Hepatic dysfunction (3 cases)
- Hematologic events (2 cases of pancytopenia and one case of leukopenia)
- Cardiovascular events (12 cases)
- Neurological events (9 cases)
- Psychiatric disorders or depression (2 cases of suicidal ideation, 2 cases of depression, 1 completed suicide)

Based on AERS searches conducted by the safety evaluator (Charlene M. Flowers, R.Ph.) on July 7, 2007, and September 21, 2007, four Tysabri-associated serious hepatic injury cases were selected and reviewed by the safety evaluator. (See safety evaluator review by Charlene M. Flowers, R.Ph.) Elevated hepatic enzymes included peak ALT of 2,212 IU/L, and peak AST of 1,863 IU/L, and elevated bilirubin included peak level of 16.1 g/dL; elevations occurred as early as six days after the first dose, and have also been reported for the first time after multiple doses. In some patients, liver injury recurred upon rechallenge, providing strong evidence that Tysabri caused the injury. Although no cases of death or liver transplant have been reported as a result of liver injury following Tysabri infusion(s), the outcomes were serious; two patients were hospitalized including one patient who was placed on the liver transplant list, but subsequently recovered prior to transplant.

A specific diagnosis for liver injury was not reported although three cases provided relevant clinical details including liver biopsies. The three cases had negative hepatic viral screens, and no case provided clinical details to ascertain an alternative etiology. The diagnostic interpretations of the biopsies in each of the three cases were as follows: (1) "the appearance of hepatitis and confluent hepatic necrosis are highly suggestive of drug-induced liver injury"; (2) "active chronic hepatitis with portal inflammation and primarily lobular and peri-portal fibrosis";

and (3) "acute hepatitis with portal hepatitis and a mild pericellular fibrosis." (See safety evaluator review by Charlene M. Flowers, R.Ph.)

A mechanism of liver injury remains to be elucidated. The safety evaluator review discusses two possibilities: "(1) a form of hypersensitivity to Tysabri as a component of the formulation; and (2) unmasking of an unusual yet to be identified pathogen causing liver injury due to immunosuppression." (See safety evaluator review by Charlene M. Flowers, R.Ph.)

Based on these cases, the safety evaluator concluded that an association between Tysabri use and severe liver injury could not be ruled out. (See safety evaluator review by Charlene M. Flowers, R.Ph.)

In her review, the safety evaluator had the following suggestions:

(1) Current labeling should include clinical characteristics of cases of liver injury associated with Tysabri use in the Precautions section. The language to be added should state that clinically significant liver injury has been reported in patients taking Tysabri, that signs of liver injury occurred as early as six days subsequent to the first dose, that other causes were not identified, and that therefore a causal association with Tysabri cannot be excluded.
(2) Surveillance for new cases of Tysabri associated liver injury events through the TYGRIS observational study should be considered. Though the currently reported cases were serious and well-documented, there were too few cases to adequately characterize risk for this event.
(3) The Applicant should expedite reporting of all AERS cases of liver injury with increased liver transaminase levels (AST and ALT) of greater than 3 X ULN and should thoroughly follow-up on all such cases including clinical information to enable a differential diagnosis for etiology of the liver event.
(4) The Applicant should follow up on the existing four cases, highlighted in the safety evaluator review to determine if late serological conversion (or RNA/DNA levels) were determined in order to definitively rule out viral Hepatitis A, B, or C.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

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 87. 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 Applicant'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.

7.2.1.1 Study type and design/patient enumeration

See Section 4.2 Tables of Clinical Studies. In particular, see Table 3. Clinical Development in Crohn's Disease.

7.2.1.2 Demographics and Baseline Characteristics

7.2.1.2.1 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 88. 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.)

7.2.1.2.2 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 89. 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.)

7.2.1.3 Extent of exposure (dose/duration)

7.2.1.3.1 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 90. 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 91. 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).

7.2.1.3.2 CD Development Program

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

7.2.1.3.2.1 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 92. 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.

7.2.1.3.2.1.1 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 93. 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)

7.2.1.3.2.2 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.

7.2.1.3.2.2.1 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 94. 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	681	509	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+
Monotherapy	20%	20%	21%	19%	20%	24%
Steroid#	65%	66%	64%	65%	64%	58%
Immunosuppressant#	48%	50%	50%	52%	50%	53%

* 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.)

Steroid refers to concomitant steroids with or without immunosuppressants. Immunosuppressant refers to concomitant immunosuppressants with or without steroids.

(Values in the table above were obtained in a response to an information request; the request was sent June 14, 2007 and the response to this item was received July 13, 2007)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

See Section 4.2 Tables of Clinical Studies. In particular, see Table 4. Clinical Development in Multiple Sclerosis, Ulcerative Colitis, and Rheumatoid Arthritis.

7.2.2.2 Postmarketing experience

Post-marketing data were submitted from the three month period between approval and market withdrawal. These data are discussed in selected sections of the review.

Four Tysabri-associated serious hepatic injury cases were reviewed by the safety evaluator, Charlene M. Flowers, R.Ph. These cases were selected from the AERS database based on AERS searches conducted by the safety evaluator on July 7, 2007, and September 21, 2007. (See Section 7.1.17.2 and see safety evaluator review by Charlene M. Flowers, R.Ph.)

7.2.2.3 Literature

A review of the scientific literature was conducted with regard to the three cases of PML, and the dose suspension safety assessment (see Section 7.1.3.3.1).

7.2.3 Adequacy of Overall Clinical Experience

The database is sufficiently large to allow for adequate assessment of the safety profile of natalizumab, although events that occur rarely (in fewer than 1/1000 patients) may not have been detected. In addition, the median length of exposure to natalizumab does not permit the adequate assessment of the rate and risk of events that may need long exposures to develop, such as malignancies (and, potentially, opportunistic infections other than PML). (See Section 7.2.1.3.1.)

The demographics of patients treated with natalizumab in CD and MS trials are adequate for the purposes of analyzing the safety of natalizumab for the treatment of patients with CD. The number of non-Caucasian patients exposed to natalizumab in clinical trials was small, but the known characteristics of neither natalizumab nor CD suggest that the safety profile of natalizumab would be appreciably different in non-Caucasian populations.

The experience with natalizumab in the pediatric and geriatric populations has been negligible. It must be noted that the safety profile of natalizumab may be different in patients younger than 18 and older than 64. The safety data currently available cannot necessarily be extrapolated to children, adolescents, and older patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No additional animal or in vitro testing has been submitted with this efficacy supplement.

7.2.5 Adequacy of Routine Clinical Testing

The methods for acquisition of laboratory, vital signs, immunogenicity, and adverse event data in the development program are described in the relevant sections (7.1.5, Common Adverse Events; 7.1.7, Laboratory Findings; 7.1.8, Vital Signs; and 7.1.10, Immunogenicity). The routine clinical testing that was done was adequate to assess the safety of natalizumab.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Applicant submitted a population PK study with the efficacy supplement submission that is reviewed in detail by the clinical pharmacology reviewers Dr. Abimbola Adebowale and Dr. Christoffer Tornoe (see Clinical Pharmacology Review). The findings of the population PK in CD patients (N=1156) from three Phase 2 studies (two studies #305 and #352 conducted in the adolescent population were excluded) and three Phase 3 studies were similar to those obtained for MS patients, i.e.,

- In both patient populations, an (unexplained) time dependency of CL was found to reduce CL by 25% with repeated administration.
- Anti-natalizumab antibodies occurring in approximately 10% of the patients were found to increase CL by approximately 40%. This is likely to be an underestimate of the true effect due to many antibody positive subjects having PK trough samples below LOQ.
- Body weight, age, race (categorized as black vs. other races), ALT, AST, bilirubin, and creatinine clearance had no clinically relevant influence on the PK of natalizumab suggesting that a fixed dosing regimen is appropriate.

The clinical pharmacology data submitted by the Applicant as a part of the efficacy supplement was considered adequate by the Clinical Pharmacology Team (see Clinical Pharmacology Review of this submission).

See Section 5. Clinical Pharmacology also.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events of particular concern for natalizumab included the following: (1) infections, (2) malignancies, and (3) adverse events related to immunogenicity. The assessment of the risk for these events was generally adequate, and is discussed in detail in the pertinent sections as follows:
(1) Infections: Sections 7.1.3.3.1 and 7.1.3.3.2
(2) Malignancies: Section 7.1.11
(3) Immunogenicity and Hypersensitivity: Sections 7.1.10 and 7.1.3.3.3

Although the assessment for these events has been adequate, there is limited data to allow detection of adverse events that are rare, or adverse events that require a long duration of exposure to occur. The Applicant conducted a thorough review of 3116 subjects that received natalizumab during drug development to determine the incidence of PML associated with natalizumab administration (see Section 7.1.3.3.1).

The magnitude of the natalizumab-associated risk for opportunistic infections and for malignancies cannot be well characterized based on the current data. The risk for opportunistic infections and malignancies will need to be better characterized in the post-marketing setting.

Although there is evidence that natalizumab increases the risk of hepatotoxicity based on four Tysabri-associated serious hepatic injury cases selected from the AERS database (see Section 7.1.17.2 and the safety evaluator review by Charlene M. Flowers, R.Ph.), the magnitude of the natalizumab-associated risk for hepatotoxicity cannot be well characterized, and the mechanism of natalizumab-associated liver injury cannot be well elucidated, based on the existing data. Information about the risk for hepatoxicity will need to be better characterized in the post-marketing setting. Information about the mechanism of liver injury will require close follow-up of the existing four cases (and any new cases) such that the etiology can be determined.

The effect of natalizumab on pregnancy outcomes (see Section 7.1.14, Human Reproduction and Pregnancy Data) has not been adequately studied. This is an important area for further study given that many patients who may take natalizumab or consider taking natalizumab are women of child-bearing age.

In her review, the safety evaluator had the following suggestions:

(1) Current labeling should include clinical characteristics of cases of liver injury associated with Tysabri use in the Precautions section. The language to be added should state that clinically significant liver injury has been reported in patients taking Tysabri, that signs of liver injury occurred as early as six days subsequent to the first dose, that other causes were not identified, and that therefore a causal association with Tysabri cannot be excluded.

(2) Surveillance for new cases of Tysabri associated liver injury events through the TYGRIS observational study should be considered. Though the currently reported cases were serious and well-documented, there were too few cases to adequately characterize risk for this event.

(3) The Applicant should expedite reporting of all AERS cases of liver injury with increased liver transaminase levels (AST and ALT) of greater than 3 X ULN and should thoroughly follow-up on all such cases including clinical information to enable a differential diagnosis for etiology of the liver event.

(4) The Applicant should follow up on the existing four cases, highlighted in the safety evaluator review to determine if late serological conversion (or RNA/DNA levels) were determined in order to definitively rule out viral Hepatitis A, B, or C.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

Data from the following submissions have been included in this safety review:

- Efficacy supplement dated December 15, 2006
- Periodic Safety Update Reports dated March 23, 2007 and June 22, 2007
- Responses to FDA queries and requests, including responses with FDA received date of:
  - March 20, 2007
  - July 13, 2007
  - July 16, 2007
  - July 19, 2007
  - July 25, 2007

See Section 4.1 also.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 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).

7.3.2 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.

7.3.3 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.

7.3.4 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.

Hepatotoxicity was associated with natalizumab use based on four natalizumab-associated serious hepatic injury cases selected from the AERS database (See Section 7.1.17.2 and the safety evaluator review by Charlene M. Flowers, R.Ph.), but the mechanism of liver injury is not well elucidated, and the magnitude of the risk is not well characterized. Additional post-marketing data would be necessary to characterize the risk of natalizumab-associated

hepatotoxicity, and close follow up of new and existing cases would be required to ascertain the etiology of the liver events.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

For CD, the Applicant's primary safety data presentations were based on pooled data from short-term acute treatment placebo-controlled CD studies and pooled data from short- and long-term CD studies. (See Section 7.2.1.3.2.) The pooled data from short-term acute treatment placebo-controlled CD studies was used for the assessment of adverse events relation to natalizumab therapy as it was controlled data. The larger database of short and long term CD studies had longer duration of exposure, but the data was not controlled. Results from Study CD303, the maintenance study, had longer duration of exposure but a smaller number of subjects, and were also used in the assessment of adverse events relation to natalizumab therapy as it was controlled data.

For MS, the primary safety data presentations were based on pooled data from MS placebo-controlled studies, but as stated in the review by Drs. Hughes and McDermott in their review of June 2006, there is the limitation of that approach of not permitting the assessment of differences in the safety profile of natalizumab taken as monotherapy versus with concomitant Avonex.

This safety review considered pooled data of the MS and CD placebo-controlled studies only for the assessment of the association between natalizumab and malignancies.

7.4.1.2 Combining data

This review pools studies by simple combination of numerators and denominators and does not employ other pooling procedures.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The Applicant conducted analyses of the association between adverse events and body weight. The finding of a higher frequency of adverse events at lower patient weight indicates a dose-response relationship with natalizumab and suggests that an adverse event is drug-related.

In short-term placebo-controlled CD studies, headache, CD, pharyngolaryngeal pain, and back pain tended to increase in incidence with decreasing weight in the natalizumab-treatment group.

(See table below.) No clear association of these adverse events and dose of natalizumab can be made because of the limited number of subjects in each weight group.

Table 95. Incidence, by Body Weight, of Adverse Events Experienced By at Least 5% of Subjects Who Received Natalizumab (Short-Term Placebo-Controlled Treatment Studies of Active CD)

	Natalizumab Weight Group			
	<50 kg	50-75 kg	76-100 kg	>100 kg
Number of Subjects Dosed	81 (100%)	709 (100%)	318 (100%)	74 (100%)
Number of Subjects with an Event	74 (91.4%)	619 (87.3%)	274 (86.2%)	66 (89.2%)
Event				
Headache	27 (33.3%)	239 (33.7%)	82 (25.8%)	16 (21.6%)
Nausea	12 (14.8%)	124 (17.5%)	41 (12.9%)	15 (20.3%)
Nasopharyngitis	16 (19.8%)	94 (13.3%)	34 (10.7%)	14 (18.9%)
Abdominal pain NOS	11 (13.6%)	89 (12.6%)	36 (11.3%)	9 (12.2%)
Crohn's disease	12 (14.8%)	79 (11.1%)	36 (11.3%)	5 (6.8%)
Arthralgia	7 (8.6%)	69 (9.7%)	20 (6.3%)	10 (13.5%)
Fatigue	8 (9.9%)	62 (8.7%)	27 (8.5%)	11 (14.9%)
Vomiting NOS	5 (6.2%)	62 (8.7%)	22 (6.9%)	6 (8.1%)
Dizziness	4 (4.9%)	58 (8.2%)	24 (7.5%)	5 (6.8%)
Pharyngolaryngeal pain	6 (7.4%)	51 (7.2%)	14 (4.4%)	3 (4.1%)
Back pain	8 (9.9%)	48 (6.8%)	18 (5.7%)	4 (5.4%)
Pyrexia	6 (7.4%)	48 (6.8%)	21 (6.6%)	5 (6.8%)
Influenza like illness	5 (6.2%)	40 (5.6%)	22 (6.9%)	3 (4.1%)
Dyspepsia	4 (4.9%)	32 (4.5%)	11 (3.5%)	7 (9.5%)
Constipation	6 (7.4%)	25 (3.5%)	9 (2.8%)	3 (4.1%)
Diarrhoea NOS	1 (1.2%)	25 (3.5%)	15 (4.7%)	4 (5.4%)
Influenza	6 (7.4%)	25 (3.5%)	12 (3.8%)	3 (4.1%)
Rash NOS	5 (6.2%)	24 (3.4%)	12 (3.8%)	2 (2.7%)
Myalgia	5 (6.2%)	22 (3.1%)	7 (2.2%)	2 (2.7%)
Upper respiratory tract infection NOS	4 (4.9%)	22 (3.1%)	19 (6.0%)	5 (6.8%)
Flatulence	6 (7.4%)	20 (2.8%)	10 (3.1%)	3 (4.1%)
Abdominal distension	7 (8.6%)	18 (2.5%)	10 (3.1%)	1 (1.4%)
Depression	1 (1.2%)	18 (2.5%)	4 (1.3%)	4 (5.4%)
Pharyngitis viral NOS	4 (4.9%)	12 (1.7%)	2 (0.6%)	5 (6.8%)
Neck pain	5 (6.2%)	8 (1.1%)	6 (1.9%)	2 (2.7%)

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 group with highest number of subjects dosed.
(Table above is taken from Page 366 of the Applicant's Summary of Clinical Safety.)

7.4.2.2 Explorations for time dependency for adverse findings

Hypersensitivity reactions and infusion reactions occurred close to the time of study agent administration. No clear associations were evident between any other adverse events and the time of the most recent study agent administration.

7.4.2.3 Explorations for drug-demographic interactions

Geriatric subjects:

The clinical experience in geriatric subjects is limited in both MS and CD. Only 3 subjects in placebo-controlled MS studies (0.1%) and 42 subjects (2.5%) in placebo-controlled treatment studies of active CD were 65 years of age or older. The incidence of adverse events in subjects receiving placebo was similar to that in those receiving natalizumab. Based on the data available in the complete natalizumab program, no safety signals were identified.

Pediatric subjects:

The clinical experience in pediatric subjects is limited. One subject in the MS studies and no subjects in the placebo-controlled treatment studies of active CD were under 18 years of age. However, an open-label study in subjects aged 11 to 17 was conducted in Crohn's disease. The MS subject, in addition to receiving double the recommended dose of AVONEX®, was also treated with immunosuppressive agents that were unable to control her severe disease. In Study CD305, the adverse event profile in adolescents with CD appeared similar to that seen in the adult population with the exception of pyrexia. However, this is not alarming given a younger subject population. In addition, the incidence of acute infusion reactions in Study CD305 (13%) was similar to that observed among natalizumab-treated subjects in the short-term placebo-controlled treatment studies of active CD (10.8%). Although no safety signals have been identified in the available data, further experience would be necessary to better characterize the safety profile in pediatric subjects.

Gender:

In placebo-controlled studies of MS, the natalizumab group comprised 425 men (26%) and 1,192 women (74%), and the placebo group comprised 338 men (30%) and 797 women (70%). 93.6% of men vs. 96.8% of women in the natalizumab group and 96.4% of men vs. 97.6% of women in the placebo group experienced at least one adverse event. To determine if one gender was at greater risk than another after receiving natalizumab, difference in incidence rates between the two genders were compared with the differences seen in placebo subjects. After eliminating events where the pattern was also seen in subjects who received placebo, greater proportions of women treated with natalizumab experienced:

- depression (natalizumab: 16.3% of women vs. 12.5% of men, placebo: 14.9% of women vs. 14.5% of men)
- hypoaesthesia (natalizumab: 14.3% of women vs. 8.7% of men, placebo: 17.6% of women vs. 15.7% of men), and
- herpes simplex (natalizumab: 6.0% of women vs. 2.1%, placebo: 4.9% of women vs. 4.1% of men).

In the short-term placebo-controlled treatment studies of active CD, the natalizumab group comprised 504 men (43%) and 678 women (57%) of whom 426 (84.5%) and 607

(89.5%) experienced at least one adverse event. After eliminating events where the pattern was also seen in placebo subjects, greater proportions of women in the natalizumab group experienced:

- influenza (natalizumab, women vs. men: 4.9 vs. 2.6%; placebo: women vs. men: 4.4 vs. 4.8%)
- sinusitis NOS (natalizumab, women vs. men: 4.0 vs. 2.0%, placebo, women vs. men: 2.4 vs. 2.4%)
- pharyngolaryngeal pain (natalizumab, women vs. men: 8.7 vs. 3.0%, placebo, women vs. men: 4.7 vs. 3.3%), and
- alopecia (natalizumab, women vs. men: 2.5 vs. 0.2%, placebo, women vs. men: 1.0 vs. 0%).

Pyrexia was experienced by more men (7.9%) than women (5.9%) in the natalizumab group vs. 4.8% of men and 6.1% of women who received placebo.

Race:
In placebo-controlled MS studies, 93% of subjects were White, 3% were Black, and 4% were another racial origin. In short-term placebo-controlled studies of active CD, 95% of subjects were White, 2% were Black, and 3% were of another racial origin. Based on exploratory analyses, no clear association was found between race and the adverse event profile of natalizumab.

7.4.2.4 Explorations for drug-disease interactions

The Applicant submitted results of exploratory analyses of hypersensitivity reactions, infections, and malignancies in subjects with a history of immunological disorders in placebo-controlled studies of MS, and placebo-controlled studies of active CD (CD301 and CD307). A history of immunological disorders was recorded in 632 (40%) of the 1,580 natalizumab-treated MS subjects with data, and by 461 (42%) of the 1,099 MS subjects with data who received placebo. A history of immunological disorders was recorded in 296 (30%) of 982 CD301 and CD307 natalizumab-treated subjects with data, and by 159 (37%) of the 434 subjects with data who received placebo.

Hypersensitivity Reactions: In the MS placebo-controlled studies, subjects with a history of immunological disease were more likely to have drug hypersensitivity, hypersensitivity NOS, urticaria NOS, rash NOS, pruritus, and rigors in both the placebo and natalizumab groups. In the CD placebo-controlled studies, subjects with a history of immunological disease were more likely to have rigors, and nausea, although no difference was seen between natalizumab and placebo treatment groups. Anaphylactic reaction, hypersensitivity, drug hypersensitivity, rash, and pruritus were not predicted by a subject's prior history of immunological disease. (See tables below.)

Table 96. Incidence of Selected Adverse Events in Subjects with A History of Immunological Disease (Placebo-Controlled Studies of MS)

	Placebo		Natalizumab	
Preferred Term	History	No History	History	No History
Number of Subjects Dosed	461 (100.0%)	638 (100.0%)	632 (100.0%)	948 (100%)
Number of Subjects with an Event	456 (99%)	613 (96%)	614 (97%)	905 (95%)
Anaphylactic reaction	1 (0.2%)	1 (0.2%)	1 (0.2%)	4 (0.4%)
Hypersensitivity NOS	8 (1.7%)	1 (0.2%)	15 (2.4%)	4 (0.4%)
Drug hypersensitivity	9 (2.0%)	3 (0.5%)	20 (3.2%)	5 (0.5%)
Serum sickness	0	1 (0.2%)	0	0 2 (0.2%)
Anaphylactoid reaction	0	0	1 (0.2%)	1 (0.1%)
Nausea	88 (19.1%)	75 (11.8%)	118 (18.7%)	112 (11.8%)
Rigors	8 (1.7%)	4 (0.6%)	33 (5.2%)	22 (2.3%)
Rash NOS	40 (8.7%)	33 (5.2%)	49 (7.8%)	63 (6.6%)
Pruritus	36 (7.8%)	22 (3.4%)	33 (5.2%)	37 (3.9%)
Rash pruritic	8 (1.7%)	3 (0.5%)	7 (1.1%)	15 (1.6%)
Urticaria NOS	19 (4.1%)	8 (1.3%)	25 (4.0%)	14 (1.5%)
Urticaria generalized	0	1 (0.2%)	2 (0.3%)	3 (0.3%)

(Table above is taken from Page 370 of the Applicant's Summary of Clinical Safety.)

Table 97. Incidence of Selected Adverse Events in Subjects with A History of Immunological Disease (Placebo-Controlled Treatment Studies CD301 and CD307)

	Placebo		Natalizumab	
Preferred Term	History	No History	History	No History
Number of Subjects Dosed	159 (100.0%)	275 (100.0%)	296 (100.0%)	686 (100.0%)
Number of Subjects with an Event	143 (90%)	227 (83%)	267 (90%)	598 (87%)
Anaphylactic reaction	0	0	0	1 (0.1%)
Hypersensitivity NOS	0	0	2 (0.7%)	10 (1.5%)
Drug hypersensitivity	1 (0.6%)	0	2 (0.7%)	4 (0.6%)
Serum sickness	0	1 (0.4%)	0	0
Nausea	29 (18.2%)	36 (13.1%)	60 (20.3%)	114 (16.6%)
Rigors	6 (3.8%)	3 (1.1%)	9 (3.0%)	13 (1.9%)
Rash NOS	6 (3.8%)	7 (2.5%)	10 (3.4%)	28 (4.1%)
Pruritus	3 (1.9%)	9 (3.3%)	5 (1.7%)	23 (3.4%)
Rash pruritic	0	1 (0.4%)	2 (0.7%)	3 (0.4%)
Urticaria NOS	2 (1.3%)	2 (0.7%)	6 (2.0%)	8 (1.2%)

(Table above is taken from Page 374 of the Applicant's Summary of Clinical Safety.)

Infections: Subjects with a history of immunological disease appeared to be more likely to have infections in both MS placebo-controlled trials and placebo-controlled studies of active CD

(CD301 and CD307) regardless of treatment assignment. Of natalizumab-treated MS subjects with a history of immunological disease, 80.9% experienced an infection vs. 70.5% without such a history; in those subjects who received placebo, infections were seen in 79.2% of subjects with a history vs. 72.1% of those who did not. Of natalizumab-treated CD subjects with a history of immunological disease, 44.9% experienced an infection vs. 40.5% without such a history. In those subjects who received placebo, infections were seen in 38.4% of subjects with a history vs. 36.0% of those who did not. (See tables below.)

Table 98. Incidence of Selected Adverse Events in Subjects with A History of Immunological Disease (Placebo-controlled Studies of MS)

	Placebo		Natalizumab	
Preferred Term	History	No History	History	No History
Number of Subjects Dosed	461 (100%)	638 (100%)	632 (100%)	948 (100%)
Number of Subjects with an Infection	365 (79.2%)	460 (72.1%)	511 (80.9%)	668 (70.5%)
Nasopharyngitis	157 (34.1%)	178 (27.9%)	207 (32.8%)	268 (28.3%)
Influenza	62 (13.4%)	83 (13.0%)	91 (14.4%)	132 (13.9%)
Upper respiratory tract infection NOS	82 (17.8%)	84 (13.2%)	123 (19.5%)	122 (12.9%)
Urinary tract infection NOS	76 (16.5%)	99 (15.5%)	120 (19.0%)	121 (12.8%)
Sinusitis NOS	75 (16.3%)	47 (7.4%)	101 (16.0%)	81 (8.5%)
Upper respiratory tract infection viral NOS	34 (7.4%)	54 (8.5%)	62 (9.8%)	72 (7.6%)
Bronchial infection	41 (8.9%)	30 (4.7%)	54 (8.5%)	41 (4.3%)
Herpes simplex	26 (5.6%)	27 (4.2%)	40 (6.3%)	39 (4.1%)
Gastroenteritis viral NOS	46 (10.0%)	34 (5.3%)	50 (7.9%)	38 (4.0%)
Vaginosis fungal NOS	25 (5.4%)	15 (2.4%)	37 (5.9%)	27 (2.8%)
Bladder infection NOS	11 (2.4%)	5 (0.8%)	24 (3.8%)	14 (1.5%)

(Values in table above are taken from Page 367 of the Applicant's Summary of Clinical Safety and from Pages 2516-2527 of the Applicant's Summary of Clinical Safety Source Tables.)

Table 99. Incidence of Selected Adverse Events in Subjects with A History of Immunological Disease (Placebo-Controlled Treatment Studies CD301 and CD307)

	Placebo		Natalizumab	
Preferred Term	History	No History	History	No History
Number of Subjects Dosed	159 (100%)	275 (100%)	296 (100%)	686 (100%)
Number of Subjects with an Infection	61 (38.4%)	99 (36.0%)	133 (44.9%)	278 (40.5%)
Nasopharyngitis	16 (10.1%)	27 (9.8%)	45 (15.2%)	89 (13.0%)
Upper respiratory tract infection NOS	9 (5.7%)	9 (3.3%)	14 (4.7%)	33 (4.8%)
Viral infection NOS	1 (0.6%)	7 (2.5%)	10 (3.4%)	22 (3.2%)
Influenza	3 (1.9%)	14 (5.1%)	14 (4.7%)	21 (3.1%)
Sinusitis NOS	5 (3.1%)	6 (2.2%)	15 (5.1%)	18 (2.6%)
Gastroenteritis NOS	2 (1.3%)	5 (1.8%)	8 (2.7%)	16 (2.3%)
Pharyngitis viral NOS	1 (0.6%)	3 (1.1%)	8 (2.7%)	15 (2.2%)
Urinary tract infection NOS	4 (2.5%)	2 (0.7%)	13 (4.4%)	13 (1.9%)
Perianal abscess	2 (1.3%)	1 (0.4%)	3 (1.0%)	8 (1.2%)
Upper respiratory tract infection viral NOS	1 (0.6%)	2 (0.7%)	5 (1.7%)	8 (1.2%)
Gastroenteritis viral NOS	3 (1.9%)	3 (1.1%)	3 (1.0%)	7 (1.0%)
Herpes simplex	1 (0.6%)	3 (1.1%)	3 (1.0%)	5 (0.7%)
Vaginosis fungal NOS	0	1 (0.4%)	3 (1.0%)	4 (0.6%)
Bronchitis NOS	3 (1.9%)	6 (2.2%)	4 (1.4%)	3 (0.4%)
Bronchitis bacterial NOS	0	0	4 (1.4%)	2 (0.3%)
Folliculitis	2 (1.3%)	0	4 (1.4%)	0

(Values in table above are taken from Page 372 of the Applicant's Summary of Clinical Safety and from Pages 3658 to 3663 of the Applicant's Summary of Clinical Safety Source Tables.)

Malignancies: The overall incidence of malignancy was too low in both the MS and CD populations to allow adequate assessment of malignancy between subjects with and without a history of immunological disease by treatment group (see tables below).

Table 100. Placebo-Controlled Studies of MS: Incidence of Malignancies in Subjects with a History of Immunological Disorders

	Placebo		Natalizumab	
Preferred Term	History	No History	History	No History
Number of Subjects Dosed	461 (100%)	638 (100%)	632 (100%)	948 (100%)
Number of Subjects with a Malignancy	11 (2.4%)	4 (0.6%)	6 (0.9%)	5 (0.5%)
Basal cell carcinoma	4 (0.9%)	0	3 (0.5%)	1 (0.1%)
Breast cancer in situ	1 (0.2%)	0	0	1 (0.1%)
Cervical carcinoma stage 0	0	0	0	1 (0.1%)
Colon cancer NOS	0	0	0	1 (0.1%)
Metastatic malignant melanoma	0	0	0	1 (0.1%)
Breast cancer NOS	2 (0.4%)	1 (0.2%)	3 (0.5%)	0
Breast cancer metastatic	0	1 (0.2%)	0	0
Breast cancer stage III	1 (0.2%)	0	0	0
Malignant melanoma	1 (0.2%)	1 (0.2%)	0	0
Malignant pleural effusion	1 (0.2%)	0	0	0
Secretory adenoma of pituitary	0	1 (0.2%)	0	0
Squamous cell carcinoma of skin	1 (0.2%)	0	0	0

(Table above is taken from Page 371 of the Applicant's Summary of Clinical Safety.)

Table 101. Incidence of Malignancies in Subjects with a History of Immunological Disorders (Placebo-Controlled Treatment Studies CD301 and CD307)

	Placebo		Natalizumab	
Preferred Term	History	No History	History	No History
Number of Subjects Dosed	159 (100%)	275 (100%)	296 (100%)	686 (100%)
Number of Subjects with a Malignancy	0	1 (0.4%)	4 (1.4%)	2 (0.3%)
Lung adenocarcinoma NOS	0	0	0	2 (0.3%)
Bladder cancer NOS	0	0	1 (0.3%)	0
Breast cancer NOS	0	0	1 (0.3%)	0
Breast cancer invasive NOS	0	0	1 (0.3%)	0
Malignant melanoma	0	0	1 (0.3%)	0
Uterine cancer NOS	0	1 (0.4%)	0	0

(Table above is taken from Page 375 of the Applicant's Summary of Clinical Safety.)

No additional exploratory safety analyses for drug – disease interactions are warranted.

7.4.2.5 Explorations for drug-drug interactions

The Applicant submitted a population PK analysis which suggested that infliximab, steroids and immunosuppressants do not influence the pharmacokinetics of natalizumab on co-administration. The FDA has reviewed the data (see Clinical Pharmacology Review) and agrees with the Applicant's conclusion.

The Applicant also submitted results of Study CD306 in which CD patients concurrently received infliximab. The Applicant stated that the mean serum natalizumab PK parameters from CD306 for subjects receiving concomitant therapy with infliximab appeared to be generally comparable to those obtained in CD301 in which anti-TNF therapy was prohibited, indicating little or no readily apparent effect of infliximab on natalizumab PK. The clinical pharmacology reviewer (Dr. Abimbola Adebowale) commented that the results of the population PK analysis supported the Applicant's conclusions, but added that, due to the extrapolation of data following the third dose, AUC and half-life from Study CD306 were not truly comparable to those in Study CD301. (See Clinical Pharmacology Review.)

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

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

8.2 Drug-Drug Interactions

Because of the potential for increased risk of PML and other infections, Crohn's disease patients receiving natalizumab should not be treated with concomitant immunosuppressants (e.g., azathioprine, 6-mercaptopurine, or methotrexate) or inhibitors of TNF-α, and corticosteroids should be tapered in those patients with Crohn's disease who are taking corticosteroids when they start natalizumab therapy. Ordinarily, MS patients receiving chronic immunosuppressant or immunomodulatory therapy should not be treated with natalizumab.

The Applicant submitted a population PK analysis which suggested that infliximab, steroids and immunosuppressants do not influence the pharmacokinetics of natalizumab on co-administration. The FDA has reviewed the data (see Clinical Pharmacology Review) and agrees with the Applicant's conclusion.

The Applicant also submitted results of Study CD306 in which CD patients concurrently received infliximab. The Applicant stated that the mean serum natalizumab PK parameters from CD306 for subjects receiving concomitant therapy with infliximab appeared to be generally comparable to those obtained in CD301 in which anti-TNF therapy was prohibited, indicating little or no readily apparent effect of infliximab on natalizumab PK. The clinical pharmacology reviewer (Dr. Abimbola Adebowale) commented that the results of the population PK analysis supported the Applicant's conclusions, but added that, due to the extrapolation of data following the third dose, AUC and half-life from Study CD306 were not truly comparable to those in Study CD301. (See Clinical Pharmacology Review.)

At the time of the original approval, the PK data suggested that multiple dosing with Interferon β-1a (Avonex® 30 μg IM once weekly) reduced the clearance of natalizumab by 30% (see original Clinical Review by Dr. Wilson Bryan). A population PK analysis however suggested that Avonex® does not influence the pharmacokinetics of natalizumab (see Clinical Review by Drs. Alice Hughes and Susan McDermott).

8.3 Special Populations

Natalizumab has not adequately studied the safety and effectiveness of natalizumab in patients with renal insufficiency, hepatic insufficiency, age ≥ 65, age < 18, or in women who are pregnant or nursing to assess safety and efficacy in these populations. It is not known whether natalizumab is excreted in human milk. The currently approved labeling regarding pregnancy and breast feeding is appropriate.

8.4 Pediatrics

For the MS indication, the Applicant was granted a pediatric waiver pursuant to 21 CFR 601.27(c) prior to the original approval.

The Applicant conducted two open-label trials (CD305 and CD352) that included adolescents (11-17 years old) with CD, enrolling a total of 64 patients. There was not adequate information to assess safety and efficacy in that population.

For the proposed CD indication, the Applicant has requested the following:
(1) A partial waiver excluding subjects (b) (4) from enrollment in future pediatric CD studies with natalizumab. The Applicant's rationale for the cutoff of (b) (4) is based on a study of the pediatric inflammatory bowel diseases (which include CD and UC) by S. Kugathasan et al. (2003) that determined that the age-related annual incidence of new-onset pediatric CD was negligible in children below (b) (4)
(2) A deferral in the pediatric CD population until the safety profile of natalizumab is better understood.

In the Pre-BLA meeting for the proposed natalizumab for CD indication dated July 26, 2006, FDA suggested that the Applicant consider requesting a deferral for the pediatric CD population, and that a waiver might be appropriate for certain age ranges but might not be appropriate for the whole pediatric range. The Applicant appears to have appropriately requested a deferral for the pediatric CD population, so that the Applicant may later submit a natalizumab pediatric development plan to the FDA once the safety database for natalizumab supports its use in this patient population. In addition, the Applicant appears to have adequately justified the reason for excluding subjects (b) (4) from enrollment in future pediatric CD studies with natalizumab, specifically that the age-related annual incidence of new-onset pediatric CD was negligible in children (b) (4) based on published data. Based on the information submitted, this reviewer recommends that the Applicant be granted both of the following: (1) the request for partial waiver excluding subjects (b) (4) from enrollment in future pediatric CD studies with natalizumab; and (2) the request for deferral in the pediatric population

8.5 Advisory Committee Meeting

The Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Meeting Advisory Committee met on July 31, 2007. Although the Committee agreed that there was at least a modest response in the populations studied, with evidence showing stronger support for maintenance than for induction of response and remission, they expressed concerns regarding the lack of available data on the safety of long term exposure to this product.

Most Committee members indicated that CRP level alone is not reliable as an indicator of disease course, so that other objective laboratory and clinical markers should also be acceptable as evidence of active inflammation. Many on the Committee agreed that it would be best to restrict use of this product to patients who have had an inadequate response to all available therapies (specifically including immunosuppressants, steroids and TNF-alpha inhibitors, or who are intolerant to these therapies, or for whom these therapies are contraindicated).

There was concern that concomitant use of immunomodulators or prolonged steroid administration should be avoided. The Committee found no evidence for lesser efficacy when used as monotherapy and therefore agreed that concomitant immunomodulator or prolonged

steroid therapy should be discouraged. Although the Committee did not directly address the question of how risks might be impacted by current CD treatment strategies for induction and maintenance (e.g. 'step-up', 'top-down", or steroid sparing), they did explicitly rule out the use of Tysabri anywhere but late in the therapeutic sequence.

Although most of the committee stated that they did not believe any additional studies should be required for approval, some of the committee members commented that the efficacy and safety data are not robust and that additional studies should be conducted in the populations for whom the benefits are expected to outweigh the risks. Because the committee expressed concern that existing studies do not have sufficient numbers or follow-up periods to quantitate the risks that are of greatest concern, especially PML, opportunistic or reactivated latent infections, and liver toxicity, the committee agreed that follow-up must take place throughout the post-marketing period for risk/benefit considerations.

Most of the Committee felt that a period of six months was appropriate for steroid withdrawal and that failure to achieve this goal was an indication to discontinue Tysabri. Likewise, they felt that a single course of steroids might be reasonable to control a single flare while on Tysabri, but that repeated flares should also provide indication for stopping this drug.

Many on the Committee agreed that for CD patients, baseline general physical exams, including full neurological exams (with cognitive testing) would be most appropriate. Baseline MRIs and JC virus assay of body fluids were not considered helpful, although these studies should be performed in patients with newly emerging neurologic symptoms.

The final vote regarding approval of Tysabri for the treatment of Crohn's disease (assuming that an effective risk management plan is in place) was 12 in favor, 3 opposed, and 2 abstentions. The consensus was that the product should only be approved for use in patients who did not have an adequate response to all available therapies for CD, are intolerant to these therapies, or for whom other therapies are contraindicated. It was generally agreed by all members of the committee that there is a need for continued, intensive post-marketing surveillance and continued restricted distribution.

8.6 Literature Review

This review does not contain a significant review of the scientific literature on either natalizumab or CD. A review of the scientific literature was conducted with regard to the three cases of PML, and the dose suspension safety assessment (see Section 7.1.3.3.1).

8.7 Postmarketing Risk Management Plan

There is currently a Risk Minimization and Action Plan (RiskMAP) called the TOUCH (Tysabri Outreach: Unified Commitment to Health) Prescribing Program that is 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. (See Section 2.5.6.)

The proposed RiskMAP has been extensively reviewed by the Office of Surveillance and Epidemiology Reviewer (Dr. Claudia Karwoski); please see the Office of Surveillance and Epidemiology review for the completed review of the RiskMAP. Based on that review, the objectives and the main features of the two versions (CD-TOUCH and MS-TOUCH) are the same; however, each version differs in how forms and educational materials are customized to patients, their prescribers, and infusion site staff. Additional findings from Dr. Karwoski's review are noted briefly as follows:

The Applicant proposed some modifications to the RiskMAP specifically to address concerns in CD patients and the recommendations of the 2007 AC. There are two principal differences between CD-TOUCH and MS-TOUCH:

(1) Under CD-TOUCH, prescribers will need to evaluate the patient at 12 weeks of Tysabri treatment to determine if the patient has experienced a therapeutic benefit. Prescribers are encouraged to discontinue Tysabri in those patients that have not benefited. This will be documented by the prescribing physician and reported back to the Applicant. This 12-week evaluation for therapeutic benefit is not required under the MS-TOUCH program.
(2) Because Tysabri will not be indicated as monotherapy in CD, concomitant therapy with systemic steroids will be permissible, but the prescribing physician is encouraged to begin tapering systemic steroids and to discontinue Tysabri treatment in those patients that cannot be discontinued from their systemic steroids within six months of initiating Tysabri. Concomitant treatment with other immunomodulatory and immunosuppressive medications with other products is also discouraged and there are statements to this effect in the prescriber and patient acknowledgement sections of the patient/physician enrollment form. The Applicant has also proposed CD-specific education to infusion sites and prescribers as well as CD-specific forms.

To further assess the risks of Tysabri, the Applicant has proposed to conduct a prospective, observational cohort study of CD patients (Tysabri Global Observational Program in Safety; TYGRIS-CD) to be treated with Tysabri in the United States. The primary objective of the study is to determine the incidence and pattern of serious infections, malignancies, and other serious adverse events (SAEs) with longer-term use of Tysabri in CD. The Agency and the Applicant have agreed on the sample size (see Review by Dr. Mark Levenson, Quantititative Safety and Pharmacoepidemiology Group). This study will be outlined in the approval letter as a postmarketing commitment.

8.8 Other Relevant Materials

Review of this application included consultation from the Division of Medication Errors and Technical Support (DMETS), the Study Endpoints and Label Development (SEALD) Team, and the Division of Neurology Products (DNP).

A memorandum from Judy Park, Pharm.D. of DMETS recommended label revisions. A memorandum from Iris Masucci, Pharm.D., BCPS, of the SEALD Team recommended label revisions to comply with PLR. Laurie B. Burke, R.Ph., MPH, of the SEALD Team attended a labeling meeting on December 21, 2007, to discuss if specific patient reported outcomes should be included in the label; Ann Marie Trentacosti, M.D. of the SEALD Team provided a review regarding study endpoints that were patient reported outcomes.

The consultation with DNP was primarily to ensure that label revisions proposed by the Applicant to comply with the Physicians Labeling Rule (PLR) did not alter the sections of the labeling related to the MS indication. The DNP reviewers, Dr. Eric Bastings and Dr. Alice Hughes, provided comments to this Division regarding the Applicant's proposed label revisions.

The consultation with DNP also included a meeting with DNP held on November 26, 2007, to discuss the feasibility and utility for the CD indication of baseline neurological examinations by a neurologist (including cognitive testing) and of baseline MRIs as evaluations that may potentially decrease the risk of PML. The outcome of this meeting and labeling negotiations with the Applicant was a decision that neither baseline neurological examinations nor baseline MRIs should be recommended in the labeling for the CD indication. Part of the rationale was that neither assessment at baseline would change the management of a new onset neurological finding in a patient being treated with natalizumab.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1 Efficacy Conclusions

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 Applicant'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).

Efficacy in induction was demonstrated as the results of the second induction study (Study CD307) were consistent with the finding in the subgroup analysis of patients with elevated CRP

in Study CD301. There was no confirmation, however, that high CRP predicts clinical response because the low CRP population was not included in Study CD307 for comparison.

The magnitude of the treatment effect in induction is moderate as it was approximately 8%, 13%, and 15% for the overall population of Study CD301, the elevated CRP subgroup of Study CD301, and the prospectively selected high CRP population of Study CD307, respectively.

Maintenance

In the maintenance study (Study CD303), responders from Study CD301 were re-randomized to natalizumab or placebo. Efficacy in maintenance was demonstrated in the overall population of responders from Study CD301 as 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 proportion of patients maintaining clinical response through an additional six months was 35% higher for natalizumab than for placebo (60.5% vs. 25.8%; $p<0.001$). The results were similar to that of the overall population, suggesting that there is efficacy in maintenance regardless of CRP at baseline.

The magnitude of the treatment effect in maintenance is higher than that for induction.

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. Thus, given the limitations of the data, one cannot infer a higher or lower treatment effect in one particular subgroup compared to another.

9.1.2 Safety Conclusions

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.[4]

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

Hepatotoxicity has been associated with natalizumab use based on four Tysabri-associated serious hepatic injury cases selected from the AERS database. The mechanism of natalizumab-associated liver injury cannot be well elucidated, and the magnitude of the natalizumab-associated risk for hepatotoxicity cannot be well characterized, based on the existing data. Markedly elevated hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses. In addition, liver injury recurred upon rechallenge, providing strong evidence that Tysabri caused the injury.

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. The Applicant's proposed observational study, TYGRIS (TYSABRI Global

Observational Program in Safety) with modifications as proposed by OSE, is designed to obtain the long-term follow-up data to assess the risks of each of these safety issues. (See Section 8.7.)

9.1.3 Benefit-Risk Conclusions

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 Applicant's proposed indication is for those that have had inadequate response or inability to tolerate prior conventional therapies (where conventional therapies include mesalamine, immunosuppressants, and steroids) and inadequate response or inability to tolerate prior TNF-α inhibitors.

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, 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.

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 baseline brain MRIs, and of baseline neurological exams by a neurologist was discussed in the course of labeling negotiations, and in a meeting with the Division of Neurology Products (see Section 8.8). It was concluded that neither should be recommended in the labeling.

9.2 Recommendation on Regulatory Action

This reviewer recommends approving the efficacy supplement with revisions to the proposed labeling (see Section 9.4) and to the proposed risk management program. The information in this supplement provides substantial evidence to support the proposed additional indication, and there are data to provide adequate directions for use.

This reviewer recommends that the population be adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and an inhibitor of TNF-α.

This reviewer recommends that the indication state that concomitant immunosuppressants or inhibitors of TNF-α should not be taken with natalizumab, and that prolonged steroid therapy should be discouraged.

This reviewer recommends that natalizumab should be discontinued by three months as proposed by the Applicant if the CD patient has not experienced therapeutic benefit.

This reviewer recommends that there be continued, intensive post-marketing surveillance and continued restricted distribution. In addition, this reviewer recommends that baseline neurological exams by a neurologist, baseline MRIs, and baseline JC virus assay of body fluids

should not be required at baseline but should be performed in patients with newly emerging neurologic symptoms.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Applicant has modified the current Risk Management Plan (RiskMAP) called the TOUCH (Tysabri Outreach: Unified Commitment to Health) Prescribing Program. The objectives and the main features of the two versions (CD-TOUCH and MS-TOUCH) are the same; however, each version differs in how forms and educational materials are customized to patients, their prescribers, and infusion site staff. There are two principal differences between CD-TOUCH and MS-TOUCH:

(3) Under CD-TOUCH, prescribers are to evaluate the patient at 12 weeks of Tysabri treatment to determine if the patient has experienced a therapeutic benefit, and are encouraged to discontinue Tysabri in those patients that have not benefited. (This 12-week evaluation for therapeutic benefit is not required under the MS-TOUCH program.)

(4) Although concomitant therapy with systemic steroids will be permissible in the CD population (in contrast to the monotherapy indication for MS), the prescribing physician is encouraged to begin tapering systemic steroids and to discontinue Tysabri treatment in those patients that cannot be discontinued from systemic steroids within six months of initiating Tysabri. Similar to MS-TOUCH, concomitant treatment with other immunomodulatory and immunosuppressive medications is also discouraged.

To further assess the risks of Tysabri, the Applicant has proposed to conduct a prospective, observational cohort study of CD patients (Tysabri Global Observational Program in Safety; TYGRIS-CD). The primary objective of the study is to determine the incidence and pattern of serious infections, malignancies, and other serious adverse events (SAEs) with longer-term use of Tysabri in CD. The Agency and the Applicant have agreed on the sample size (see Review by Dr. Mark Levenson, Quantititative Safety and Pharmacoepidemiology Group). This study will be outlined in the approval letter as a postmarketing commitment.

In addition to the RiskMAP, natalizumab labeling has a description of what is known about the potential risk of PML and other adverse effects, including atypical and opportunistic infections; the existing labeling has a black BOXED WARNING for the risk of PML and general information about the RiskMAP.

9.3.2 Required Phase 4 Commitments

1. To conduct a prospective, observational study in subjects with Crohn's disease who are receiving natalizumab, by completing the protocol, "TYGRIS-CD: TYSABRI Observational Program in Safety in CD (Crohn's Disease)". (The number of patients and the duration of follow-up is pending. This will be provided in the review from Dr. Claudia Karwoski and Dr. Mary Willy.)

9.3.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

9.4 Labeling Review

Discussions between the Applicant and CDER have resolved major issues with regard to the label. Several significant changes have been made to the currently approved labeling as follows:

- The entire labeling has been re-organized to comply with the Physician's Labeling Rule (PLR) format requirements as described in 21CFR 201.57(d). Most notably, a one page **HIGHLIGHTS OF PRESCRIBING INFORMATION** was added. Most other changes mainly involved re-arrangements of existing sections in accordance with the PLR format requirements.
- In the **INDICATIONS AND USAGE** section, the CD indication was added in a separate sub-section from the MS indication. The indication for MS has not changed. The indication for CD states that Tysabri is for inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD with evidence of inflammation who have had an inadequate response or are unable to tolerate conventional CD therapies and an inhibitor of TNF-α; it further states that patients should not take concomitant immunosuppressants or inhibitors of TNF-α.
- In the **DOSAGE AND ADMINISTRATION** section, the CD indication was added in a separate sub-section from the MS indication. The CD indication sub-section contains analogous wording to that in the MS indication sub-section, namely a statement about the requirement to be registered in the CD-TOUCH prescribing program and a statement about the recommended dose. The CD indication sub-section contains additional wording that is not in the MS indication sub-section; these are statements that:
  (1) recommend against concomitant immunosuppressant or TNF-α inhibitor use,
  (2) allow concomitant aminosalicylate use,
  (3) direct the prescriber to discontinue Tysabri in patients that have not experienced therapeutic benefit by 12 weeks of induction therapy,
  (4) direct the prescriber to commence steroid tapering as soon as a therapeutic benefit has occurred,
  (5) direct the prescriber to discontinue Tysabri in patients that are unable to discontinue systemic corticosteroids within six months of starting Tysabri, and
  (6) direct the presciber to continue discontinuing Tysabri in patients who require additional steroid use that exceeds 3 months in a calendar year(other than the initial 6-month taper).
- In the **WARNINGS AND PRECAUTIONS** section, the following were added:
  (1) A statement regarding baseline brain MRI evaluation for CD patients was added. The statement for CD patients differs from the existing corresponding statement for MS patients. The statement for CD patients explains to the prescriber that although a baseline brain MRI may be helpful to distinguish pre-existent lesions from newly developed lesions, it would be uncommon for a brain lesion at baseline to cause diagnostic difficulty; in contrast, the existing statement for MS patients states that an MRI should be

obtained prior to initiating Tysabri therapy because it may be helpful in differentiating subsequent MS symptoms from PML.

(2) A section on hepatotoxicity was added. Results of postmarketing reports that indicate that Tysabri can cause clinically significant liver injury were described with regard to the signs of liver injury (including markedly elevated hepatic enzymes and elevated total bilirubin), time of occurrence (as early as six days after the first dose and for the first time after multiple doses), and liver injury recurrence upon rechallenge. In addition, recommendation to discontinue in patients with jaundice or laboratory evidence of significant liver injury was provided.

- In the **ADVERSE REACTIONS** section, adverse events that were reported more commonly in Tysabri-treated patients than placebo-treated patients were reported for the induction studies and for the maintenance study. Adverse events in the induction studies (CD301 and CD307) were reported separately from those in the maintenance study (CD303). Incidences of infections, serious infections, and infusion-related reactions, for the induction studies (CD301 and CD307), and for the maintenance study (CD303) were added.
- The currently approved **DRUG INTERACTIONS** section contained only a cross-reference to the Boxed Warning and the Warnings and Precautions sections; an additional paragraph was added that addresses use of concomitant therapies in both the CD and MS populations. That paragraph contains statements that:
  (1) recommend against concomitant immunosuppressant or TNF-α inhibitor use in CD patients,
  (2) direct the prescriber to taper corticosteroids in those CD patients that start Tysabri therapy while on chronic corticosteroids, and
  (3) explain to prescribers that (b) (4) .
- In the **CLINICAL PHARMACOLOGY** section, values of maximum serum concentration, average steady-state trough concentration, time to reach steady state, volume of distribution, clearance, and half-life following repeat intravenous administration of a 300 mg dose of Tysabri in patients with CD, were added. In addition, the positive results of a population PK analysis (effects of body weight, age, gender, race, selected hematology and serum chemistry measures, and co-administered medications [infliximab, immunosuppressants, or steroids]) were stated, in particular, the increase in natalizumab clearance associated with the presence of anti-natalizumab antibodies.
- In the **CLINICAL STUDIES** section, the following were added:
  (1) Description of the study design of each of the induction studies, and of the maintenance study, including a description of permitted concomitant medications (i.e., steroids and immunosuppressants), and percentages of subjects receiving those concomitant medications.
  (2) Induction of clinical response and clinical remission rates in Studies CD301 and CD307.
  (3) Maintenance of clinical response and clinical remission rates in Study CD303.
  (4) Induction and maintenance rates in subgroups defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF-α), and in the subgroup of patients that that were taking neither concomitant immunosuppressants nor concomitant corticosteroids.

(5) Of patients that were taking steroids at baseline, responded to Tysabri in Study CD301, and initiated a steroid taper in Study CD303, the proportion that were able to be tapered off of steroids within 10 weeks was reported.

The reader is referred to the updated, approved label.

9.5 Comments to Applicant

There are no additional comments to convey to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

The review of individual study reports has been integrated into the Integrated Review of Efficacy (see Section 6) and the Integrated Review of Safety (see Section 7). Pertinent information from individual study reports that is not integrated into the Integrated Review of Efficacy and the Integrated Review of Safety is summarized in the appendices in the sub-sections below. See Section 4.2 for features of each of the individual studies.

10.1.1 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 None = 0 Mild = 1 Moderate = 2 Severe = 3	× 5
General well-being for each of previous 7 days Well = 0 Below par = 1 Poor = 2 Very poor = 3 Terrible = 4	× 7

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

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

10.1.2 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 102. 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 103. 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 104. 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 Continued Treatment	46 (25)	111 (61)	219 (30)	423 (58)	265 (29)	534 (59)
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 105. 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	23 (13)	44 (24)	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 106. 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.)

10.1.3 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.

10.1.4 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 107. 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		
Localized 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.

10.1.5 Appendix 5: SAEs in CD Placebo-Controlled Studies

Table 108. 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)]

10.2 Line-by-Line Labeling Review

Discussions between the applicant and CDER have resolved all major issues with regard to the label. See Section 9.4 for a synopsis of significant changes made to the natalizumab label.

10.3 References

1. Kleinschmidt-DeMasters BK, Tyler KL. Brief Report: Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis. *New Engl J Med* 2005; 353:369-374, July 28, 2005.

2. Langer-Gould A, Atlas SW, Green AJ, et al. Brief Report: Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab. *NewEngl J Med* 2005; 353:375-381, July 28, 2005.

3. Van Assche G, Van Ranst M, Sciot R, et al. Brief Report: Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease. *New Engl J Med* 2005; 353:362-368, July 28, 2005.

4. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. *New Engl J Med* 2006; 354:924-933, March 2, 2006.

5. García-Enguídanos A, Calle ME, Valero J, et al. Risk Factors in miscarriage: a review. Eur J Obstet Gynecol Reprod Biol 2002; 102:111-19.

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 21, 2007

TO: Marlene Swider, Regulatory Project Manager
Anil Rajpal, M.D., Clinical Reviewer
Division of Gastroenterology Products, HFD-180

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

BLA: 125104/33

APPLICANT: Biogen Idec, Inc.

DRUG: Tysabri® (natalizumab) Infusion

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of moderately to severely active Crohn's disease (CD) and maintenance of clinical response and remission in CD.

CONSULTATION REQUEST DATE: September 27, 2007

DIVISION ACTION GOAL DATE: December 27, 2007

PDUFA DATE: January 14, 2008

I. BACKGROUND:

Tysabri® is approved for use 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 sponsor has submitted a Biologic License Application (BLA) for the use of Tysabri® for the treatment of moderately to severely active CD and to maintain clinical response and remission in CD. The following protocols were inspected:

- ELN100226-CD307 entitled "A Phase III, Multicenter, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Intravenous Natalizumab in Subjects with Moderately to Severely Active Crohn's Disease with Elevated C-reactive Protein"
- AN100226-CD301 entitled "A Phase III, International, Multicenter, Double-Blind, Placebo-Controlled Study of the Safety, Efficacy, and Tolerability of Intravenous Antegren™ (natalizumab) in Subjects with Moderately to Severely Active Crohn's Disease"
- AN100226-CD303 entitled "A Phase III, International, Multicenter, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Intravenous Antegren™ (natalizumab) (300 mg Monthly) in Maintaining Clinical Response and Remission in Subjects With Crohn's Disease"

Drs. Douglas Wolf (protocol ELN100226-CD307), Jeffrey Breiter (protocols AN100226-CD301 & AN100226-CD303), Robert Enns (protocols AN100226-CD301 & AN100226-CD303), and Jens Frederik Dahlerup (protocols AN100226-CD301 & AN100226-CD303) were inspected because these sites have a high treatment response rate. The goals of the inspection were to assess adherence to FDA regulatory requirements: specifically, investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare.

Summary Report of Domestic and Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI and site #	City/State	Country	Protocol	Inspection Date	Final Classification
Dr. Douglas Wolf. Site 558	Atlanta, GA	U.S.	ELN100226-CD307	October 22-25, 2007	VAI
Dr. Jeffrey Breiter Site 509	Manchester, CT	U.S.	AN100226-CD301 & AN100226-CD303	October 9-17, 2007	OAI
Dr. Robert Enns Site 521	Vancouver	Canada	AN100226-CD301 & AN100226-CD303	December 3-7, 2007	Pending
Dr. Jens Frederik Dahlerup Site 037	Aarhus	Denmark	AN100226-CD301 & AN100226-CD303	December 17-19, 2007	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations. See specific comments below for data acceptability
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. See specific comments below for data acceptability

Protocol # ELN100226-CD307

1. Douglas C. Wolf, MD [Site 558]
   Atlanta Gastroenterology Associates, LLC
   567 1 Peachtree-Dunwoody Rd., Ste. 600
   Atlanta, GA 30342

a. What was inspected: Dr. Wolf enrolled 10 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: None.

c. General observations/commentary: The protocol specified that at screening the CDAI will be estimated from a physician's assessment of the subject's symptoms, since diary card data will not be available to

calculate the CDAI. Dr. Wolf did not complete the estimated CDAI scores at the screening visit for at least nine subjects (CD558702, CD558703, CD558704, CD558708, CD558710, CD558712, CD558713, CD558714, and CD558715).

d. Data acceptability/reliability: Data appear acceptable.

Protocol AN100226-CD301

1. Jeffrey R. Breiter, MD [Site 509]
   Center for Medical Research, LLC
   945 Main Street, Suites 202-203
   Manchester, CT 06040

a. What was inspected: Dr. Breiter enrolled nine subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: none.

c. General observations/commentary: The inspection found the following:

- Dr. Breiter did not adhere to the protocol. The protocol specified that to be eligible for the study, any concomitant oral steroid must have been administered for a minimum of four weeks prior to week 0. For subject 002, week 0 occurred on 9/4/2002. This subject was started on Entocort on 8/19/2002, which is less than four weeks prior to the week 0 visit. Therefore, this subject was not eligible to participate in the study.
- Dr. Breiter did not maintain adequate and accurate records. Specifically, Dr. Breiter did not maintain source documents for CDAI assessments performed at one or more visits for the following subjects: 001 (weeks 0, 2, 4, 6, 8, 10 and 12), 002 (weeks 0, 2, 4, 6, and 10), 003 (weeks 2, 4, 6, and 8), 004 (weeks 2, 4, 6, 8, and 12), 006 (week 0), 007 (week 12), 008 (week 12), 009 (week 0), and 010 (week 0). In addition, prednisone doses taken during the same time period by subjects 001 are reported differently in study records for protocols AN100226-CD301 and AN100226-CD303. Specifically, on the Concomitant Medication sheet for protocol AN100226-CD301, the prednisone doses are reported as 15mg for August 23 to 29, 2002 and 10mg for August 30 to September 9, 2002. However, on the Concomitant Medication sheet for protocol AN100226-CD303, the prednisone doses for this subject are reported as 17.5mg for August 23 to 28, 2002, 15mg for August 29 to September 3, 2002, and 12.5mg for September 4 to 9, 2002.
- Dr. Breiter did not obtain adequate informed consent. Subject 006 was enrolled on October 28, 2002, and received the first infusion of study drug on November 5, 2002. However, the subject was consented to participate in study with the IRB approved informed consent document for protocol AN100226-CD303 rather than the IRB approved informed consent document for protocol AN100226-CD301. The subject did not sign the IRB approved informed consent document for protocol AN100226-CD301 until November 19, 2002.

d. Data acceptability/reliability: Due to the lack of source documents for primary endpoint data DSI recommends that the efficacy data from this site be excluded in data analysis.

2. Dr. Robert Enns [Site 521]
   IGI Clinic St. Paul's Hospital
   1081 Burrard Street
   Vancouver, BC V4Z 1Y4
   Canada

a. What was inspected: Dr. Enns enrolled 35 subjects. The inspection encompassed an audit of 12 subjects' records. Primary endpoint efficacy data were verified for 12 subjects.

b. Limitations of inspection: None.

c. General observations/commentary:

- Dr. Enns did not adhere to the protocol. Protocol section 6.1 (Study Drug Vials) requires the investigator or designee to record the subject number on each 2-panel vial label and affix the tear-off section of the labels to the Study Drug Log for each subject. For at least 10 infusions, the subject number or the subject's initials was not recorded on the tear-off portions of the study drug vial labels.
- Dr. Enns did not maintain adequate and accurate records. Instances were noted where source documents fail to identify infusion stop times, however corresponding CRF pages include infusion stop times. In many instances the 24-hour post infusion telephone calls were not documented in the source records. The records do not identify to whom study drug preparations were dispensed, and do not identify the date and time of dispensing. The records do not contain the identity of the person performing the CDAI calculations or eligibility assessments. The records do not document the actual date or time for collection of blood and serum samples, instead the records contain the time the subjects left the clinic with instructions to go to the laboratory for blood sample collection. In addition, the study records do not document the date, time, or the conditions under which the blood samples were shipped to an off-site laboratory for analysis.

d. Data acceptability/reliability: Other than the deficiencies mentioned above the data appear acceptable.

Note: Observations noted above are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. Dr. Jens Frederik Dahlerup [Site 037]
   Aarhus Kommunehospital
   Medicinsk afd. V
   Noerrebrogade 44
   DK-8000 Aarhus C
   Denmark

a. What was inspected: Dr. Dahlerup enrolled 14 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: Some source documents and case report forms were in the foreign language.

c. General observations/commentary: No significant regulatory violations were found.

d. Data acceptability/reliability: Data appear acceptable.

Note: Information noted above are based on communications with the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol AN100226-CD303

1. Jeffrey R. Breiter, MD [Site 509]
   Center for Medical Research, LLC
   945 Main Street, Suites 202-203
   Manchester, CT 06040

a. What was inspected: Dr. Breiter enrolled nine subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: none.

c. General observations/commentary: The inspection found the following:

- Dr. Breiter did not adhere to the protocol. The protocol specified that subjects who have responded to treatment at weeks 10 and 12 of Study CD-301 (defined as ≥ 70 point decrease from baseline CDAI score) and have mildly active disease (CDAI score of < 220 and ≥ 150), or disease in remission (CDAI score of < 150), and no use of rescue intervention are eligible for enrollment. For subject 008, rescue intervention was used while the subject was enrolled in protocol AN100226-CD301 (increase of Prednisone dose from 10mg to 20mg on 12/21/2002, prior to the week 10 visit). As such, this subject was not eligible to participate in protocol AN100226-CD303.
- Dr. Breiter did not maintain adequate and accurate records. Specifically, Dr. Breiter did not maintain source documents for the physician assessments and the response to questions "Did the subject take Lomotil or another anti-diarrheal?" and "Was an abdominal mass noted on examination?" for subjects 002 (month 5) and 004 (month 4). In addition, prednisone doses taken during the same time period by subjects 001 are reported differently in study records for protocols AN100226-CD301 and AN100226-CD303. Specifically, on the Concomitant Medication sheet for protocol AN100226-CD301, the prednisone doses are reported as 15mg for August 23 to 29, 2002 and 10mg for August 30 to September 9, 2002. However, on the Concomitant Medication sheet for protocol AN100226-CD303, the prednisone doses for this subject are reported as 17.5mg for August 23 to 28, 2002, 15mg for August 29 to September 3, 2002, and 12.5mg for September 4 to 9, 2002.

d. Data acceptability/reliability: Other than the deficiencies mentioned above the data appear acceptable.

2. Dr. Robert Enns [Site 521]
IGI Clinic St. Paul's Hospital
1081 Burrard Street
Vancouver, BC V4Z 1Y4
Canada

a. What was inspected: Dr. Enns enrolled 12 subjects. The inspection encompassed an audit of 4 subjects' records. Primary endpoint efficacy data were verified for 4 subjects.

b. Limitations of inspection: None.

c. General observations/commentary:

- Dr. Enns did not adhere to the protocol. Protocol section 6.1 (Intravenous Infusion Bags) requires the investigator or designee to complete and detach the tear-off infusion bag label and affix it to the corresponding CRF page. For at least 6 infusions, CRF pages retained at the study site did not include the tear-off portions of the intravenous bag labels. Examples include subject 521019 month 10 infusion; subject 521012 month 3 and month 4 infusions; subject 521026 month 13 and month 14 infusions; and subject 521026 month 3 infusion.
- Dr. Enns did not maintain adequate and accurate records. Instances were noted where source documents did not identify infusion stop times; however, corresponding CRF pages included the stop times. In many instances the 24-hour post infusion telephone calls were not documented in the source records. The records do not identify to whom study drug preparations were dispensed, and do not identify the date and time of dispensing. The records do not contain the identity of the person performing the CDAI calculations or eligibility assessments. The records do not document the actual date or time for collection of blood and serum samples, instead the records contain the time the subjects left the clinic with instructions to go to the laboratory for blood sample collection. In addition, the study records do not document the date, time, or the conditions under which the blood samples were shipped to an off-site laboratory for analysis.

d. Data acceptability/reliability: Other than the observations mentioned above the data appear acceptable.

Note: Observations noted above are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. Dr. Jens Frederik Dahlerup [Site 037]
Aarhus Kommunehospital
Medicinsk afd. V
Noerrebrogade 44
DK-8000 Aarhus C
Denmark

a. What was inspected: Dr. Dahlerup enrolled 8 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: Some source documents and case report forms were in the foreign language.

c. General observations/commentary: There were no significant regulatory violations.

d. Data acceptability/reliability: Data appear acceptable.

Note: Information noted above are based on communications with the FDA Investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As mentioned above, inspection of Dr. Jens Frederik Dahlerup (protocols AN100226-CD301 & AN100226-CD303) found no significant regulatory violation. The inspection of Dr. Douglas Wolf found protocol violations. The inspection of Dr. Robert Enns (protocols AN100226-CD301 & AN100226-CD303) found protocol violations and record keeping deficiencies. The data from these sites appear acceptable in support of the respective indication.

The inspection of Dr. Jeffrey Breiter found inadequate informed consent (protocol AN100226-CD301), protocol violations, and inadequate and inaccurate records (protocols AN100226-CD301 & AN100226-CD303). As mentioned above, regarding protocol AN100226-CD301, due to the lack of source documents for primary endpoint data DSI recommends that the efficacy data from this site be excluded in data analysis. .

As previously mentioned, observations noted above for Dr. Robert Enns and Dr. Jens Frederik Dahlerup are based on the Form FDA 483, Inspectional Observations and communications from the FDA Investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Sherbet Samuels

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

Constance Lewin MD MPH

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

BLA:	125104
SERIAL:	33
DATE:	14-Sept-07 (updated on 3-Oct-07)
FROM:	Barbara Rellahan Ph.D. DMA/OBP, CDER Brellahan 1/10/08
THROUGH:	Patrick Swann Ph.D., Deputy Director DMA/OBP/CDER 1-11-08
PRODUCT:	Tysabri, humanized IgG4
INDICATION:	Treatment of Crohn's Disease
SPONSOR:	

RPM: Marlene Swider

Executive summary/recommendations: Much of the information contained in the mechanism of action section for Tysabri in CD could not be corroborated with clinical data or by information contained within the published scientific literature. Alternative wording is therefore proposed. It is recommended that the sponsor be given an opportunity to comment on the wording and provide additional support for their original wording if they so choose.

On 28-Sept-07 Biogenidec emailed two journal articles to the agency that were to address the expression of VCAM-1 in CD. A summary of the pertinent information is included below in the appropriate section and is indicated as having been submitted by Biogenidec. Two articles were submitted that address VCAM-1 expression in CD. One indicates no increase in expression in CD, the other shows data that may suggest an increase in CD but does not specifically state VCAM-1 expression is increased in CD patients. As a whole the published literature contains contradictory information on VCAM-1 expression in CD, with the majority of the data indicating no alteration in its expression pattern in CD. I therefore recommend adhering to the initial wording we suggested for this section of the label.

Review summary:

This review concerns the language used in the Clinical Pharmacology section (specifically section 12.1, Mechanism of Action) of the proposed Tysabri label. The sponsor added a new section on the proposed mechanism of action of Tysabri in Crohn's disease (CD). The proposed wording is as follows:

" (b) (4)

[redacted]

"

Created on 2/2/07 BLR

The actual clinical pharmacology studies that are reported in the BLA monitored aspects of Tysabri activity such as receptor saturation and peripheral, circulating leukocyte numbers. The expression of MadCAM-1 and VCAM-1 in the colon were not measured, nor were the number of infiltrating leukocytes. Therefore, as was primarily the case for presumption of the mechanism of action in MS, the basis for the proposed mechanism is derived primarily on in vitro studies and studies/information reported in the literature. Brief summaries of pertinent scientific articles are included at the end of this review. A discussion of what I found in the literature in relation to the proposed label wording is as follows: One major issue is that there is little information available on the expression of VCAM-1 in CD. There are a number of reports that look at VCAM-1 in IBD but the results concerning its role in IBD are contradictory. I found one article that suggests an increase in expression is seen in a specific subset of CD patients (Lesniowski-CD) but the article was published in a Polish journal which I have not been able to access. An increase in the expression of MadCam-1 has been reported in CD patients, and there are both mouse and non-human primate models that support a role for MadCam-1 in CD. There is also data from mouse models to support a role for VCAM-1 in leukocyte recruitment in IBD but without solid information on its expression in CD patients I am hesitant to allow statements indicating it definitively plays a role in CD. In addition, I found little to support a role for either osteoponin or fibronectin in CD so references to these proteins were removed. Based on this literature search, the following alternative wording is proposed. The underlined sections are based on the original proposed wording. The italic section is completely original but is based on wording used for the MS indication.

"In Crohn's disease, the interaction of the α4ß7 integrin receptor with the endothelial receptor MadCam-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease. MadCam-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to gut lymph tissue found in Peyer's patches. MadCam-1 expression has been found to be increased at active sites of inflammation in patients with CD which suggests it may play a role in the recruitment of leukocytes to the mucosa and contribute to the inflammatory response characteristic of CD. *The clinical effect of natalizumab in CD may therefore be secondary to blockade of the molecular interaction of the α4ß7-integrin receptor with MadCam-1 expressed on the venular endothelium at inflammatory foci. VCAM-1 expression has been found to be upregulated on colonic endothelial cells in a mouse model of IBD and appears to play a role in leukocyte recruitment to sites of inflammation. The role of VCAM-1 in CD however, is not clear.* "

Summary of literature search

1. Expression/Role of VCAM-1:
   - ✓ Found to be constitutively expressed in lymphoid aggregates in normal colonic mucosa and was not significantly enhanced or altered in mucosa of patients with IBD (Koizumi et al (1992) Gastro 103:840-abstract only).
   - ✓ Authors found an increase in the level of soluble VCAM-1 in the circulation of of UC and CD patients but no upregulation of the expression of VCAM-1 in sections taken from inflamed areas of small or large bowel in patients with CD and UC compared to controls. There was constitutive expression of VCAM-1 in tissue sections but the expression was not significantly different from the control samples. ICAM-1 and E selectin expression was upregulated. (Jones et al 1995. Gut 361:724, article submitted by Biogenidec on 28-Sept-07.)
   - ✓ This article reported on the affect of infliximab treatment on CD40/CD40L expression in CD but included some data on VCAM-1 expression. The text indicates the infliximab treatment reduced the expression of VCAM-1 in CD. Figure 1 in the article shows VCAM-1 expression in one patient sample and a control sample. In the patient sample VCAM-1 expression appears increased relative to the control. The figure legend indicates the samples are representative of 7 CD patients and 5 controls. The article text does not, however, state that VCAM-1 expression is upregulated in CD. (Danese et al. 2006. JI 176:2617, article submitted by Biogenidec on 28-Sept-07.)
   - ✓ In Lesniowski-CD, higher expression values were characteristic of VCAM-1 (Zurawski J et al. 2007, Pol J Path 68:13-abstract only).
   - ✓ In UC, E-selectin expression, but not VCAM-1, ICAM-1 or ICAM-3, correlated with disease severity (Cellier et al. (1997 Eur. J Gast Hepat 9:1197-abstract only)
   - ✓ In DSS mouse model of CD there was an increased expression of VCAM-1 and MadCAM-1. TRR2 pre-treatment reduced VCAM-1 expression and reduced the number of adherent cells in vivo. (Soriano-Izquierdo et al 2001, J Leuk Biol. 75:214.)
   - ✓ In a SMAP-1/Yit adoptive transfer model of CD in mice an anti-VCAM-1 antibody in combination with an anti-ICAM-1 antibody showed a 70% resolution of the active inflammation, but not chronic inflammation. (Burns RC et al. 2001. Gastro. 121:1428 abstract only).
   - ✓ Anti-VCAM-1 mAb, but not an anti-MAdCAM-1 or ICAM-1 mAb, resulted in significant attenuation of colitis in terms of disease activity index, colon length and ratio of colon weight to colon length. The VCAM-1 mAb decreased leukocyte recruitment and blockade did have a high therapeutic effect-higher than the MAdCAM mAb. (Soriano et al. (2000) Lab Invest. 80:1541).
   - ✓ VCAM-1 mAb did not significantly inhibit DSS-induced T and B lymphocyte adherence to colonic microvessels (MadCAM did) (Teramoto et al. (2005) Clin Exp Immunol. 139:421).
   - ✓ In the cotton-top Tamarin model of chronic colitis, an anti-α4 integrin mAb that bound VLA-4 (receptor for VCAM-1) was shown to reduce colitis activity (Podolsky et al. (1993) J. Clini. Invest. 92:372).

2. Expression/Role of MadCAM-1 in CD:
   - ✓ Expression of human MAdCAM-1 shown to be largely tissue restricted to both large and small intestine and associated lymphoid tissue. Constitutively expressed on endothelium

of venules of intestinal lamina propria. Expression was found to be increased (compared to normal tissue) on the venular endothelium within the lamina propria at inflammatory foci associated with UC and Crohn's disease. (Briskin et al. (1997) American J. of Path. 151:97).

- ✓ In the DSS mouse model the accumulation lymphocytes in the mucosa and submucosa was significantly inhibited by an anti-MadCAM-1 mAb but not by an anti-VCAM-1 mAb. They also report that MadCAM-1 expression is increased in the mucosal and submucosal micovessels in DSS treated mice. (Teramoto et al. (2005) Clin Exp Immunol. 139:421).
- ✓ An Anti-MAdCAM-1 mAb significantly reduced colonic injury as well as the infiltration of β7+lymphocytes in the colonic mucosa (Same group earlier paper-Kato et al (2000) J. Pharmacol exp. 295:183).
- ✓ In the cotton-top Tamarin model of chronic colitis, a mAb against the α4β7 receptor, which binds MadCam-1, reduced colitis activity and reduced the number of inflammatory cells that migrated into the colon (α4β7+ lymphocytes and α4β7- neutrophils and macrophages) (Hesterberg et al. (1996) Gastroenterology 111:1373).

3. Osteoponin in CD:
   - ✓ Osteopontin expression shown to be upregulated in the plasma and in intestinal mucosa from UC and CD patients compared to normal controls (Sato et al (2005) Gut 54:1254).
   - ✓ Osteopontin is a chemokine and can act as a co-stimulatory factor for Th1 responses while inhibiting Th2 responses (o'Regan et al. (2000) Immunol Today 21:475).
   - ✓ One report that OPN deficiency protects mice from Dextran sodium-sulfate induced colitis (Zhong et al. (2006) Inflamm Bowel Disease 12:790).
   - ✓ One report that OPN deficiency exacerbates tissue destruction in DSS mouse model (Da Silva et al. (2006) J. of Cell Physiology 208:629). Found increased spleen enlargement, bowel shortening, and mucosal destruction in the OPN-null mice. Authors speculate that the increased destruction is due to higher neutrophil infiltrate and apoptosis and lower macrophage infiltrate with decreased clearance of dead/dying neutrophils--get increased necrosis. Infiltration of lymphocytes, macrophages is decreased.

4. Little information on the role of fibronectin in Crohn's disease.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125104/33

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Tysabri (natalizumab) BLA STN 125104/33
Filing Meeting
Wednesday, January 31, 2007
3:00 – 4:00 P.M.
Room 5201

AGENDA

Introduction		Marlène Swider
Due Dates:	PDUFA Deadline October 15, 2007 Final Reviews Due on September 7, 2007 Consult Reviews Due on August 30, 2007 Filing Meeting (Today)	
Filing Review Memo Parts and Issues		Everyone
Any other Consult needed, e.g. DDMAC, DMETS?		
Advisory Committee needed?		Brian Harvey/John Hyde
Review Period (10 months)		Brian Harvey
Site Selections – Have they been identified already? Is any site outside of U.S.?		Reviewers
Background information		Marlène Swider
Clinical Outline		Anil Rajpal
Other requests or issues		Everyone
Adjourn		

List of attendees for Tysabri Filing Meeting
Tuesday, January 31, 2007

NAME	SIGNATURE
Anil Rajpal	
Christoffer TORNOE	
ABI ADEBUNALE	
Joyce Korenblat	
Lisa Kammerman	
Ann Mackey	
John Hyde	
Brian Thackery	
Brian Strongin	

FILING MEETING: TYSABRI FOR CD

Background

Regulatory History

11/23/04	Original Approval for MS
2/28/05	Withdrawal from market b/c 3 cases of PML: 2 cases in MS pts, 1 case in a CD pt
3/7/06-3/8/06	Advisory Committee: monotherapy, mandatory patient registry, monitoring for PML
6/5/06	Re-approval of Tysabri for MS: monotherapy and RiskMAP

Key Studies in CD

Induction – 2 Phase 3 studies (moderate to severe active CD)

- CD301 (n=904, 4:1): Response 56% vs. 49% (p=0.051)
  Post-hoc analysis in ↑CRP subset (n=660): 58% vs. 45% (p=0.007)
- CD307 (n=510, 1:1, ↑CRP): Response 48% vs. 32% (p<0.001)

Maintenance – 1 Phase 3 study

- CD303 (n=338, 1:1): Response at 6 months: 61% vs. 28% (p<0.001);
  Response at 12 months: 54% vs. 20% (p<0.001)

Safety Database

- 1182 CD pts treated in placebo-controlled studies (72% received 3 infusions)
- 1563 CD pts enrolled in short- & long-term dosing
  - 33% exposed for ≥ 52 wks, 18% exposed for ≥ 104 wks
  - 1343 received ≥ 1 infusion with fixed dose (300 mg)
- 2,799 patients treated in combined MS & CD placebo-controlled studies
- ~7,000 MS pts treated while on market (11/04-2/05; majority received only 1 or 2 doses)

Risk Minimization Action Plan (RiskMAP)

- TOUCH (TYSABRI Outreach: Unified Commitment to Health) program developed for MS pts
  - Training and mandatory enrollment for prescribers, infusion centers, and pharmacies; mandatory enrollment of patients
  - MRI prior to therapy initiation
  - Evaluations at 3 and 6 months and every 6 months after (regular status reports to Sponsor)
- (b) (4)
  - [redacted]
  - [redacted]
  - [redacted]

Risk of PML and Prior or Concomitant Immunosuppressive Therapy

- Based on the 3 cases of PML, there is a concern that the risk of PML may be higher in patients that have received prior or concomitant immunosuppressive therapies than in those that are receiving monotherapy.
- CD versus MS patients:
  - CD patients are more likely than MS patients to have been treated chronically with immunosuppressive therapies.
  - 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.

Recommendations

Filing: Recommend filing.

Clinical Site Inspection

Recommend inspection of the following sites:

(1) Study CD307 – Site No. 558 (n=10); United States
(2) Study CD303 – Site No. 509 (n=9); United States
(3) Study CD301 – Site No. 521 (n=35); Canada
(4) Study CD301 – Site No. 037 (n=14); Denmark

Rationale: Compared to the overall mean response rates by treatment group for that study, each of these sites had a higher response rate attributed to the natalizumab group and a lower response rate attributed to the placebo group. (See Appendix 1.)

Advisory Committee: Recommend an Advisory Committee. The AC may provide us with recommendations regarding the safety and risk-benefit assessment of the product in the CD population, particularly with regard to risk of PML with prior or concomitant immunosuppressive therapy.

Other: Based upon press reports in the fall of 2006, the EMEA has asked the sponsor to conduct an additional clinical trial. Information about this clinical trial (study design, endpoints, number of patients, duration, etc.) was not submitted, and should be requested in the 74 day letter.

Appendix 1

Study No.	Country	Site No.	PI/Hospital Name	% of Study Popln	Response Rate Tysabri	Response Rate Placebo
CD307	United States	558	Douglas C. Wolf, MD Atlanta Gastroenterology Associates, LLC 5671 Peachtree-Dunwoody Rd., Ste. 600 Atlanta, GA 30342	2.0%	80% (4/5)	20% (1/5)
CD303	United States	509	Jeffrey R. Breiter, MD Center for Medical Research, LLC 945 Main Street Suites 202-203 Manchester, CT 06040	2.7%	80% (4/5)	0% (0/4)
CD301	Canada	521	Robert Enns, MD IGI Clinic St. Paul's Hospital 1081 Burrard Street Vancouver, BC V4Z 1Y4	3.9%	60% (18/30)	20% (1/5)
CD301	Denmark	037	Dr. Jens Frederik Dahlerup Aarhus Kommunehospital Medicinsk afd. V Noerrebrogade 44 DK-8000 Aarhus C	1.6%	70% (7/10)	25% (1/4)

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125104/33 Product: Tysabri Applicant: BiogenIdec

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 1/31/2007 Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ____ Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____ _____ _____ _____
- ☐ Memo of Filing Meeting

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y (N)	
Introduction to the summary documents (1 page) [2.2]	Y (N)	
Quality overall summary [2.3]	Y (N)	
❑ Drug Substance	Y N	There are no changes to the manufacturing process or changes to the product quality in this supplement.
❑ Drug Product	Y N	
❑ Facilities and Equipment	Y N	
❑ Adventitious Agents Safety Evaluation	Y N	
❑ Novel Excipients	Y N	
❑ Executed Batch Records	Y N	
❑ Method Validation Package	Y N	
❑ Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y (N)	See Above
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y N	
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	Y N	
❑ process validation (prospective plan, results, analysis, and	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance	Y N	
❑ control of drug substance o specification o justification of specs. o analytical procedures o analytical method validation o batch analyses o consistency (3 consecutive lots) o justification of specs.	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N	
Drug Product [3.2.P]		
❑ description and composition	Y N	
❑ pharmaceutical development	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin) ❑ control of drug product (justification of specifications; analytical method validation) ❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N Y N Y N	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: o 3 <u>consecutive</u> lots o other needed validation data ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards	Y N Y N Y N Y N Y N Y N Y N Y N Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	Y N Y N Y N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): (File) RTF

Reviewer: [signature] 1/23/07 Type (circle one): (Product) (Chair) Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: [signature] 1/23/07 Division. Director: Kathleen Clouse 1/23/07
(signature/ date) (signature/ date)

STN 125104 Product Tysabri

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
☐ Biopharmaceutics and associated analytical methods	Y	N	
☐ Clinical pharmacology [includes immunogenicity]	Y	N	
☑ Clinical Efficacy [for each indication]	Y	N	
☑ Clinical Safety	Y	N	
☑ Synopses of individual studies	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	Y	N	
Study Reports and related information [5.3]	Y	N	
☐ Biopharmaceutic	Y	N	
☐ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	
☐ Pharmacokinetics (PK)	Y	N	
☐ Pharmacodynamic (PD)	Y	N	
☑ Efficacy and Safety	Y	N	
☐ Postmarketing experience	Y	N	
☑ Case report forms	Y	N	
☑ Individual patient listings (indexed by study)	Y	N	
○ electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y	N	
☐ legible	Y	N	
☐ English (or certified translation into English)	Y	N	
☐ compatible file formats	Y	N	
☐ navigable hyper-links	Y	N	
☐ interpretable data tabulations (line listings) & graphical displays	Y	N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	Y N/A N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N N/A	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N N/A	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N/A N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
202	(Y) N	Y N/A N NR	(Y) N	Y N NR
301	(Y) N	Y N NR	(Y) N	Y N NR
303	(Y) N	Y N NR	(Y) N	Y N NR
307	(Y) N	Y N NR	(Y) N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125104/33 Product: Tysabri (natalizumab) Applicant: Biogen Idec, Inc.

Final Review Designation (circle one): (Standard) Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date 1/31/07 Committee Recommendation (circle one): (File) RTF

RPM: [signature] 2/13/07
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ✓ Part A – RPM
  - ✓ Part B – Product/CMC/Facility Reviewer(s): Elena Gabina
  - N/A Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____
  - ✓ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Anil Rajpal, Lisa Kammerman
- ☐ Memo of Filing Meeting

STN 125104/33 Product Tysabri

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	(Y) N	
☐ including list of all establishment sites and their registration numbers	Y N	
☐ If foreign applicant, US Agent signature.	Y N	N/A
Comprehensive Table of Contents	Y (N)	N/A
Debarment Certification with correct wording (see * below)	(Y) N	
User Fee Cover Sheet	(Y) N	
User Fee payment received	(Y) N	Rcvd on 12/12/06 No. 3006937
Financial certification &/or disclosure information	(Y) N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	
Pediatric rule: study, (waiver), or (deferral)	(Y) N	Waiver for children under 6yrs old Deferral for adolescents (11-17yrold)
Labeling:	(Y) N	
☑ PI –non-annotated	(Y) N	
☑ PI –annotated	(Y) N	
☑ PI (electronic)	(Y) N	
☑ Medication Guide	(Y) N	
☐ Patient Insert	Y (N)	no changes to previously approved
☐ package and container	Y (N)	
☐ diluent	Y (N)	
☐ other components	Y (N)	
☑ established name (e.g. USAN)	(Y) N	along with proprietary name (established)
☐ proprietary name (for review)	Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y) N	
☑ legible	(Y) N	
☑ English (or translated into English)	(Y) N	
☑ compatible file formats	(Y) N	
☑ navigable hyper-links	(Y) N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
☑ summary reports reference the location of individual data and records	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ protocols for clinical trials present	Y N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	N/A
if CMC supplement:		
☐ description and results of studies performed to evaluate the change	Y N	
☐ relevant validation protocols	Y N	
☐ list of relevant SOPs	Y N	
if clinical supplement:		
☑ changes in labeling clearly highlighted	(Y) N	
☑ data to support all label changes	(Y) N	
☐ all required electronic components, including electronic datasets (e.g. SAS)	Y N	Some
if electronic submission:		
☑ required paper documents (e.g. forms and certifications) submitted	(Y) N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo). N/A

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? Yes Remicade received exclusivity Aug 24, 1998. So its orphan exclusivity has expired.

Does this submission relate to an outstanding PMC? No.

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:
- Dates:

(Decision of AC would be confirmed March '07. AC Meeting would be scheduled after that.

Recommendation (circle one): File RTF

RPM Signature: Yvette Jones Branch Chief concurrence: Brian Strongin

STN 125104/33 Product TYSABRI

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y (N)	Missing – PM will follow up with sponsor
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
☑ Biopharmaceutics and associated analytical methods	(Y) N	
☑ Clinical pharmacology [includes immunogenicity]	(Y) N	
☐ Clinical Efficacy [for each indication]	Y N	
☐ Clinical Safety	Y N	
☐ Synopses of individual studies	Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y (N)	Missing – PM will follow up with sponsor,
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
☐ Biopharmaceutic	Y N	
☐ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
☑ Pharmacokinetics (PK)	Y N	
☐ Pharmacodynamic (PD)	Y N	
☐ Efficacy and Safety	Y N	
☐ Postmarketing experience	Y N	
☐ Case report forms	Y N	
☐ Individual patient listings (indexed by study)	Y N	
○ electronic datasets (e.g. SAS)	Y N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y N	
☑ legible	(Y) N	
☑ English (or certified translation into English)	(Y) N	
☐ compatible file formats	Y N	
☑ navigable hyper-links	(Y) N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	Y	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y	N	
adequate characterization of product specificity or mode of action	Y	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BIMO sites identified?		
EN100220-CD901 (POP PK)	(Y)	N	(Y)	N	NR	Y	(N)	(Y)	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

STN 125104/33 Product Natalizumab

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
▫ Biopharmaceutics and associated analytical methods	(Y) N	
▫ Clinical pharmacology [includes immunogenicity]	(Y) N	
▫ Clinical Efficacy [for each indication]	(Y) N	
▫ Clinical Safety	(Y) N	
▫ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
▫ Biopharmaceutic	(Y) N	
▫ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y) N	
▫ Pharmacokinetics (PK)	(Y) N	
▫ Pharmacodynamic (PD)	(Y) N	
▫ Efficacy and Safety	(Y) N	
▫ Postmarketing experience	Y (N)	Post-marketing experience is discussed in summary of Clinical Safety (2.7.4)
▫ Case report forms	(Y) N	
▫ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
▫ legible	(Y) N	
▫ English (or certified translation into English)	(Y) N	
▫ compatible file formats	(Y) N	
▫ navigable hyper-links	(Y) N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y (N)	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y (N)	N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y) N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
CD307	(Y) N	(Y) N NR	(Y) N	(Y) N NR
C0303	(Y) N	(Y) N NR	(Y) N	(Y) N NR
C0301	(Y) N	(Y) N NR	(Y) N	(Y) N NR
C0202	(Y) N	(Y) N NR	(Y) N	Y N (NR)
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

STN 125104/33 Product Natalizumab Part D Page 4

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

N/A

Is clinical site(s) inspection (BiMo) needed?

Yes. Inspection of the folloing sites is recommended: Study CD307 Site No. 558 (US), Study CD303 Site No. 509 (US), Study CD301 Site No. 521 (Canada), and Study CD301 Site No. 037 (Denmark)

Is an Advisory Committee needed?

Yes. The AC may provide us with recommendations regarding the safety and risk-benefit assessment of the product in the CD population, particularly with regard to risk of PML with prior or concomitant immunosuppressive therapy.

Recommendation (circle one): File RTF

Reviewer: [signature] 1/31/07 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

~~Branch Chief:~~ Team Leader [signature] Division. Director: _____
(signature/ date) (signature/ date)
1-31-07

67 page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

TYSABRI® RISK MINIMIZATION ACTION PLAN: SUMMARY OF TOUCH™

The TOUCH™ (TYSABRI®Outreach: Unified Commitment to Health) Prescribing Program 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.

The TOUCH Prescribing Program is being applied to both CD and MS patients. The versions differ slightly to address patient population (see below). The two versions of the TOUCH Prescribing Program are the MS-TOUCH program for the Multiple Sclerosis, and CD-TOUCH for the Crohn's Disease.

1. Prescribing Program

1.1 General Requirements

Biogen Idec, Inc. will ensure that the following requirements are addressed by its Risk Minimization Action Plan, the TOUCH™ Prescribing Program:

- TYSABRI® will only be available under a special restricted distribution program called the TOUCH™ Prescribing Program.
- Only prescribers enrolled in the TOUCH™ Prescribing Program and who agree to comply with the TOUCH™ program will be able to prescribe TYSABRI®.
- Only infusion sites enrolled in and authorized under the TOUCH™ Prescribing Program will be able to administer TYSABRI®.
- Only pharmacies enrolled in the TOUCH™ Prescribing Program will be able to dispense TYSABRI® to affiliated authorized infusion sites.
- Only patients enrolled in the TOUCH™ Prescribing Program and who agree to comply with the TOUCH™ Prescribing Program will be able to receive TYSABRI®.
- All TOUCH™ prescribers, pharmacies, infusion sites, and patients will be educated about the TOUCH™ Prescribing Program and the risks of TYSABRI® treatment.
- Safety surveillance, including monitoring and expedited reporting of PML infections, other serious opportunistic infections, malignancies, and deaths and systematic tracking of patients and drug disposition will be conducted.

1.2 Pharmacy and Infusion Site Requirements

Biogen Idec, Inc. will limit the distribution of TYSABRI® only to authorized infusion sites and their associated central pharmacies. The agreements between Biogen Idec and the central pharmacies and infusion sites require the following:

- All pharmacies and infusion sites will be enrolled in the TOUCH™ Prescribing Program, and agree to comply with the TOUCH™ Prescribing Program.
- Infusion sites and central pharmacies will obtain TYSABRI® directly from a single contract distributor or specialty pharmacy providers.
- All appropriate pharmacy and infusion site staff will be trained by Biogen Idec and/or Elan Pharmaceuticals about the TOUCH™ Prescribing Program and about the known risks, potential benefits, and appropriate use of TYSABRI®.
- All appropriate pharmacy and infusion site 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, malignancies (in CD patients) and deaths.
- Infusion site staff are to follow the infusion guidelines outlined below:
  - [cbk1]Only infuse patients who are enrolled and authorized in the TOUCH™ Prescribing Program.
  - Prior to infusing a patient, the infusion site will verify the patient is authorized to receive TYSABRI®.
    - TOUCH On-Line Infusion Sites: Patient Authorization Status must be "Authorized"
    - Paper-based Infusion Sites: Current Notice of Patient Authorization on file, and confirm that there is not a Notice of Discontinuation on file in the patient's medical record
  - Prior to infusing a patient, the infusion site will provide the patient the Tysabri Medication Guide and give the patient time to read it.
  - Prior to infusing a patient, the infusion site will complete the MS or CD Pre-Infusion Patient Checklist, as appropriate, and confirm prescriber clearance if needed.
  - Within one day of completing the Pre-Infusion Patient Checklist, the infusion site will submit the form to Biogen Idec via TOUCH On-Line or fax, regardless of whether the patient was infused TYSABRI®.
  - The infusion site will not infuse TYSABRI® if it is determined that the patient (or their prescriber) is not in conformance with the TOUCH™ Prescribing Program.
  - For Paper-based Infusion Sites, keep a record of the current Notice of Patient Authorization, the Pre-infusion Patient Checklist, and/or Notice of Patient Discontinuation for each corresponding patient. [cbk2]
- Central pharmacies are to follow the dispensing guidelines outlined below:
  - [cbk3]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.
- Read and understand the full Prescribing Information for TYSABRI®.
- To understand that TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic infection of the brain that usually leads to death or severe disability.
- To determine that a patient has a relapsing form of MS based on clinical and radiological evidence before prescribing TYSABRI® (MS Prescribers).
- To determine that a patient has moderately to severely active Crohn's disease with evidence of inflammation (CD Prescribers).
- [cbk4]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 instruct all patients to promptly report any continuously worsening symptoms that persists over several days.
- To not prescribe TYSABRI® to any patient who is inappropriate for receiving the drug under the TOUCH™ program.
- To sign and complete the MS or CD Prescriber/Patient Enrollment form for each patient as appropriate, 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, malignancy 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 evaluate the CD patient by 12 weeks of TYSABRI® therapy to determine if the patient has experienced a therapeutic benefit.
- 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 enrolled in the TOUCH™ Prescribing 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 MS or CDPrescriber/Patient Enrollment Form, as appropriate, 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™ Prescribing Program if they switch infusion sites and/or prescribers
- Must provide information about all medicines and treatments during the past month 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™ Prescribing 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™ Prescribing Program Educational Materials and forms include:

- The Patient Medication Guide and Package Insert (for patients and prescribers)
- TOUCH™ Prescribing Program Education Slide Set
- TYSABRI® and the TOUCH™ Prescribing Program Slide Set (for prescribers and patients)
- The TOUCH™ Prescribing Program Overview (general description)
- Prescriber/Patient Enrollment Form (MS and CD specific form to be signed by patients and prescribers)
- Infusion Site Enrollment Form (for infusion site enrollment)
- Central Pharmacy Enrollment Form (for central pharmacy enrollment)
- TYSABRI® Inventory Tracking Log (central pharmacies use to document dispensing of TYSABRI® to affiliated authorized infusion sites)
- Pre-infusion Patient Checklist (MS and CD specific forms to be completed by infusion site prior to each scheduled infusion)
- Patient Status Report and Reauthorization Questionnaire (MS and CD specific forms to be filled out ever 6 months by prescribers)
- [cbk5]TYSABRI® Patient Discontinuation Questionnaire (MS and CD specific forms for prescribers to complete at discontinuation and 6 months after the patient discontinues TYSABRI®)
- 12-Week Questionnaire for Crohn's Disease (CD specific form for prescribers to complete to determine if patient has experienced a therapeutic benefit)
- The TOUCH™ Prescribing Program Enrollment Kit (MS or CD specific folder for prospective prescribers -- contains above information and describes program)
- Dear Doctor and Dear Patient Letters
- Patient Getting Started Brochure (MS and CD specific versions with information for patients about the TOUCH™ Prescribing Program and TYSABRI®)
- Healthcare Professional Infusion Guide (for infusion sites)
- Guidance for Evaluation of New Neurologic Symptoms in Patients Receiving TYSABRI® (for healthcare professionals caring for MS patients treated with Tysabri)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125104/33

OTHER REVIEW(S)

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; WO22, Mail Stop 4447 Center for Drug Evaluation and Research

TO: Brian Harvey, MD, PhD
Director, Division of Gastroenterology Products, HFD-180

THROUGH: Nora Roselle, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director 4/18/07
Carol Holquist, RPh, Director 4/17/07
Division of Medication Errors and Technical Support, HFD-420

FROM: Judy Park, PharmD, Safety Evaluator 4/16/07
Division of Medication Errors and Technical Support, HFD-420

DATE: April 4, 2007

SUBJECT: DMETS Labeling Review
Tysabri® (Natalizumab) Injection
300 mg/15 mL
BLA #: 125104/33

OSE PROJECT #: 2007-561

This memorandum is in response to a request from the Division of Gastroenterology Products for a review of the revised labeling for Tysabri submitted on December 14, 2006. The sponsor is proposing a new indication of use for the treatment of Crohn's Disease under Supplement 33 and revised the labeling to meet the new Physician Labeling Rule (PLR) format.

A. GENERAL COMMENT

1. [redacted] (b) (4) [redacted] " Revise accordingly. Please consult Rick Lostritto, Chair of the CDER Labeling and Nomenclature Committee if there are any questions regarding the proper designation of the dosage form.

2. DMETS does not recommend the use of [redacted] (b) (4) [redacted]

B. INSERT LABELING

1. Highlights of Prescribing Information

   a. See General Comments A1 and A2.

   b. Under Dosage and Administration, the third bullet should read "Observe patients during the infusion and for 1 hour after the infusion is complete" to be consistent with the directions in the Full Prescribing Information.

   c. Under Dosage and Administration, include the usage requirement (i.e. Tysabri solution must be administered within 8 hours of preparation) to be consistent with the directions in the Full Prescribing Information.

   d. Under Dosage Forms and Strength, DMETS recommends [redacted] (b) (4)

2. Full Prescribing Information: Contents

   See General Comment A2.

3. Full Prescribing Information

   a. See General Comments A1 and A2.

   b. Dosage and Administration

      i. Under "General Dosing Information," include the length of infusion in the last sentence to better clarify the dosing instructions and ensure the proper rate of administration (i.e. [redacted] (b) (4)

      ii. DMETS recommends [redacted] (b) (4)

      iii. Consider [redacted] (b) (4)" and "2.4 Administration Instructions" since they are redundant. Relocate this section to after subsection "[redacted] (b) (4) since administration will occur sequentially after the preparation of the solution.

      iv. Consider changing the subsection header [redacted] (b) (4) to "Dilution Instructions" to correctly reflect the process.

      v. Under [redacted] (b) (4) ;" [redacted] (b) (4)

c. Dosage Forms and Strengths

i. See comment B3(a)(ii).

ii. DMETS recommends including the total vial volume (15 mL) in order to provide complete information to practitioners regarding the product.

d. How Supplied/Storage and Handling

i. See comments B3(a)(ii) and B3(b)(ii).

ii. Separate the third paragraph regarding storage information into 2 separate paragraphs; one paragraph concerning the storage of injection vials and second paragraph concerning the storage of diluted solution.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence sent to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Tanya Clayton, OSE Project Manager, at 301-796-0871.

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2007.002.A.00007
APPLICATION NUMBER	BLA 125104/33
LETTER DATE/SUBMISSION NUMBER	December 14, 2006
PDUFA GOAL DATE	October 15, 2007
REVIEW DIVISION	Division of Gastroenterology Products
MEDICAL REVIEWER	Anil Rajpal
REVIEW DIVISION PM	Marlene Swider
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	June 6, 2007
ESTABLISHED NAME	Natalizumab
TRADE NAME	Tysabri
APPLICANT	Biogen, Idec
ENDPOINT(S) CONCEPT(S)	Health Related Quality of Life
INSTRUMENT(S)	Inflammatory Bowel Disease Questionnaire (IBDQ); Short Form-36 Health Status Questionnaire (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS)
INDICATION	Induction and Maintenance of Sustained Response and Remission, and Eliminating Corticosteroid Use in Patients with Moderately to Severely Active Crohn's Disease with Inflammation (CD) as Evidenced by Elevated CRP Level or Other Objective Marker
INTENDED POPULATION(S)	Adults with Moderately to Severely Active Crohn's disease

Table 9. Change from Baseline in Health-Related Quality of Life Outcomes in CD Study 3*

	TYSABRI® *n=168*	*Placebo* *n=171*	*p-value*
	mean (SD)	*mean (SD)*	
Total IBDQ	*54 (34)*	*36 (40)*	*<0.001*
bowel symptoms	*18 (12)*	*10 (14)*	*<0.001*
systemic symptoms	*9 (7)*	*6 (7)*	*<0.001*
social function	*10 (7)*	*7 (8)*	*<0.001*
emotional function	*17 (13)*	*13 (15)*	*<0.001*
SF-36 Physical Components Summary	*13 (9)*	*7 (9)*	*<0.001*
SF-36 Mental Component Summary	*10 (11)*	*7 (12)*	*<0.001*

The IBDQ developers would probably say their instrument measures inflammatory bowel disease-specific quality of life. Overall, we do not recommend using the IBDQ for labeling purposes, albeit this position differs from previous SEALD consults on this instrument in association with the review for Remicade (infliximab). We do not find evidence that the items and domains of the IBDQ are appropriate, comprehensive, and interpretable relative to its intended measurement concept(s), population and use. This inadequate content validity can be exemplified by the following:

- Many of the questions in the IBDQ are double-barreled in that they combine two or more issues in a single question.
- Posing a question concerning the extent bowel habits limits sexual activity as proposed would only be informative if the patient is sexually active.
- Asking patients how happy or pleased they are about their personal life as proposed is a question which encompasses all aspects of a patient's "quality of life" (i.e. economic and/or marital status) and is not adequate to evaluate HRQOL specific to patients with Crohn's disease.
- The IBDQ requires patients average and recall their symptoms over a 2 week period and in some questions compare their state to a previous non-quantified time period. The choice of recall period and averaging of symptoms has the propensity to increase error and jeopardize the validity of the data.
- The sponsor has not provided evidence to support the fact that the IBDQ has been translated or culturally adapted from the original Canadian English into acceptable versions to support its use in their international clinical trials.

The SF-36 is a multi-purpose, short form health survey and therefore does not represent health related quality of life issues which are specific to the target population and indication. The SF-36-PCS and SF-36-MCS subscales, include domains that are unrelated to the concepts of interest (physical and mental function, respectively), and are therefore inadequate measures of these concepts.

Table 9. Change from Baseline in Health-Related Quality of Life Outcomes* in CD Study 3

	TYSABRI® n=168	Placebo n=171	p-value
	mean (SD)	mean (SD)	
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bowel symptoms	18 (12)	10 (14)	<0.001
systemic symptoms	9 (7)	6 (7)	<0.001
social function	10 (7)	7 (8)	<0.001
emotional function	17 (13)	13 (15)	<0.001
SF-36 Physical Components Summary	13 (9)	7 (9)	<0.001
SF-36 Mental Component Summary	10 (11)	7 (12)	<0.001

2.3 Endpoint Model

To support their proposed indication, the sponsor has submitted the clinical data reports from two pivotal studies, AN100226-CD307 (CD307) and AN100226-CD303 (CD303), and one supportive study (AN100226-CD301. All three trials were conducted in North America, Europe, and as noted by the sponsor, throughout the rest of the world.

Study CD301 was a randomized, multicenter double-blind, placebo-controlled, parallel-group trial of natalizumab in 905 subjects with moderately to severely active CD (CDAI score ≥220 and ≤450). Subjects were randomized in a 4:1 ratio to natalizumab 300 mg fixed dose or placebo administered IV every 4 weeks for three infusions. The primary endpoint was the proportion of subjects achieving clinical response (defined as a ≥70-point reduction in baseline CDAI score) at Week 10 and the contingent primary endpoint was the proportion of subjects achieving remission (defined as a CDAI score <150) at Week 10. Tertiary objectives included the comparison of the effects of natalizumab versus placebo on quality of life at all additional time points, as measured by the IBDQ, 36-item short form health survey questionnaire (SF-36), at weeks 6 and 10.

Study CD301 evaluated the ability of natalizumab to induce a response and remission in 905 subjects with moderately to severely active CD, and although this study did not reach statistical significance on its primary endpoint of response at Week 10 (natalizumab 56%, placebo 49%; p=0.051), a subgroup analysis of the 660 subjects who enrolled in the trial with an elevated CRP at baseline indicated significant benefit in clinical response and remission for these subjects. This finding led to Study CD307, a confirmatory study that assessed the efficacy of natalizumab in CD subjects with elevated CRP levels.

CD307 was a multicenter, randomized, double-blind, placebo-controlled, and parallel-group study in subjects with moderately to severely active CD (based on clinical evaluation and CDAI score ≥ 220 to ≤ 450) and elevated CRP levels (defined as >2.87 mg/L, the upper limit of normal [ULN]) as assessed by the study central laboratory at the screening visit. Subjects were screened for eligibility and randomized 7 to 14 days later at the baseline (Week 0) visit to receive monthly intravenous (IV) infusions of natalizumab 300 mg or placebo (1:1 ratio) at Weeks 0, 4, and 8. Following the Week 0 visit, subjects returned to the clinic for safety and efficacy assessments at Weeks 4, 8, and 12. The primary endpoint was defined as the proportion (%) of subjects with a

population. As noted by the sponsor, for the individual scales and the PCS and MCS summary scales, a change of five or more points defines an important change or a responder.

The SF-36-PCS and SF-36-MCS are obtained from questions from the parent SF-36 instrument. Although the scoring of each subscale is weighted to primarily include items which relate to the domain of interest, items from other domains are included as well. For instance, the SF-36-PCS scores includes items from the Physical Functioning, Role-Physical, and Bodily Scales, as well as items from other domains, such as mental health, vitality, and social function.

Comments: Since domains not relating to the concept of interest (physical and mental functioning for the PCS and MCS, respectively) are included in the scoring, the SF-36 PCS and MCS cannot be considered adequate measurements of the concepts proposed.

In addition, since the content validity of both the IBDQ and SF-36 PCS and MCS has not been sufficiently defined for the target population and indication, interpretation of study data for these measures is not possible and results are not adequate to support claims in labeling. .

2.5 Content Validity

The sponsor has not provided any specific documentation to support the content validity of the IBDQ or SF-36 to justify that the instrument items and response options are relevant (appropriate), understandable, and complete in relation to the desired claims.

Comments: The IBDQ requires patients average and recall their symptoms over a 2 week period and in some questions, compare their state to a previous non-quantified time period (i.e. Question: How frequent have your bowel movements been over the last two weeks? Response: Bowel movements as or more frequent than they have ever been.) The choice of recall period and averaging of symptoms has the propensity to increase error and jeopardize the validity of the data. It is usually better to ask patients to describe their current state rather than compare their current state with an earlier period or average their experiences over time.

Many of the questions in the IBDQ are double-barreled in that they combine two or more issues in a single question. For example, asking patients if they have a problem "maintaining or getting to a desired weight" is essentially combing the concept of weight gain with weight stability into a single question.

Posing a question concerning the extent bowel habits limits sexual activity, makes the underlying assumption that the patient is sexually active. This question would not be appropriate for a patient who is not sexually active. Asking patients how happy or pleased they are about their personal life is a question which encompasses all aspects of a patient's "quality of life" (i.e. economic and/or marital status) and is not appropriate for use in an instrument that evaluates HRQOL in Crohn's disease patients.

The SF-36 is a generic health related quality of life instrument and therefore does not necessarily capture the most clinically relevant issues for the target population. In addition, the one-week recall period may jeopardize the validity of the data.

subgroup analysis is obtained, this identical analysis should be considered for all other endpoints in the trial.

Study CD307:

A significantly greater improvement (mean [SD] increase from baseline) was demonstrated for natalizumab- than placebo-treated subjects by Week 12 for total IBDQ score (26.7 [32.34] vs. 15.2 [28.92], respectively, p-value <0.001) and for each of the IBDQ dimensions of bowel symptoms, systemic symptoms, emotional function, and social function with p-value of <0.001 for each dimension, except emotional function (p-value = 0.002).

For the SF-36 health survey, natalizumab-treated subjects showed a significantly greater improvement than placebo-treated subjects in 6 of the 8 SF-36 scale scores and the PCS score (5.8 [8.17] natalizumab vs. 2.7 [6.70] placebo, p-value <0.001) by Week 12. Individual SF-36 scales with significantly greater improvements for natalizumab patients included physical functioning (8.1 [17.59] natalizumab vs. 3.1 [14.86] placebo, p-value <0.001), role-physical (22.7 [38.25] vs. 13.4 [38.10], respectively, p-value = 0.013), bodily pain (18.0 [24.13] vs. 7.0 [18.37], respectively, p-value <0.001), general health (10.7 [17.66] vs. 5.6 [14.77], respectively, p-value <0.001), vitality (12.2 [21.30] vs. 5.8 [18.94], respectively, p-value = 0.001), and social functioning (14.4 [24.75] vs. 7.9 [22.48], respectively, p-value = 0.001).

Using the a responder-type analysis for each IBDQ dimension and each SF-36 component, significant results were also obtained for the total IBDQ score and all IBDQ dimensions, for the same six components of the SF-36 listed above, PCS, and MCS at Week 12, favoring natalizumab.

Study CD303:

For the total IBDQ scale and each of the component scales, significantly greater improvements from Study CD301 baseline were initially observed for the natalizumab group at the Month 6 visit, with differences for each of the scales being sustained throughout the remaining three timepoints (Months 9, 12, and 15) of Study CD303. Figure 1 delineates the IBDQ scores for each treatment group over time.

4 APPENDICES

4.1 IBDQ

#	Question
Bowel symptoms	
1	How frequent have your bowel movements been during the last 2 weeks?
5	How much of the time during the last 2 weeks have your bowel movements been loose?
9	How often during the last 2 weeks have you been troubled by cramps in your abdomen?
13	How often during the last 2 weeks have you been troubled by pain in the abdomen?
17	Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas?
20	How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?
22	How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements?
24	How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?
26	How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants?
29	How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach?
Systemic symptoms	
2	How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?
6	How much energy have you had during the last 2 weeks?
10	How often during the last 2 weeks have you felt generally unwell?
14	How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?
18	Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight they would like to be at?
Emotional function	
3	How often during the last 2 weeks have you felt frustrated, impatient, or restless?
7	How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?
11	How often during the last 2 weeks have you been troubled because of fear of not finding a washroom?
15	How often during the last 2 weeks have you felt depressed or discouraged?
19	Many subjects with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious?
21	How often during the last 2 weeks have you felt relaxed and free of tension?
23	How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem?
25	How much of the time during the last 2 weeks have you felt tearful or upset?
27	How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?
30	How much of the time during the last 2 weeks have you felt irritable?
31	How often during the past 2 weeks have you felt lack of understanding from others?
32	How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks?

4.2 SF-36

1. In general, would you say your health is:				
Excellent	Very Good	Good	Fair	Poor

2. Compared to one year ago, how would you rate your health in general now?				
Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now thanone year ago	Much worse now than one year ago

3. The following questions are about activities you might do during a typical day. *Does your health now limit* you in these activities? If so, how much?			
	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
Lifting or carrying groceries	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐
Climbing one flight of stairs	☐	☐	☐
Bending, kneeling, or stooping	☐	☐	☐
Walking more than a mile	☐	☐	☐
Walking several hundred yards	☐	☐	☐
Walking one hundred yards	☐	☐	☐
Bathing or dressing yourself	☐	☐	☐

The following questions are about activities you might do during a typical day. *Does your health now limit* you in these activities? If so, how much?					
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Cut down the amount of time you spent on work or other activities	☐	☐	☐	☐	☐
Accomplished less than you would like	☐	☐	☐	☐	☐
Were limited in the kind of work or other activities	☐	☐	☐	☐	☐
Had difficulty performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

9. During the *past 4 weeks*, how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting friends, relatives, etc.)?				
All of the time	Most of the time	Some of the time	A little of the time	None of the time

10. How TRUE or FALSE is *each* of the following statements for you?					
	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
I am as healthy as anybody I know	☐	☐	☐	☐	☐
I expect my health to get worse	☐	☐	☐	☐	☐
My health is excellent	☐	☐	☐	☐	☐

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

Date: October 4, 2007

To: Russell Katz, Director
Division of Neurology Drug Products

Dan Shames, Acting Director
Division of Gastrointestinal Products (DGP)

Thru: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)

From: Charlene M. Flowers, R.Ph., Safety Evaluator
Division of Drug Risk Evaluation (DDRE)

Subject: Serious liver Injury

Drug Name(s): Natalizumab, Tysabri™
Applicant/sponsor: Biogen Idec BLA # 125104
OSE RCM #: 2007-1888

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

EXECUTIVE SUMMARY

We reviewed Tysabri-associated serious hepatic injury cases that contained documentation of biopsies and increased hepatic function studies including peak ALT=2,212 UL/L, AST=1,863 IU/L, and bilirubin=16.1. The outcomes were serious: medically significant (2) and hospitalization (2) including one patient who was placed on the liver transplant list, but subsequently recovered prior to transplant. Based on these cases, we cannot rule out an association between Tysabri use and severe liver injury. We suggest that current labeling include clinical characteristics of cases of liver injury associated with Tysabri use in the Precautions section. We suggest language such as "clinically significant liver injury has been reported in patients taking Tysabri. Signs of liver injury occurred as early as six days subsequent to the first dose. Other causes were not identified; therefore a causal association with Tysabri cannot be excluded."

Additionally, we suggest surveillance for new cases of Tysabri associated liver injury events through the TYGRIS observational study be considered. Though the currently reported cases were serious and well documented, there were too few cases to adequately characterize risk for this event. We further recommend the sponsor expedite reporting of all AERS cases of liver injury with increased liver transaminase levels (AST and ALT) of greater than 3 X ULN and to thoroughly follow-up on all such cases including clinical information to enable a differential diagnosis for etiology of the liver event. Finally, we suggest that the sponsor follow-up on the

existing 4 cases, highlighted in this document, to determine if late serological conversion (or RNA/DNA levels) was determined in order to definitively rule-out Type A, B, or C viral hepatitis.

1 BACKGROUND

1.1 INTRODUCTION

During routine postmarketing adverse event surveillance for Tysabri, we noticed cases of hepatic injury that required further investigation. An AERS search was conducted in July 2007 and resulted in 28 cases of hepatic injury, including four cases of serious hepatic injury and 24 non-serious cases of abnormal hepatic function (i.e. "increase LFT," "abnormal liver enzyme," etc.).

1.2 REGULATORY HISTORY

On November 23, 2004, Tysabri was approved by FDA for the treatment of relapsing forms of multiple sclerosis (MS) to delay the progression of physical disability and to reduce the frequency of clinical exacerbations. In early February 2005, the sponsor, Biogen Idec and Elan, notified The Agency of three cases of progressive multifocal leukoencephalopathy (PML) associated with Tysabri occurring in patients with MS (2) and Crohn's (1); two cases had fatal outcomes - 1 MS and 1 Crohn's.

On 2/23/05, the Agency gathered information in response to the emergence of PML cases which included a summary[1] of AERS data that ascertained no additional cases of PML with Tysabri or potential co-suspect Avonex, a beta-interferon, and its drug class[2]. A second search of AERS for PML cases with non-beta-interferon products revealed antiretrovirals that are used in the treatment of patients with HIV, immunomodulators, and anti-tumor agents - all of which are associated with patient populations with suppressed immune functions. On February 28, 2005, Tysabri was voluntarily suspended from marketing. Clinical trials for similar types of agents were also suspended.

An Advisory Meeting convened on 3/8/06 and the committee members unanimously voted in favor of returning Tysabri to the market within the constraints of a Risk Management Plan (RMP) named Tysabri Outreach: Unified Commitment to Health (TOUCH), which was designed to promote informed risk benefit decisions regarding TYSABRI use in MS patients, to minimize the risk of PML, and to minimize death and disability due to PML. On June 5, 2006, marketing of Tysabri resumed.

On 6/20/06, individual case-reports of liver injury began to emerge while at the same time the drug was under review for a supplemental indication for the treatment of Crohn's disease, which if approved will adopt a similar RMP.

1.3 PRODUCT LABELING

The current product label includes in the Adverse Reaction section: Gastrointestinal: *Abdominal discomfort, Diarrhea, and Abnormal liver function test* . . . Also, the labeling has Black Boxed Warnings for PML, Hypersensitivity, and Immunosuppression.

---

[1] Charlene Flowers, AERS search results for Tysabri related PML, 2/23/05, PID# 050112

[2] U.S marketed beta-interferons: Rebif, and Betaseron

The approved Tysabri labeling can be viewed at the website of the U.S. Food and Drug Administration at http://www.fda.gov/cder/foi/label/2006/125104s015LBL.pdf

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

An AERS search was performed on July 7, 2007, and again on September 21, 2007. The following preferred and higher level hepatic related terms were used: Hepatic and hepatobiliary disorders (HLGT), Hepatic failure and associated disorders (HLT), hepatic fibrosis and cirrhosis (HLT), hepatic necrosis (PT), Hepatitis fulminant (PT), liver transplant (PT), and liver function analysis (HLT level) which includes all hepatic laboratory tests.

2.2 LITERATURE SEARCH

A search of the published literature, PubMed, was conducted on September 21, 2007, utilizing the terms Tysabri AND hepatic%, liver%, hepto% injury.

2.3 Other Materials

The 11th Periodic Safety Update Report (PSUR) is a report by Biogen Idec and Elan Pharmaceutical that summarizes adverse drug reactions (ADRs) received, from May 24 – August 23, 2007; included is drug use data from market approval through 8/23/07. We extracted U.S. postmarketing drug use data from the patient exposure section 5.

3 RESULTS

3.1 ADVERSE EVENTS (AERS CASES)

As of September 21, 2007, AERS contained 1,898 reports of all adverse events reported to Tysabri. Using the search criteria described in Section 2.1, 28 cases of liver dysfunction were identified. Twenty four of the cases described non-serious liver function tests which could be considered labeled; the 24 cases are listed in Appendix II.

Four cases of serious hepatic injury were identified. Demographics and other characteristics of the cases are found below in Table 1. Additionally, a line listing of cases is also available in a summary table in Appendix I.

Table 1. Demographics and clinical characteristics of Tysabri-associated serious liver injury* AERS cases - as of 9/21/07 (n=4)

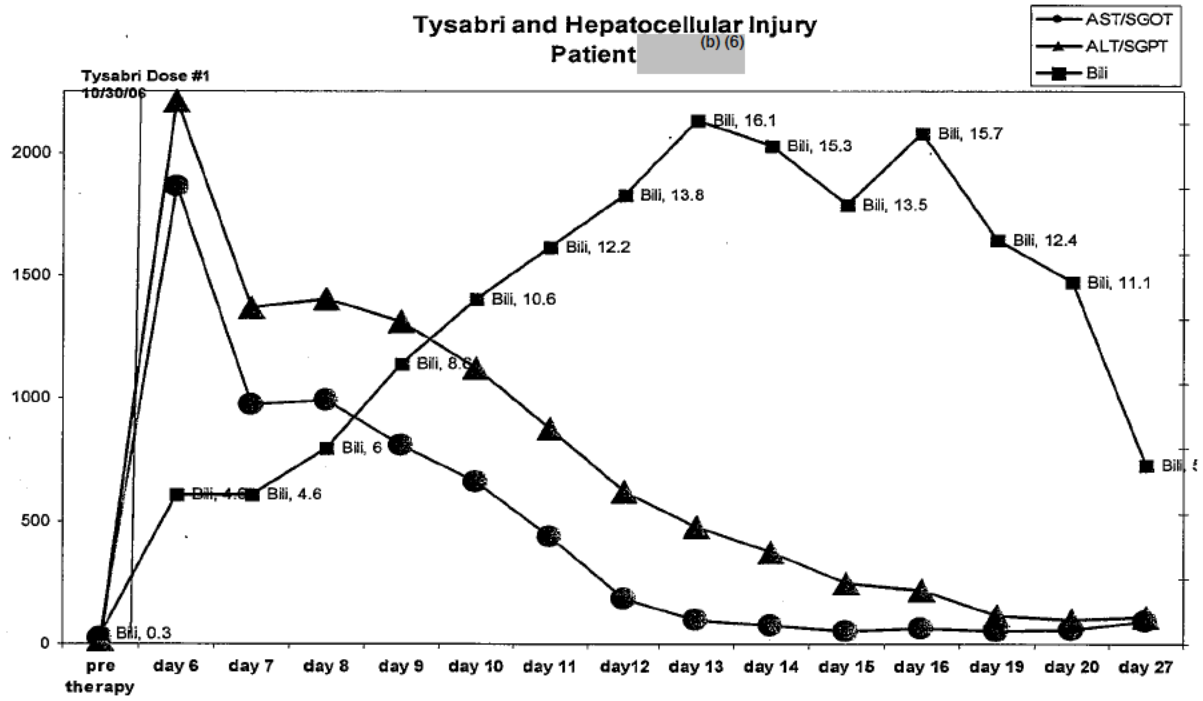
Age (yrs)	Range: 26 – 59	Median -38	Mean -40
Gender:	Male -1	Female -3	
Indications:	Multiple sclerosis - 4		
Monthly dose (4 wks):	1st dose – 3	5th dose -1	
Estimated Time to onset (after dose administration):	Range: 6 – 18 days	Median – 8 days	Mean – 8 days
Viral screen (Hepatitis A, B, and C):	Negative – 4		
Source of Reports:	U.S. – 3	Canada – 1	

	(all enrolled in TOUCH RMP)	(enrolled in RMP other than TOUCH)
Outcome:	Hospitalization -2	Important medical event - 2

*Serious liver injury defined: Cases with an outcome of hospitalization and important medical event.

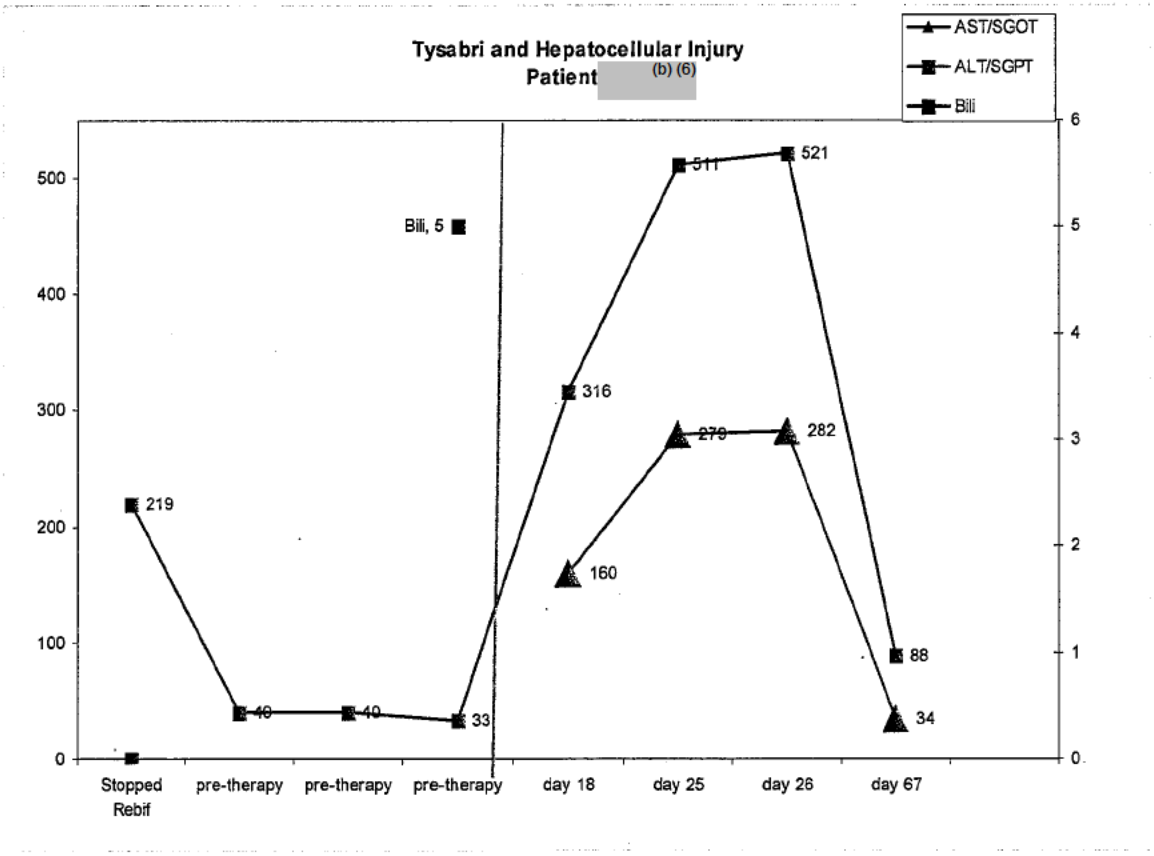
Patient 1 – (b) (6)
ISR#5316257,U.S., 2007

- 26 year old female with MS
- Time to onset : 10/30/06: first dose – day 6
- Symptoms: weakness, constipation, tachycardia
- Concomitant medications: Tylenol with recent dose increase over several months, however patient admits to little use. Oral contraception, calcium, potassium, baclofen, Xanax, Rebif – no hepatic disorder.
- Liver biopsy results: Drug reaction (steroids, interferon-beta or other recent medication (i.e. Tysabri), and obesity could be underlying mechanism for the features of non-alcoholic steatohepatitis (NASH) and there could be a concomitant autoimmune hepatitis.
- Viral screening = negative for hepatitis A(total), B (Core Ab, sAb, and sAg), and C (Ab)
- Illustration of patient's laboratory findings: AST, ALT, and bilirubin follows:



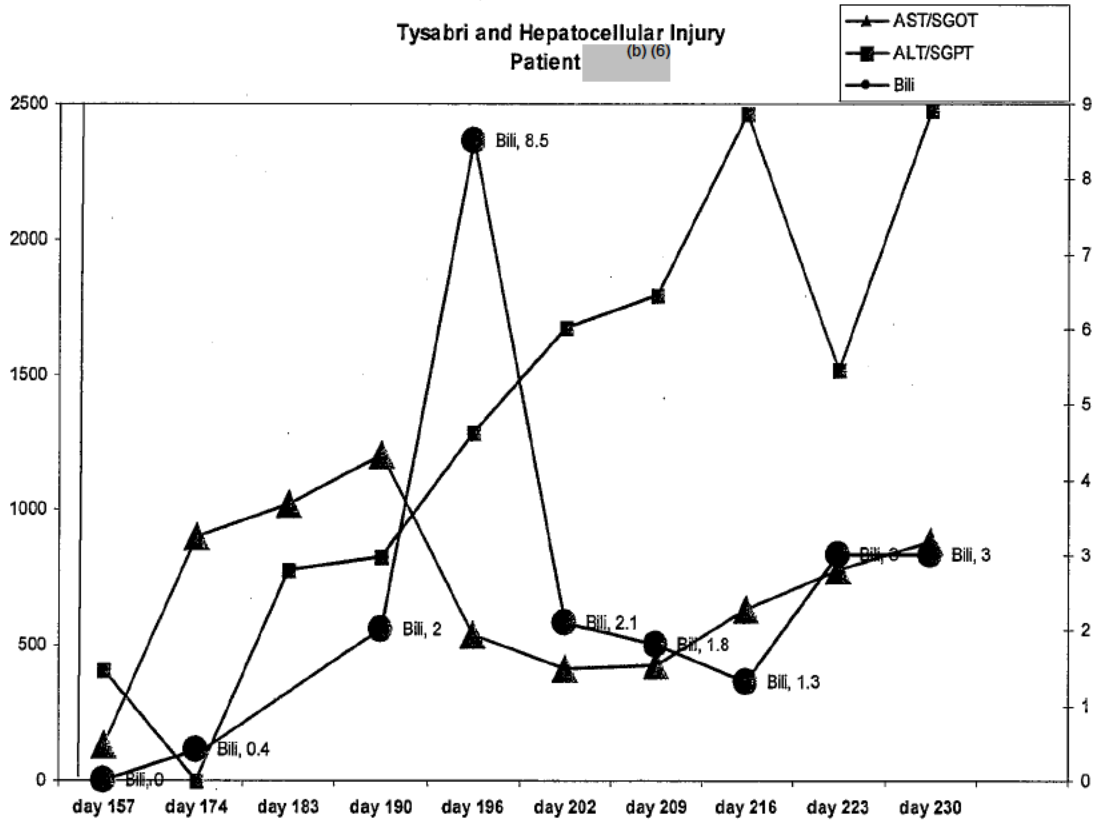
Patient 2 (b) (6)
ISR#5353394, Canada, 2007

- 33 year old female nurse
- Medical history: Rebif associated hepatic injury that recovered before Tysabri initiated. Tysabri use resulted in "re-increasing hepatic transaminase levels." Patient is an ICU nurse who might be at risk for hepatitis.
- Time to onset: 3/28/07: first dose – day 18
- Symptoms: Tired eyes and dark urine
- Concomitant medications: Rebif (11/06 – 1/27/07); drug discontinued and liver function recovering; Neurontin, no over-the-counter products, no alcohol use, ICU nurse who might be at risk of hepatitis.
- Liver biopsy results: 4/27/07: Active chronic hepatitis with portal inflammation and primarily lobular and peri-portal fibrosis. The gastroenterologist stated "The type of hepatitis the patient has remains in question."
- Viral screening = negative for hepatitis A (Ab), B(sAg), and C (Ab)
- Illustration of patient's laboratory findings: AST, ALT, and bilirubin follows:



Patient #3 – (b) (6)
ISR#5363075, MFR#2007BIO16258, U.S., 2007

- 43 year old male with MS
- Time to onset: 10/6 – 2/07: 5th dose – day 150
- Symptoms: fatigue, back pain, fever, fall to abdomen, and "kidney stone"
- Concomitant medications: Spirulina[3], MVI, prednisone; no Tylenol, NSAID, or alcohol.
- Liver biopsy results: The etiology of his increased LFTs in unknown. The differential is Tysabri or autoimmune hepatitis. Follow-up[4] was attempted to retrieve further details from liver tissue sample, however the sample was a "fixed in paraffin blocks," which did not permit further testing (i.e. RNA typing for hepatitis virus).
- Clinical course: despite discontinuation of Tysabri, patient continued to deteriorate. Liver transplant was considered, but the patient recovered.
- Viral screening = negative for hepatitis A (IgM), B (sAg, core IgM), and C (Ab)
- Reviewer comment: reporter was requested to provide RNA hepatic viral studies.
- Illustration of patient's laboratory findings: AST, ALT, and bilirubin follows:

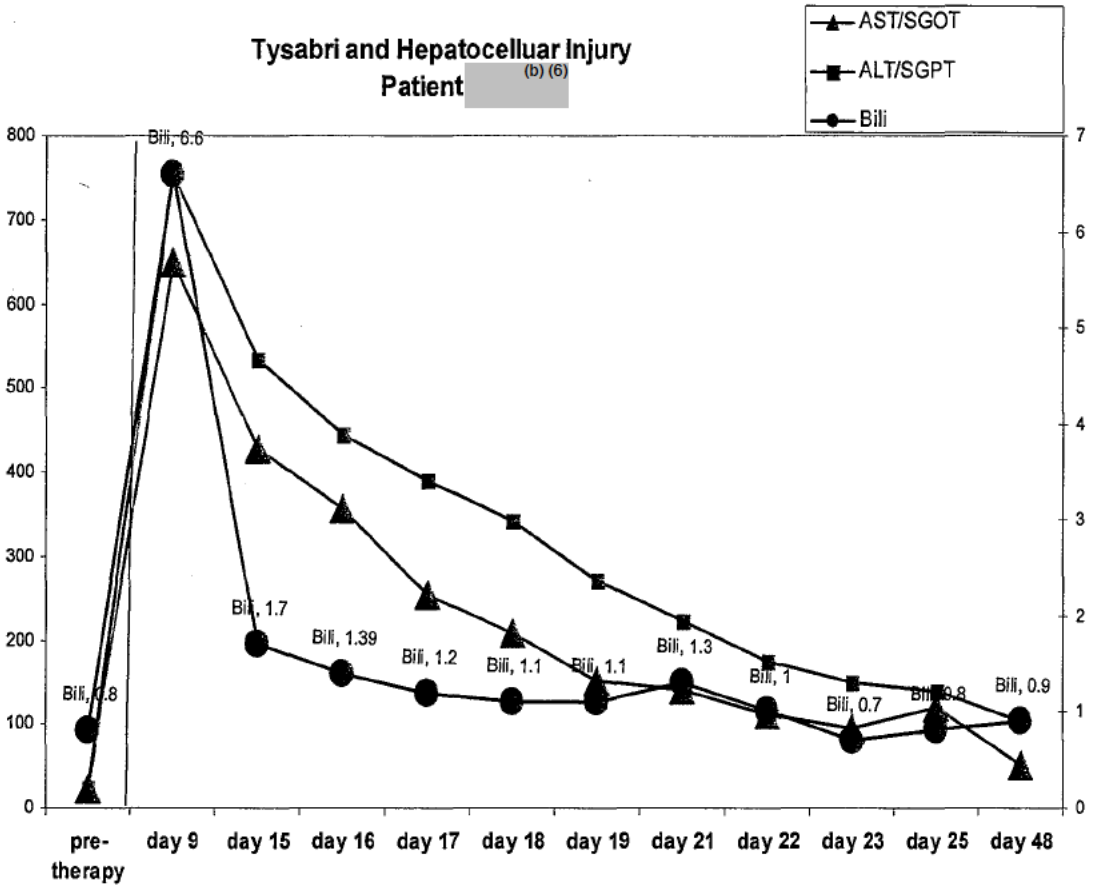


[3] Spirulina: common names: spirulina, dihe, Techuitlatl, blue-green algae: Its a cyanobacterium valued as a food or nutritional supplement for its high protein

[4] (b) (4)

Patient # 4 - (b) (6)
ISR#5286211, MFR#2006BIO16391, U.S., 2007

- 59 year old female with MS
- Time to onset: 10/25/06: first dose – day 8
- Symptoms: Pitting edema, jaundice, red tongue and lips
- Concomitant medications: Tylenol (Pt reported "little use"), NSAID, MVI
- Viral screening = negative for hepatitis A (IgM), B (sAg, core IgM), and C (Ab)
- Illustration of patient's laboratory findings: AST, ALT, and bilirubin follows:



3.2 LITERATURE SEARCH

Our literature search did not reveal any citations relevant to Tysabri associated hepatic injury.

3.3 Other Materials – Usage data

- Periodic Safety Update Report (PSUR)

U.S. Drug Use Data: Postmarketing: Based on sales data, it is estimated that from approval until voluntary marketing suspension [redacted] (b) (4) a maximum of [redacted] (b) (4) patients were treated with Tysabri with a maximum of [redacted] (b) (4) patient-years of exposure, and a mean of [redacted] (b) (4) patient-years of exposure.

In the U.S., from [redacted] (b) (4) a total of [redacted] (b) (4) patients received at least one dose of Tysabri with an estimated [redacted] (b) (4) person-years of exposure.

4 DISCUSSION

We reviewed four relatively unconfounded cases of serious liver injury associated with Tysabri of which its contribution to the event could not be ruled out. None of the cases reported death as an outcome, although one patient was considered for liver transplant, but recovered.

The cases described patients (male -1 and female-3) with their ages ranging from 26 – 59 with the mean of 40 years. All cases reported treatment with Tysabri at recommended doses for multiple sclerosis (MS). Two cases with a potential hepatotoxin, Tylenol, were followed-up to determine the quantity of product consumption, of which minimal quantities were ingested. The estimated duration from the starting dose to the onset of symptoms was eight days (mean and median) subsequent to patient's first dose in three cases; one other patient experienced symptoms shortly after (11 days) the fifth dose.

A specific diagnosis for liver injury was not reported although three cases provided relevant clinical details including liver biopsies; all cases provided the following: (1) impressive increases in liver function studies (peak AST and ALT levels were 1,863 IU/L and 2,212 IU/L respectively, and bilirubin peak of 16.1.), (2) findings of negative hepatic viral screens, and (3) no case provided clinical details to ascertain an alternative etiology. The diagnostic interpretations of the biopsies in each of the three cases were as follows: (1) "the appearance of hepatitis and confluent hepatic necrosis are highly suggestive of drug-induced liver injury"; (2) "active chronic hepatitis with portal inflammation and primarily lobular and peri-portal fibrosis"; and (3) "acute hepatitis with portal hepatitis and a mild pericellular fibrosis." The Results section 3.1 contain summaries of the 4 cases of serious liver injury with graphic representation of the patient's liver function studies (AST, ALT, and bilirubin values).

A mechanism of liver injury remains to be elucidated. The rapid onset of liver injury after the initiation of treatment with Tysabri in three of the cases is remarkable. We propose two possibilities: (1) a form of hypersensitivity to Tysabri as a component of the formulation; and (2) unmasking of an unusual yet to be identified pathogen causing liver injury due to immunosuppression. If the putative pathogen is a virus, current tools that screen for hepatitis A, B, or C would be inadequate for its detection.

5 CONCLUSION/RECOMMENDATIONS

We reviewed Tysabri-associated serious hepatic injury cases that contained documentation of biopsies and increased hepatic function studies including peak ALT=2,212 UL/L, AST=1,863 IU/L, and bilirubin=16.1. Based on these cases, we cannot rule out an association between Tysabri use and severe liver injury. We suggest the following:

Include clinical characterization of liver injury cases associated with Tysabri use in the Precautions section of labeling.

- We suggest that current labeling include clinical characteristics of cases of liver injury associated with Tysabri use in the Precautions section. We suggest language such as "(b) (4) ."
- Consider surveillance for new cases of Tysabri associated liver injury events through the TYGRIS observational study.
- Expedite reporting of all cases of liver injury with increased liver transaminase levels (AST and ALT) of greater than 3 X ULN.
- Thoroughly follow-up on all expedited cases of liver injury and include clinical information to enable a differential diagnosis for etiology of the liver events.
- Follow-up on the existing 4 cases, highlighted in this document, to determine if late serological conversion (or RNA/DNA levels) was determined in order to definitely rule-out Type A, B, or C viral hepatitis.

Signed,

Charlene Flowers, RPh

Safety Evaluator 10/3/07

concur:

Cindy Kortepeter, Pharm.D.

Safety Evaluator Team Leader 10/3/07

APPENDICES

Appendix I
Table 1 AERS cases as of Tysabri associated serious liver injury, as of 9/21/07 (N=4)

ISR#/ID	FDA Receive Date	Source	Age/ Sex	# Doses –IV monthly (Q4 weeks)	Ind[a]	TTO[b]	Symptoms	Concomitant medications	Biopsy Results
5316257/ (b) (6)	4/30/07	U.S.	26/F	#1 300 mg (10/30/06)	MS	6 days	Weakness, constipation, tachycardia HR = 110, BP 96/60	Tylenol w/ recent dose increase over several months, Oral contraceptive, Calcium, potassium, baclofen, Xanax, Rebif – no hepatic disorder.	11/13/ 07: Liver biopsy: Diagnostic Interpretation of liver biopsy: Drug reaction (steroids, interferon-beta or other recent medication (i.e. Tysabri), and obesity could be underlying mechanism for the features of NASH and there could be a concomitant autoimmune hepatitis.
5363394[6]/ (b) (6)	6/15/07	Canada	33/F	#1 300 mg (3/28/07)	MS	18 days	"Tired eyes" Dark urine. No icterus	Rebif (11/06 – 1/27/07) w/ hepatic disorder – DCd; Neurontin	4/27/07: Diagnostic interpretation of liver biopsy: Active chronic hepatitis with portal inflammation and primarily lobular (grade ¼) and peri-portal fibrosis (stage 2/4). "The type of hepatitis the patient has remains in question."
5363075/ (b) (6)	6/15/07	U.S.	43/M	#5 300 mg (10/06-2/07)	MS	11 days since last infusion; 150 days since 1st dose	Fatigue Back pain, fever Fall to abdomen Kidney stone	Spuirulina MVI, prednisone, No -Tylenol, naproxen, and ibuprofen. No – ETOH use.	Diagnostic Interpretation of liver biopsy The etiology of his increased LFTs in unknown. The differential is Tysabri or autoimmune hepatitis. Consideration for liver transplant.
5286211/ (b) (6)	3/30/07	U.S.	59/F	#1 300MG 10/25/06	MS	8 days	Pitting edema, jaundice, red tongue, and lips	Tylenol, NSAIDS, MVI	None

[a] Ind = indication

[b] TTO= Time To Onset

Appendix II

Table 2. As of 9/21/07, AERS cases of liver disorders (n= 24)

SRNUM	IMAGE	RECVDATE	MFRCNTRL	CNTRY	ID (b) (6)	AGE	SEX	# doses	Labs	Biopsy Y/N	Other meds	OUTC1	RPTYPE
4568139	4568139-	31-Jan-05	ANTE001346	IL		51	F		"increase liver function studies"	N		OT	Expedited (15-Day)
4627887	4627887-	1-Apr-05	2005BI002294	US		45	F	#29	Colon cancer, mild elevation of LFTs	N		HO	Expedited (15-Day)
4663824	4663824-1-00	16-May-05	2005BI007367	US		NR	F	#1	LFTs inc 2ndy to other med	N	mitoxantrone	HO	Expedited (15-Day)
4668921	4668921-2-00	19-May-05	2005BI005712	US		NR	F	#1	"abnormal LFTs"	N		HO	Expedited (15-Day)
4701387	4701387-2-00	24-Jun-05	2005BI006728	US		NR	F	#1	"Incr LFTs"	N			Periodic
4702039	4702039-5-00	24-Jun-05	2005BI006328	US		52	F	#1	"inc LFTs"	N			Periodic
4703163/ 4703113	4703163-3-00	24-Jun-05	2005BI010057	US		49	F	#1	"inc liver enzymes"	N	Avonex		Periodic
4703261	4703261-4-00	24-Jun-05	2005BI007959	US		NR	F		"high liver enzyme"	N			Periodic
4703323	4703323-1-00	24-Jun-05	2005BI008048	US		NR	F	#1	"elevated liver enyz"	N	Avonex		Periodic
4710285/ 4628804		11-Jul-05	US-JNJFOC-20050400785	US		69	M	#34	PCP, hx liver DZ (crohn's dx)	N		DE (2/1/05)	Expedited (15-Day)
4855633	4855633-5-00	14-Dec-05	2005BI001332	PL		29	M	#4	"high GGT"	N		OT	Expedited (15-Day)
4902231	4902231-0-00	2-Feb-06	2005BI010383	US		31	F	#2	ALT = 430 AST = 162 (abdominal pain			HO	Expedited (15-Day)
4906025	4906025-1-00	6-Feb-06	2006BI001252	US		NR	F	#2	"autoimmune hepatitis	N	Avonex	OT	Expedited (15-Day)
5011555	5011555-0-00	24-May-06	2006BI007150	AT		62	F	#20	Intrahepatic cholangiocarcinoma	N		OT	Expedited (15-Day)

					(b) (6)								
5169163	5169163-7-00	1-Dec-06	US-2006-036704	US		64	M	NR	HX liver failure	N		HO	Expedited (15-Day)
5241126	5241126-2-00	14-Feb-07	CTU 295894E	US		61	M		"elevated liver function test"	N		HO	Direct
5242796	5242796-5-00	14-Feb-07	2007BI002409	DE		40	M	#4	"incr bilirubin", icterus	N		OT	Expedited (15-Day)
5242919	5242919-8-00	15-Feb-07	2007BI002399	US		39	F	NR	"ammonia levels incr	N		HO	Expedited (15-Day)
5289520	5289520-8-00	2-Apr-07	2005BI013695	US		NR	F	#1	"liver damage" ; fatty liver and fatty pancreas	N		HO	Expedited (15-Day)
5314529	5314529-5-00	27-Apr-07	2007BI007883	US		75	F	NR	"incr LFTs"	N		HO	Expedited (15-Day)
5325722	5325722-X-00	9-May-07	2007BI007109	US		25	F	#2	Septic shock, AST = 1,057, ALT = 1,147	N		DCd Ty LFTs decr'd	Expedited (15-Day)
5353207	5353207-3-00	8-Jun-07	2007BI007305	US		76	F	NR	Gm – sepsis, "transaminitis"	N		HO	Expedited (15-Day)
5361628	5361628-8-00	15-Jun-07	2007BI010195	US		68	F	NR	"Inc LFT"		Levoquin	HO	Expedited (15-Day)
5371386	5371386-9-00	22-Jun-07	2007BI007699	US		51	F	NR	"mild increase LFTs"	N		HO	Expedited (15-Day)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Date: November 1, 2007

To: Mary Willy
Senior Drug Risk Management
Office of Surveillance and Epidemiology

Through: George Rochester, Ph.D., R.A.C., Team Leader
Quantitative Safety and Pharmacoepidemiology Group
Division of Biometrics VI
Office of Biostatistics

From: Mark Levenson, Ph.D.
Quantitative Safety and Pharmacoepidemiology Group
Division of Biometrics VI
Office of Biostatistics

Brand Name: Tysabri

Active Ingredient Natalizumab

Sponsor Biogen Idec

BLA: 125104/33

Subject: Sample size for protocol concept for postmarketing safety of Tysabri (natalizumab) study

Executive Summary

The Office of Surveillance and Epidemiology (OSE) has requested a consult on the proposed sample size for a protocol concept for an observational study of the safety of Tysabri for the treatment of Crohn's disease. FDA is currently reviewing an application for an indication of Tysabri for the treatment of patients with moderately to severely active Crohn's disease. FDA and the sponsor are discussing the observational study as part of a post-marking commitment.

The proposed concept describes a prospective, single-cohort, observational study with external comparison groups. The objective of the study is "to determine the incidence and pattern of serious infections, malignancies, and other serious adverse events (SAEs) in

patients with CD [Crohn's disease] treated with Tysabri." Comparisons will also be made with external control groups. Tysabri patients will be recruited from the TOUCH™ Prescribing Program.

The protocol concept calls for 2,000 patients to be enrolled and followed for 5 years. It estimates 4,000 patient-years of Tysabri exposure and 5,000 person-years of off-treatment exposure based on assumptions on discontinuation and lost-to-follow-up rates.

The protocol concept claims the study will be able "detect SAEs with an incidence of 0.10% with 98% probability." The meaning of this statement is that if the true incidence were 0.10% there would be a 98% chance of observing one or more events. Additional probabilities are provided for various events based on observed incidence in short-term placebo controlled trials.

In an internal meeting, members of OSE, the Division of Gastroenterology Products, and the Quantitative Safety and Epidemiology Group proposed an alternative framework to determine a sufficient sample size. The sample size should be sufficient to rule out a 1 in 1000 rate of events. Additionally, the patient sample should have at least one year of drug exposure. Therefore, sufficient patients should be enrolled to allow for drug discontinuation and still produce the necessary sample size with one year of drug exposure. The sponsor should also specify the methods to be used to estimate incidence rates and any associated statistical testing or confidence intervals. Proposed language to sponsor conveying these recommendations is provided in the body of this consult.

Background

The Office of Surveillance and Epidemiology (OSE) has requested a consult on the proposed sample size for a protocol concept for an observational study of the safety of Tysabri for the treatment of Crohn's disease. The protocol concept is described in a 28 September 2007 submission and further clarified in a response to FDA questions, submitted on 16 October 2007.

Tysabri is currently 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 product carries a black box warning for increased risk of progressive multifocal leukoencephalopathy. It is available in the U.S. only through the TOUCH™ Prescribing Program. FDA is currently reviewing an application for an indication of Tysabri for the treatment of patients with moderately to severely active Crohn's disease. FDA and the sponsor are discussing an observational study as part of a post-marking commitment.

The proposed study is a prospective, single-cohort, observational study with external comparison groups. The study endpoints are serious infections, malignancies, and other serious adverse events. Approximately 2,000 patients will be enrolled in the U.S from the TOUCH™ Prescribing Program. Patients will be follow-up for 5 years during regularly scheduled medical visits. Based on assumptions on discontinuation rates (50% in the first year and 10% annually thereafter) and a lost-to-follow-up of 1,000 patient-years, the

protocol concept calculates 4,000 patient-years of Tysabri exposure and 5,000 patient-years of off-treatment follow-up.

Three comparisons will also considered: (1) a comparison between event rates in the study and those in a Crohn's registry, (2) a comparison between event rates in the study and those from epidemiology literature, and (3) a comparison of study event rates between patients with less than 6 months and 6 or more months of Tysabri exposure. Comparisons will be based on t-test for means and χ^2 for categorical variables.

The protocol concept claims the study will be able "detect SAEs with an incidence of 0.10% with 98% probability." Additional probabilities are provided for various events based on observed incidence in short-term placebo controlled trials.

Issues and Recommendations

The meaning the statement "detect SAEs with an incidence of 0.10% with 98% probability" is that if the true incidence were 0.10% there would be a 98% chance of observing one or more events. It is not clear what the value of this probability statement is. For example, does observing a single event imply a safety issues for the drug? The safety implications of observing events are not given by the sponsor.

In an internal meeting, members of OSE, the Division of Gastroenterology Products, and the Quantitative Safety and Epidemiology Group proposed an alternative framework to determine a sufficient sample size. The sample size should be sufficient to rule out a 1 in 1000 rate of events.

A common approach to ruling out a given rate of events is known as the "rule of threes."[1] The rule says to rule out an event rate r, a sample size of $3/r$ is needed. For example, to rule out a rate of 1 in 1000, a sample size of 3000 is needed. The approach is based on a one-sided test of the null hypothesis of the rate at the 0.05 level.

At the internal meeting, the staff also recommended that the patient sample should have at least one year of drug exposure. Therefore, sufficient patients should be enrolled to allow for drug discontinuation and still produce the necessary sample size with one year of drug exposure.

This consult recommends the language below be sent to the sponsor.

> Based on our review of the protocol concept for the Tysabri CD Observational Study (dated 28 September 2007) and your response to FDA comments (dated 16 October 2007), we have the following recommendations on the sample size and the statistical analysis of the study.
>
> (1) Provide sample size calculations in terms of a statistical hypothesis or confidence interval on the incidence rate. We recommend that the sample size be

[1] Van Belle G. *Statistical Rules of Thumb*. New York (NY): John Wiley & Sons, 2002.

based on ruling out rates of 1/1000 patients. Using a one-sided test at the level of 0.05, "the rule of threes" gives a sample size of 3000 (see Van Belle, *Statistical Rules of Thumb* 2002).

(2) The patient sample should have at least one year of drug exposure. Therefore, sufficient patients should be enrolled to allow for drug discontinuation and still produce the necessary sample size with at least one year of drug exposure. For example, if 3000 patients are determined necessary for the statistical analysis, ensure that the enrollment is sufficient that given reasonable assumptions on drug discontinuation, there will be 3000 patients with 1 year of drug exposure.

(3) Submit a protocol and statistical analysis plan for review by the agency. The statistical analysis plan should specify the statistical methods to be used to estimate incidence rates and any associated statistical testing or confidence intervals.

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

Date: October 4, 2007

To: Russell Katz, Director
Division of Neurology Drug Products

Dan Shames, Acting Director
Division of Gastrointestinal Products (DGP)

Thru: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)

From: Charlene M. Flowers, R.Ph., Safety Evaluator
Division of Drug Risk Evaluation (DDRE)

Subject: Serious liver Injury

Drug Name(s): Natalizumab, Tysabri™
Applicant/sponsor: Biogen Idec BLA # 125104
OSE RCM #: 2007-1888

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

EXECUTIVE SUMMARY

We reviewed Tysabri-associated serious hepatic injury cases that contained documentation of biopsies and increased hepatic function studies including peak ALT=2,212 UL/L, AST=1,863 IU/L, and bilirubin=16.1. The outcomes were serious: medically significant (2) and hospitalization (2) including one patient who was placed on the liver transplant list, but subsequently recovered prior to transplant. Based on these cases, we cannot rule out an association between Tysabri use and severe liver injury. We suggest that current labeling include clinical characteristics of cases of liver injury associated with Tysabri use in the Precautions section. We suggest language such as "clinically significant liver injury has been reported in patients taking Tysabri. Signs of liver injury occurred as early as six days subsequent to the first dose. Other causes were not identified; therefore a causal association with Tysabri cannot be excluded."

Additionally, we suggest surveillance for new cases of Tysabri associated liver injury events through the TYGRIS observational study be considered. Though the currently reported cases were serious and well documented, there were too few cases to adequately characterize risk for this event. We further recommend the sponsor expedite reporting of all AERS cases of liver injury with increased liver transaminase levels (AST and ALT) of greater than 3 X ULN and to thoroughly follow-up on all such cases including clinical information to enable a differential diagnosis for etiology of the liver event. Finally, we suggest that the sponsor follow-up on the

MEMORANDUM

To: **Marlene Swider, MHSA**
Division of Gastroenterology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **December 13, 2007**

Re: **Comments on draft labeling for Tysabri (natalizumab) injection**
BLA 125104/33

We have reviewed the proposed label for Tysabri (FDA version received 12/9/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

HIGHLIGHTS

- *"These highlights do not include all the information needed to use TYSABRI® (natalizumab) safely and effectively. See full prescribing information for TYSABRI."*

  Please delete both the "®" symbol and the established name from this line. If trademark or copyright symbols are used in the label, they may appear only upon first use of the tradename in the Full Prescribing Information (FPI) instead of in Highlights.

  An extra hard return should be inserted after "See full prescribing information for Tysabri" to make the product title line below easier to read.

- *"TYSABRI (natalizumab) INJECTION FOR INTRAVENOUS USE"*

  Please change "INJECTION FOR INTRAVENOUS USE" to all lower case lettering.

- A hard return should be inserted between the "Initial U.S. Approval" line and the beginning of the Boxed Warning.

- The preferred formatting for the dashed lines around the section headings in Highlights is to have them span the entire length of the column. Please revise.

Recent Major Changes

- This section of Highlights included changes to only five sections of labeling: Boxed Warning, Contraindications, Warnings and Precautions, Indications and Usage, and Dosage and Administration. As such, the lines for [redacted] (b) (4)

- The preferred formatting for Recent Major Changes is to include the subsection title that contains the changes, not just the main section title. We recommend:

Indications and Usage	
Crohn's Disease (1.2)	1/2008
Warnings and Precautions	
Progressive Multifocal Leukoencephalopathy (5.1)	1/2008
Distribution Program for TYSABRI (5.2)	1/2008
[redacted] (b) (4)	1/2008

Indications and Usage

- [redacted] (b) (4)

- *"As monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS) to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies."*

  [redacted] (b) (4)

  Note that we also removed "(MS)" from the first bullet because it is defined in the subheading.

- [redacted] (b) (4)

- (b) (4)

Dosage and Administration

- (b) (4)

  We suggest a slight reorganization of these two bullets to keep all the administration information together, followed by the monitoring recommendations. We recommend:

  - 300 mg infused intravenously over approximately one hour, every four weeks. Do not give as an IV push or bolus. (2.1, 2.2)
  - Observe patients during the infusion and for one hour afterward. (2.4)

- The cross-reference at the end of the last bullet in this section should be 2.2, not 2.1.

Warnings and Precautions

- The first bullet about the PML risk is slightly wordy and length for Highlights. There is also some identical information to what already appears in the boxed warning. We recommend (b) (4)

- *"Anaphylaxis or serious allergic reactions have occurred (5.3)"*

  This statement should be the second bullet in this section. It currently appears at the end of the PML bullet.

- Each topic discussed in this section should state the risk and then give a clinical recommendation on how to avoid/mitigate/treat it. As such, we recommend revising this statement to:

  Hypersensitivity reactions: Serious allergic reactions (e.g., anaphylaxis) have occurred. Permanently discontinue TYSABRI if such a reaction occurs. (5.3)

- *"Immunosuppression/Infections - TYSABRI may increase the risk for certain infections (5.4)"*

As above, we recommend revising to something similar to:

> Immunosuppression/Infections: Monitor patients for development of infections due to increased risk with use of TYSABRI. (5.4)

Patient Counseling Statement

- *"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide."*

(b) (4)

Revision Date

- Please ensure that the proper month/year of approval for this label is filled in.

CONTENTS

- *"FULL PRESCRIBING INFORMATION: CONTENTS*"*

  Please correct the font size for this line to match the rest of the section.

- The title for section 15 should be "REFERENCES" (plural) even if there is only one reference there. Also, please make the word in all upper case lettering.

- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.

FULL PRESCRIBING INFORMATION

- The text in the FPI that corresponds to the new information from "Recent Major Changes" must have a vertical line inserted in the left margin next to it.

Boxed Warning

- A cross-reference to section 5.1 should be added to the end of the first paragraph in the boxed warning.

1.1 Multiple Sclerosis

- Because the warning against combination use with immunosuppressants in included in Highlights as a limitation of use under Indications and Usage, it should appear in Indications and Usage in the FPI as well.

- *"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."*

  Because a full explanation of PML appears in the boxed warning directly above this statement, we suggest deleting [redacted] (b) (4)

- *"Safety and efficacy in patients with chronic progressive multiple sclerosis have not been studied."*

  [redacted] (b) (4)

1.2 Crohn's Disease (CD)

- [redacted] (b) (4)

2.1 Multiple Sclerosis (MS)

- The cross-reference in this section should be to section 5.2, not [redacted] (b) (4) as written. The same change should be made to the first sentence of section 2.2 for CD.

2.3 [redacted] (b) (4) Instructions

- To improve readability, we recommend that the text accompanying each bullet be fully intended rather than in paragraph format. The same recommendation applies to sections 2.4 and 4.

- "[redacted] (b) (4)

  We recommend deletion of this sentence from the label. General recommendations that could apply to every drug are generally not included in labeling.

- *"The final dosage solution has a concentration of 2.6 mg/mL."*

  [redacted] (b) (4)

4 Contraindications

- *"TYSABRI should not be administered to a patient who has had a hypersensitivity reaction to TYSABRI"*

  When a contraindication exists due to hypersensitivity reactions, a brief description of the type and nature of the observed reactions should be included (along with the cross-reference to the fuller discussion in Warnings and Precautions). We suggest something similar to, "Observed reactions range from urticaria to anaphylaxis" or something similar. The intent here is to clarify that these are not theoretical, but have actually been observed.

5 Warnings and Precautions

- Throughout this section, the term "associated with" is used (e.g., "TYSABRI has been associated with hypersensitivity reactions"). We are currently discouraging the use of this phrase in labeling because it is vague and may have legal implications when used in labeling. If we believe the drug actually causes these reactions, then we should say "has caused" or something similar, as appropriate. Please revise throughout this entire section.

5.1 Progressive Multifocal Leukoencephalopathy (PML)

- *"Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML."*

  Because PML is a rare disease and practitioners may not be familiar with its presentation, please consider adding a brief description of the "signs and symptoms suggestive of PML."

5.2 Distribution Program for TYSABRI

- *"For prescribers and patients, the TOUCH™ Prescribing Program has* (b) (4)*: MS TOUCH™ and CD TOUCH™."*

  To improve clarity, we suggest revising this sentence slightly. Saying that the program has (b) (4) could be confusing. We recommend,

  > "For prescribers and patients, the TOUCH™ Prescribing Program has two components: MS TOUCH™ (for patients with multiple sclerosis) and CD TOUCH™ (for patients with Crohn's disease)."

- *"TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the MS or CD TOUCH™ Prescribing Program [see Boxed Warning and/or contact the TOUCH™ Prescribing Program at 1- 800-456-2255]."*

  We recommend putting the contact phone number in text, rather than in the cross-reference, e.g.,

TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the MS or CD TOUCH™ Prescribing Program. Contact the TOUCH™ Prescribing Program at 1-800-456-2255 *[see Boxed Warning]*.

- "[redacted (b) (4)]."

  Saying that prescribers "[redacted (b) (4)]" this information seems awkward for labeling. Please consider revision.

- [redacted (b) (4)]

  [redacted (b) (4)] Wouldn't it be more accurate to say that prescribers should "ensure that the patient receives the Medication Guide" or something similar?

5.4 Immunosuppression/Infections

- *"In CD clinical studies, opportunistic infections (pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been observed in <1% of TYSABRI-treated patients; some of these patients were receiving concurrent immunosuppressants [see Boxed Warning, Warnings and Precautions (5.1, 5.4), Adverse Reactions [redacted (b) (4)] (6.1)]."*

  The preferred formatting for cross-references is to simply give the section title and number. Thus, the reference to the Adverse Reactions section should just be "Adverse Reactions (6.1)." We note that the same formatting is used later in the section as well.

5.[redacted (b) (4)]

- [redacted]

6.1 Clinical Trials Experience

- *"In Studies CD1 and CD2 [see Clinical Studies (14.2)], the rate of any type of infection was 1.70 per patient-year in TYSABRI-treated patients and 1.44 per patient year in placebo-treated patients."*

  In this sentence under "Infections," we note that a similar sentence citing infection rates for the MS studies uses one decimal place (1.5) instead of two as is done here. For consistency, please consider if all these rates should be rounded off or not rounded off.

- [redacted (b) (4)]

What is the comparator in this sentence (i.e., more common that what)? Please consider revising for clarity.

- Please consider if the discussion of immunogenicity should be its own numbered subsection. While there is no requirement to do so, some labels have made Immunogenicity section 6.2 so it can be more easily located in Contents.

- The last two paragraphs under the section on immunogenicity discuss antibody testing. In general, recommendations for the clinician do not appear within the Adverse Reactions section, which instead reports on trial findings. If there are recommendations to perform antibody testing in particular patients, the full discussion may be more appropriate under Warnings and Precautions (and cross-references from Adverse Reactions to there).

- [redacted] (b) (4)

  The word "other" should be deleted from the beginning of this sentence.

7 Drug Interactions

- *"Ordinarily, MS patients receiving chronic immunosuppressant or immunomodulatory therapy should not be treated with TYSABRI [see Boxed Warning, Warnings and Precautions (5.1, 5.4),* [redacted] (b) (4) *(2)]."*

  The cross-reference to [redacted] (b) (4) should be deleted here. In addition, a cross-reference to Indications and Usage (where we recommend this statement also appear), should be added (e.g., "*[see Boxed Warning, Indications and Usage (1.1), Warnings and Precautions (5.1, 5.4)]*").

8.1 Pregnancy

- For this section, we recommend that the first paragraph remain as is, but that the remainder of the section be moved to "13.2 Animal Toxicology and/or Pharmacology." As is done with other sections of PLR labeling, the pregnancy section should provide a summary of the relevant findings along with clinical recommendations, and the detailed description of the animal studies should appear in 13.2 (under a subheading "Reproductive toxicology studies"). As such, we recommend a cross-reference to 13.2 be added to the end of the first sentence (beginning with "TYSABRI has been shown to reduce pup survival…").

8.5 Geriatric Use

- This section is not entirely consistent with the required wording from the labeling regulations. CFR 201.57(b)(9)(v)(1) contains additional information to be added here.

12.3 Pharmacokinetics

- This section currently presents the pharmacokinetic (PK) findings in MS patients first, followed by the same information for CD patients. It appears that most of the PK parameters (from paragraphs 1 and 3) showed similar results, and the same doses were used in both patient populations. To avoid redundancy, please consider if it would be appropriate to pool these findings and present only one set of PK data. Then, the data from the population PK studies could be presented separately if appropriate. If pooling is not appropriate, we suggest adding underlined subheadings for MS and CD to this section for clarity.

- *"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."*

  We suggest that this sentence be revised to make it clear that this was a population PK study in patients with MS. As written, this is unclear. The same change is needed in the paragraph on population PK analysis in CD patients.

  Please add the number of patients (n=XX) to this sentence.

- *"Pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency have not been studied."*

  Does this sentence apply only to CD patients or MS patients too? If it applies to all, a hard return should be added before this sentence so it appears as a new paragraph. If it applies to only CD patients, should a similar sentence be added to the MS PK discussion as well (if appropriate)?

14.1 Multiple Sclerosis

- Throughout the text and tables in this section, we recommend [redacted] (b) (4)

- Figure 1

  We recommend that this figure appear before Tables 3 and 4 because it is cited first in the text that precedes them all.

14.2 Crohn's Disease

- *"The safety and efficacy of TYSABRI were evaluated in three randomized, double-blind, placebo-controlled clinical trials in 1414 adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥220 and ≤450) [see Reference (15)]."*

  Even though section 15 contains only one reference, the title for the section must be "References" (plural).

- *"Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunosuppressants (e.g., 6-mercatopurine, azathioprine, or methotrexate) were permitted, and 89% of patients continued to receive at least one of these medications."*

  Should this sentence be accompanied by a statement that the combination therapies used in the studies are not recommended?

- Is there a reason why the results for study CD1 are presented in text while those for study CD2 are presented in a table?

15 Reference

- As noted above, the title for this section must be "References."

- Because only one reference is cited here and a number is not used in the text with the citation, we recommend deletion of "1" from this section. The reference may appear alone or may be preceded by a bullet.

16 How Supplied/Storage and Handling

- *"If not used immediately, store the TYSABRI solution for infusion at 2 to 8°C (36° to 46°F)."*

  For clarity, we recommend saying "... store the diluted TYSABRI solution..."

17 Patient Counseling Information

- As written, this section discusses only general information and hypersensitivity reactions. This section should convey a summary of all information that prescribers should convey to patients (not in patient-friendly language). Referring to the Medication Guide is inadequate to summarize these risks (e.g., PML). Section 17.1 can describe the overall recommendations as written, but we suggest 17.2 summarize the PML risk and 17.3 discuss hypersensitivity reactions. Should a 17.4 also be added about the risk of infections?

- *"Promptly report any continuously worsening symptoms that persist over several days to their prescriber [see Boxed Warning, Warnings and Precautions (5.1)]."*

(b) (4)

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

Date:	January 8, 2008
To:	Dan Shames, M.D., Acting Director Division of Gastroenterology Products (DGP)
Thru:	Gerald Dal Pan, M.D., M.H.S., Director Office of Surveillance and Epidemiology (OSE)
From:	OSE Tysabri RiskMAP Review Team Mark Avigan, M.D., C.M., Director, DDRE Jeanine Best, MSN, RN, PNP, Senior Risk Management Analyst, OSE-IO Shewit Bezabeh, M.D., Medical Epidemiologist, DDRE Ann Corken, R.Ph., M.P.H., Safety Evaluator, DDRE Mary Dempsey, Project Management Officer, OSE-IO Claudia B. Karwoski, Pharm.D., Risk Management Team Leader, OSE-IO Mary Willy, Ph.D., Senior Risk Management Analyst, OSE-IO
Subject:	Revised Tysabri Risk Minimization Action Plan (incorporating Crohn's Disease indication)
Drug Name(s):	TYSABRI (Natalizumab)
Application Type/Number:	BLA 125104/33
Applicant/sponsor:	Biogen Idec
OSE RCM #:	2007-431

CONTENTS

EXECUTIVE SUMMARY

This memorandum follows a request from the Division of Gastroenterology Products (DGP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Risk Minimization Action Plan (RiskMAP) for Tysabri in patients treated with Crohn's disease (CD). The Sponsor initially submitted, with the supplemental application for CD, a proposed RiskMAP for patients with CD that was essentially the same as the program already in place for Multiple Sclerosis (MS). At their presentation to the Joint Gastrointestinal Drugs Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee (AC) and in subsequent submissions to the Agency, the Sponsor proposed some modifications to the RiskMAP specifically to address concerns in CD patients.

The two versions of the Tysabri RiskMAP are entitled MS-TOUCH and CD-TOUCH, for MS and Crohn's Disease patients, respectively. There are two principal differences between CD-TOUCH and MS-TOUCH. Under CD-TOUCH, prescribers will need to evaluate the patient at 12 weeks of Tysabri treatment to determine if the patient has experienced a therapeutic benefit. Prescribers are encouraged to discontinue Tysabri in those patients who have not benefited. This will be documented by the prescribing physician and reported back to the Sponsor. This 12-week evaluation for therapeutic benefit is not required under the MS-TOUCH program. Secondly, because Tysabri will not be indicated as monotherapy in CD, concomitant therapy with systemic steroids will be permissible. However, the prescribing physician is encouraged to begin tapering systemic steroids and to discontinue Tysabri treatment in those patients who cannot be discontinued from their systemic steroids within six months of initiating Tysabri. The Sponsor has also proposed CD-specific education to infusion sites and prescribers as well as CD-specific forms.

The Sponsor has also proposed to conduct a prospective, observational cohort study of CD patients to be treated with Tysabri in the United States. The primary objective of the study is to determine the incidence and pattern of serious infections, malignancies, and other serious adverse events (SAEs) with longer-term use of Tysabri in CD. The full protocol has not yet been submitted for review, but the Agency and the Sponsor have agreed on the sample size. This study will be outlined in the approval letter as a postmarketing commitment.

OSE finds the Tysabri RiskMAP for CD patients acceptable and in line with the recommendations from the GIDAC/DSaRM AC with minor modifications to the December 27, 2007 Tysabri Risk Management Plan (see section 5 of this review). The Sponsor will need to work with the Agency to complete the TYGRIS-CD study protocol.

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 MS to reduce the frequency of clinical exacerbations. Its mechanism of action is inhibition of the alpha-4 integrin-mediated transvascular migration of leukocytes. The recommended dose of Tysabri is 300mg IV infusion administered every 4 weeks.

Marketing was voluntarily suspended and clinical trials were placed on hold on February 28, 2005 after two patients enrolled in a long-term clinical trial developed progressive multifocal leukoencephalopathy (PML). 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]

The risk of Tysabri-associated PML 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 about 4,300 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).[2]

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 (PCNS) 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 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 exclusively at authorized infusion centers, 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 monotherapy indication, and a performance-linked access systems (PLAS)[3] RiskMAP that is consistent with the PCNS Advisory Committee's recommendations. The Tysabri RiskMAP is titled the "TOUCH (Tysabri Outreach: Unified Commitment to Health) Prescribing Program."

The Supplemental BLA for Tysabri for Crohn's Disease (CD) was submitted on December 14, 2006. On July 31, 2007 a Joint Meeting of the GIDAC and the DSaRM AC convened to consider the efficacy, safety, and proposed RiskMAP of Tysabri in the treatment of CD. The AC recommended that the FDA approve Tysabri for the treatment of CD. AC members additionally recommended the following:[4]

- Use of Tysabri for CD should be restricted to patients who have had an inadequate response to all available therapies (specifically including immunosuppressants, steroids, and TNF-alpha inhibitors, or who are intolerant to these therapies, or for whom these therapies are contraindicated).

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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.

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

[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.

[4] OSE interpretation of recommendations based upon Final Minutes of the Joint GIDAC/DSaRM Meeting, July 31, 2007 and the Joint GIDAC/DSaRM Meeting Transcript, July 31, 2007

- CD patients should undergo a baseline neurological exam with cognitive testing. Baseline MRIs and JC virus assays of body fluids were not considered helpful but should be performed in patients with newly emerging neurologic symptoms.
- Concomitant immunosuppressant therapy or prolonged steroid therapy should be discouraged.
- There is a continued need for intensive post-marketing surveillance and risk assessment. The AC agreed with a postmarketing observational study; however, the specifics of how the study would be designed were not discussed. There was a suggestion that the TYGRIS observational study in CD patients include a control group.

1.2 REGULATORY HISTORY

- November 23, 2004: Approval of Tysabri® (natalizumab) Injection for the treatment of patients with relapsing forms of MS
- February 28, 2005: Voluntarily suspended from U.S. market and INDs for CD, MS, and other indications were placed on clinical hold after the occurrence of two cases of PML in MS Study 1802.
- March – September 2005: Independent PML Safety Evaluation of subjects in clinical trials (additional case of PML identified in CD patient)
- September 26, 2005: Supplemental BLA for MS was submitted to FDA; granted priority review by FDA
- February 15, 2006: Clinical hold on MS trials removed.
- March 7-8, 2006: PCNS AC convened to discuss the possible return of Tysabri to the marketplace.
- March 22, 2006: Goal date extended by three months to June 28, 2006
- June 6, 2006: Tysabri approved for resumed marketing in MS patients.
- December 14, 2006: Supplemental BLA for CD was submitted to FDA.
- July 31, 2007: Joint GIDAC/DSaRM AC convened to discuss use of Tysabri for CD
- October 12, 2007: Goal date extended by three months to January 13, 2008

2 METHODS AND MATERIALS

The following Biogen Idec documents were reviewed:

- Tysabri (Natalizumab) Risk Management Plan, Serial No. 0151, dated September 7, 2007 and submitted on September 7, 2007
- Tysabri CD RiskMAP Forms, Serial No. 0156, submitted September 14, 2007
- s/BLA Amendment: Postmarketing Study Protocol Concept, Serial No.0159, September 28, 2007
- Response to RiskMAP Questions and Revised Forms, Serial No. 0161, submitted October 3, 2007
- s/BLA Amendment: Postmarketing Study Protocol Concept, Serial No.0164, October 16, 2007

- Tysabri CD RiskMAP Forms, Serial No. 0171, submitted November 9, 2007
- Sponsor commentary on the need for baseline neurological examinations and MRI scans, STN BL 125104, Serial No. 0173, submitted November 16, 20007
- TOUCH Educational Materials, Serial No. 0179, submitted December 12, 2007
- TOUCH Educational Materials, Serial No. 0181, submitted December 14, 2007
- TYGRIS CD: Response to FDA Questions, Serial No. 0182, submitted December 14, 2007
- Response to FDA comments on CD forms, Serial No. 0.184, submitted December 17, 2007
- CD Observational Study Protocol Concept, Serial No. 0.189, submitted December 26, 2007
- Tysabri (Natalizumab) Risk Management Plan, Serial No. 0190, dated December 26, 2007 and submitted on December 27, 2007
- Draft Tysabri Labeling, Serial No. 0192, submitted December 31, 2007 (and multiple earlier versions)

The Sponsor's submissions were reviewed for responsiveness to FDA comments[5] and recommendations from the members of the Joint GIDAC/DSaRM AC and for comparison to previous versions of the Tysabri RiskMAP.

3 RESULTS OF REVIEW

3.1 SPONSOR'S PROPOSED TYSABRI RISKMAP FOR CD

(b) (4)

[redacted]

[5] FDA Comments on CD-TOUCH and CD TYGRIS are provided in the attached appendices (1-4).
[6] OSE Tysabri RiskMAP Review Team. Review of Tysabri Risk Minimization Action Plan, dated July 2, 2007.

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

Date: January 8, 2008

To: Dan Shames, M.D., Acting Director
Division of Gastroenterology Products

Through: Jodi Duckhorn, MA
Team Leader/Patient Labeling and Education Team
Office of Surveillance and Epidemiology

From: Jeanine Best, MSN, RN, PNP
Senior Drug Risk Management Analyst
Office of Surveillance and Epidemiology

Subject: Tysabri Medication Guide

Drug Name(s): Tysabri (Natalizumab)

Application Type/Number: BLA 125104/033

Applicant/sponsor: Biogen Idec

OSE RCM #: 2007-431

INTRODUCTION

Biogen Idec Inc. submitted a Supplemental Biologics License Application (BLA) for Tysabri (Natalizumab) on December 15, 2006, for the treatment of Crohn's disease. Tysabri was initially approved on November 23, 2004, for the treatment of Multiple Sclerosis. Marketing was voluntarily suspended February 28, 2005, after two reports of progressive multifocal leukoencephalopathy (PML) were received in patients treated with Tysabri in combination with Avonex in Multiple Sclerosis clinical trials. Tysabri was reintroduced to the market on June 5, 2006, with approval of Supplemental BLA (015) as monotherapy treatment for relapsing forms of Multiple Sclerosis. Approval was granted under 21 CFR 601.42 (Subpart E) with restrictions for safe use under a Risk Minimization Action Plan (RiskMAP) called the TOUCH program. Approved labeling included a Medication Guide for patients.

A joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on July 31, 2007, recommended Tysabri be used only for those with moderate to severe Crohn's disease symptoms, and with the same strict controls in place for the Multiple Sclerosis indication.

MATERIAL REVIEWED

- Tysabri Medication Guide submitted December 15, 2006 with S-033 and revised throughout current review cycle
- Tysabri Prescribing Information (PI) submitted December 15, 2006 with S-033 and revised throughout current review cycle

DISCUSSION

The Tysabri Medication Guide was approved June 5, 2006, with the reintroduction of Tysabri (033), as monotherapy treatment for relapsing forms of Multiple Sclerosis. The Sponsor submitted a revised draft Medication Guide with S-033 that reflected the addition of the Crohn's disease indication and some minor editorial revisions. The Crohn's disease indication was refined during the review of S-033 and additional information was added to the Warnings and Precautions section of the PI regarding postmarketing cases of hepatotoxicity. The Tysabri Medication Guide was revised to ensure consistency with the revised information in the Prescribing Information.

RECOMMENDATIONS

Our suggested revisions to the Medication Guide include the following:

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Rockville, MD 20852
Tel. 301-827-1274

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125104/33
Name of Drug: Tysabri® (natalizumab)

Sponsor: Biogen Idec Inc.

Material Reviewed: Tysabri® (natalizumab) Carton and Container Labels

CDER Receipt Date: December 15, 2006
OBP Receipt Date: December 27, 2007

Background:

Biogen Idec Inc. has submitted a supplement to their biologics license application (BLA) for a new indication for the treatment of Crohn's disease.

Labels Reviewed:

Tysabri® (natalizumab) Carton Label
Tysabri® (natalizumab) Container Label

Review

The carton and container labels for Tysabri® (natalizumab) were reviewed, found to be adequate and approved in a previous supplement (STN 125104/15) on June 5, 2006.

Conclusions:

No changes were made to the carton and container labeling.

It is the Agency's understanding that there have been no changes to the carton and container labels since the final labels were approved on June 5, 2006. Revision of the Medication Guide is the only labeling change in this supplement. All other printing, fonts and coloring on the labels and labeling remained unchanged.

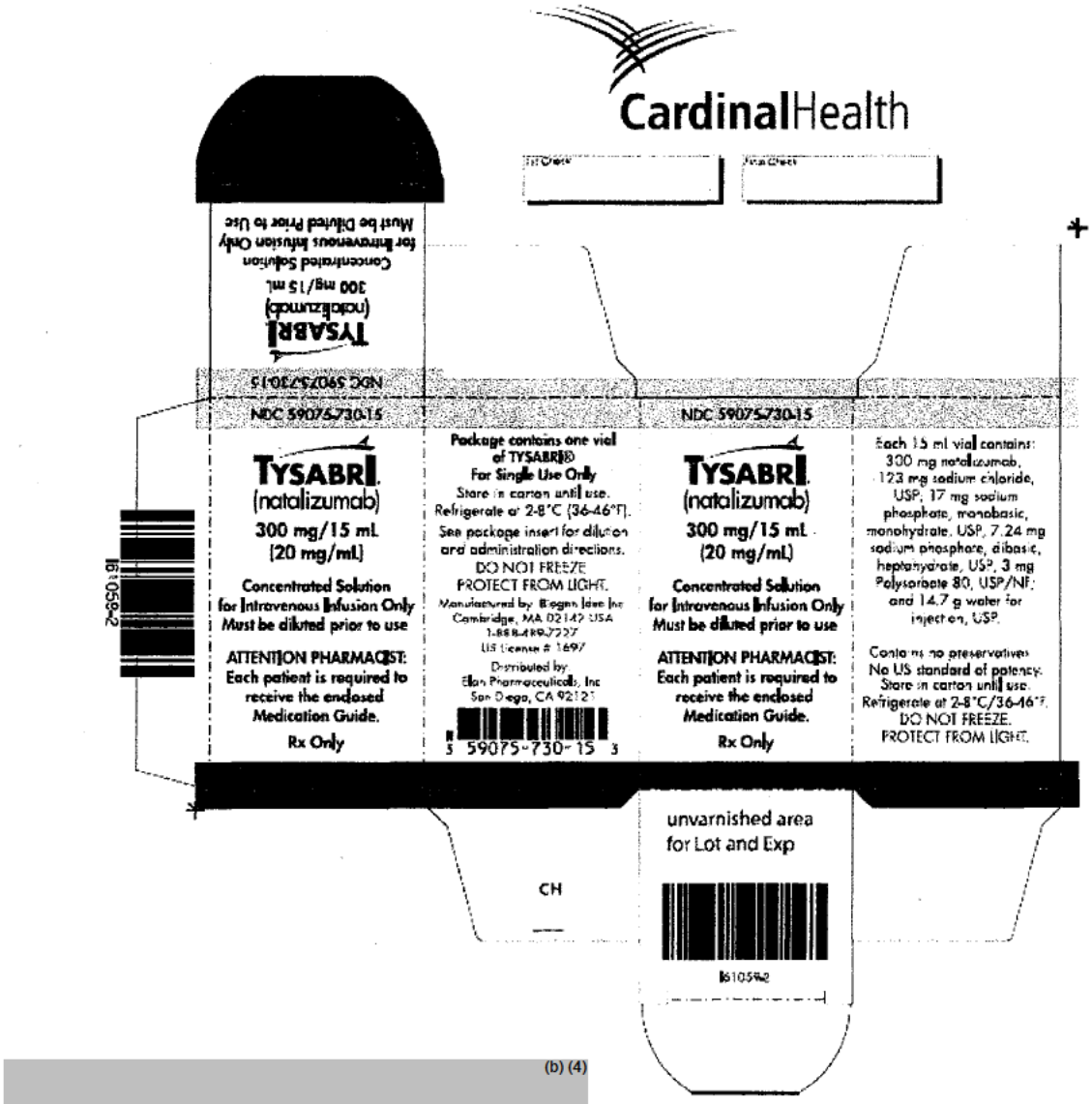
Sheila M. Rawls 1/14/08

Sheila M. Rawls
Regulatory Project Manager
CDER/OPS/OBP/IOD

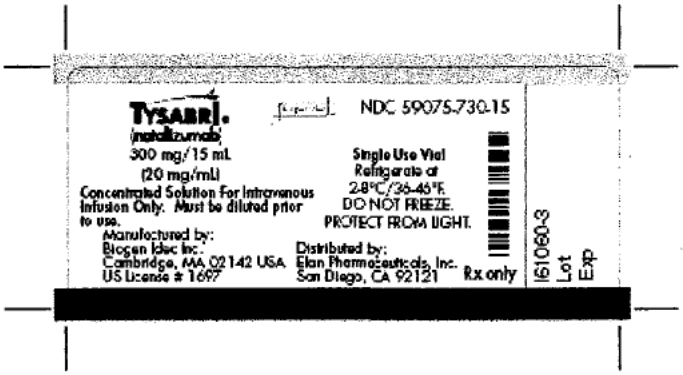
Comment/Concurrence:

Barbara Rellahan 1/14/08

Barbara Rellahan, Ph.D.
Product Reviewer
CDER/OPS/OBP/DMA


CardinalHealth
TYSABRI
(natalizumab)
300 mg/15 mL
Concentrated Solution for Intravenous Infusion Only
Must be Diluted Prior to Use
NDC 59075-730-15
TYSABRI
(natalizumab)
300 mg/15 mL
[20 mg/mL]
Concentrated Solution for Intravenous Infusion Only Must be diluted prior to use
ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.
Rx Only
Package contains one vial of TYSABRI®
For Single Use Only
Store in carton until use.
Refrigerate at 2-8°C (36-46°F).
See package insert for dilution and administration directions.
DO NOT FREEZE
PROTECT FROM LIGHT.
Manufactured by: Biogen Idec Inc
Cambridge, MA 02142 USA
1-888-BIOGEN
US License # 1697
Distributed by:
Elan Pharmaceuticals, Inc
San Diego, CA 92121
5 59075-730-15 3
Each 15 mL vial contains: 300 mg natalizumab, 123 mg sodium chloride, USP, 17 mg sodium phosphate, monobasic, monohydrate, USP, 7.24 mg sodium phosphate, dibasic, heptahydrate, USP, 3 mg Polysorbate 80, USP/NF, and 14.7 g water for injection, USP.
Contains no preservatives.
No US standard of potency.
Store in carton until use.
Refrigerate at 2-8°C/36-46°F.
DO NOT FREEZE.
PROTECT FROM LIGHT.
unvarnished area for Lot and Exp
CH

(b) (4)



PM LABEL REVIEW FOR STN 125104/33

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: January 14, 2008

From: Michael Brony, Division of Drug Marketing, Advertising, and Communications (DDMAC)

To: Marlene Swider, Division of Gastrointestinal Drug Products

Re: BLA 125104/33 TYSABRI (natalizumab)

Line 21 states:

[redacted] (b) (4) TYSABRI® should not be used with concomitant immunosuppressant therapy"

[redacted] (b) (4)

Throughout the label, there were statements like [redacted] (b) (4) for clarity, if possible, we recommend including the actual data figures to quantify the statement.

Michael Brony

1/14/08

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

MEMORANDUM

DATE: 1/14/08

FROM: Joyce A Korvick, MD, MPH Joyce Korvick was with 1/14/08

DGP/ODE III

SUBJECT: Deputy Division Director Action Recommendations

APPLICANT: Biogen Idec, Inc. (in collaboration with Elan Pharmaceuticals)

BLA/STN#: 125104/33

PRODUCT: **TYSABRI ™ (natalizumab)**

FORMULATION: 300 mg natalizumab in 15 mL solution in sterile glass vial, for dilution in saline prior to infusion.

PROPOSED REGIMEN: 300 mg intravenous infusion every four weeks.

DIVISION RECOMMENDATION:
I concur with the medical review team and medical Team Leader Memo regarding the efficacy/safety evaluation for this product. We recommend the approval of Tysabri, and the proposed labeling indication of:

"TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α"

We recommend approval under 21 CFR 601, subpart E (restricted distribution) due to serious safety issues. There is an agreed upon Risk Minimization Action Plan which is similar to the previous approval of this product for the treatment of Multiple Sclerosis. (Refer to the approval letter [1/14/08] for further details)

I. Regulatory History:

This biologic supplemental application follows the approval of Tysabri for Multiple Sclerosis. Since its original approval in 2004 cases of PML (progressive multifocal leukoencephalopathy) resulted in its being withdrawn from the market. A timeline is presented below of the major events. The current application was submitted in December 2006 and targets adult patients with moderately to severely active Crohn's disease.

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
7/31/07	Joint Gastrointestinal Drugs / Drug Safety and Risk Management Advisory Committee
1/07	Major amendment received- PDUFA goal date extended to 1/14/08

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OSE/DDMAC/DMETS/:

We have worked closely with these divisions with regard to assessment and negotiation with the sponsor of the risk management program. Because of the potential for serious adverse events related to the effects of Tysabri on the immune system, especially PML, it was agreed that Tysabri for Crohn's Disease patients be allowed on the market under a restricted access program similar to the one in place for MS. There are provisions in this plan (CD TOUCH), which are specific to the CD indication and labeling. These areas include:

- All appropriate pharmacy and infusion site 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, malignancies (in CD patients) and deaths.
- Prior to infusing a patient, the infusion site will complete the MS or CD Pre-Infusion Patient Checklist, as appropriate, and confirm prescriber clearance if needed.
- Prescriber to determine that a patient has moderately to severely active Crohn's disease with evidence of inflammation (CD Prescribers).
- Prescriber to sign and complete the CD Prescriber/Patient Enrollment form for each patient as appropriate, and to fax it to Biogen Idec before the patient can begin to receive infusions.
- Prescriber to evaluate the CD patient by 12 weeks of TYSABRI® therapy to determine if the patient has experienced a therapeutic benefit.
- Patient must complete and sign the CD Prescriber/Patient Enrollment Form, as appropriate, indicating the patient's understanding of the potential risks associated with TYSABRI® treatment.

The TOUCH™ Prescribing Program Educational Materials and forms include:

- Specific CD Patient enrollment form, CD Pre-infusion Patient Check List, CD patient Status report and Reauthorization questionnaire, patient Discontinuation Questionnaire, CD Prescribing Program Enrollment Kit, CD Patient Getting Started Brochure,
- 12-Week Questionnaire for Crohn's Disease (CD specific form for prescribers to complete to determine if patient has experienced a therapeutic benefit)
- Understanding PML for Gastroenterologists (for healthcare professionals caring for CD patients treated with Tysabri).

The TOUCH™ Prescribing Program 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. In the case of malignancies, CD prescribers will be actively queried every 6 months. 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

Please see review by OSE Tysabri RiskMAP Team for further details.

B. SEALD:

The submission of this supplement required the re-formatting of the label into the PLR format. We worked closely with the SEALD team and the Division of Neurology to ensure that the previously approved label was converted correctly, in addition there were a few proposals regarding the MS sections of the label that the Neurology Division was negotiating with the sponsor. All changes were agreed upon by both SEALD and the Division of Neurology.

C. Chemistry and Manufacturing:

Since the product currently marketed will be used in the Crohn's disease population, and there were no changes submitted to this supplement, there are no actions to be taking regarding CMC.

D. Pre-Clinical Phamacology/Toxicology:

No new data were submitted.

E. Biopharmaceutics:

The following are summary points from the Clinical Pharmacology review by A. Adebowale and C. Tomoe (for complete details refer to review).

"Noncompartmental analyses in CD patients found steady-state values of 101 μg/mL for Cmax, 10 μg/mL for trough concentration, mean t1/2 of 10

days, mean Vd of 5.2 L and Mean CL of 22 mL/hr, which were fairly similar to values found in MS patients."

"A population PK analysis in CD patients found a fall in CL by about 25% with repeated administration; antibodies occurred in about 10% of CD patients and increased CL by about 40%, which the reviewer felt could be an underestimate. The effects of weight, age, race, liver enzymes, bilirubin, and creatinine clearance were examined. Despite the finding of some statistically significant effects, the reviewers noted that the effects were minor. They concluded that the covariates had no clinically relevant effect on PK, suggesting that fixed dosing was appropriate."

"Exposure-response analyses found an inverted U dose- and exposure-response relationship for CDAI. No reason for this was identified. A trend toward higher incidence of herpes simples infection with higher exposed was observed with the probability appearing to increase for natalizumab AUCss over 20 mg*hr/mL, but no correlation with natalizumab exposure was found for serious infections, UTI's, or serious AE's."

The reviewers concluded that that the supplement was approvable from the Clinical Pharmacology standpoint, provided certain clarifying changes were made to the labeling as described in the Clinical Pharmacology Review. No Phase 4 commitment was recommended.

F. Clinical/Statistical:

Efficacy:

Two Phase 3 induction studies (Studies 301 and 307) and one Phase 3 (Study 303) maintenance study in CD were conducted.

The Clinical and Statistical reviewers concluded that Studies 301 and 307, taken together, showed superiority over placebo of Tysabri for efficacy in inducing clinical response. The reviewers also concluded that Study 303 showed superiority of Tysabri over placebo for maintenance of clinical response. The Statistical reviewer concluded the finding of efficacy in reducing steroids should be considered only exploratory. I am in agreement with this conclusion.

The commentary provided in Dr. Hyde's review summarizes the reasoning regarding our efficacy conclusions.

"Although Study 301 (indication study) did not succeed on its formal primary endpoint analysis ($p = 0.067$ after eliminating a disqualified site), Study 307 provided statistically persuasive evidence of efficacy (one study with $p < 0.001$ provides similar statistical strength of evidence as two studies with $p < 0.05$ [both two-sided]), with evidence bolstered clinically by consistency with the effect size found in the post hoc analysis of Study 301 (with nominal p-value of 0.01). The two induction studies, Study 301

and Study 307, are two well-controlled studies that, considered in the entirety of data in the supplemental application, together provide substantial evidence of the efficacy of Tysabri in inducting clinical remission in patients with moderately to severely active Crohn's disease and who have elevated CRP. The observed effect sizes of 13% more patients in clinical response in Study 301 and 16% more patients in Study 307, while not dramatic, are sufficient to be considered clinically significant."

"Given the substantial evidence of efficacy for induction, and given the clinically significant and statistically persuasive findings from the relatively large multicenter maintenance study, Study 303, there is also substantial evidence that Tysabri has efficacy as therapy for maintaining response and remission in Crohn's disease following induction with Tysabri."

"Tysabri did not show dramatically better effectiveness compared to approved therapy for Crohn's disease they way it did for MS. The effect in CD appears to be roughly on par with what has been seen in clinical studies of the TNF blockers (infliximab and adalimumab) approved for CD. Nonetheless, a substantial fraction of CD patients with moderate to severe disease fail to obtain a clinical response from TNF blockers, some patients who respond to TNF blockers develop intolerance, and TNF blockers have serious risks of their own. There is still a place for additional therapeutic options in moderate to severe CD, particularly options that may offer a different putative mechanism of action, even if they carry significant risks."

Clinical Site Inspections

As per Medical Team review, the clinical sites in Atlanta, GA (Dr. Wolf), Manchester, CT (Dr. Breiter), Vancouver, Canada (Dr. Enns), and Aarhus, Denmark (Dr. Dahlerup) were inspected. The Atlanta site participated in study CD307; the other three participated in both Study CD301 and Study CD303. At the sites in Manchester, CT, inspections found some protocol violations, errors in informed consent, and lack of source documentation for certain CDAI assessments. The DSI Reviewer recommended that the efficacy data from that site be excluded in the data analysis. The DSI Reviewer concluded that the data appeared acceptable from the other three sites. (See Clinical Inspection Summary of S. Samuels for details.) I agree with this recommendation.

Safety:

The Clinical reviewer felt that the major safety findings from the clinical studies were reasonably consistent with the safety information currently in the Tysabri labeling for MS, but he provided a revised separate table of common adverse events for CD patients. The DDRE review team, in collaboration with the DNP safety reviewers, recommended a new warning be added regarding the risk of liver injury. For full details please refer to label and reviews from the Medical Officer, OSE reviewer, and Medical Team Leader, and Neurology Reviewer.

G. Pediatric Use:

Due to the serious and relatively infrequent nature of the adverse reactions associated with Tysabri, especially PML, opportunistic infections and malignancies, it was felt that use in children not be recommended at this time. Due to requirements 21 CFR etc, the sponsor must address the pediatric development plan. This issue was discussed with the sponsor and a reasonable approach was agreed upon. We will waive the requirements for pediatric patients 5 years and younger because the necessary studies are impossible or highly impracticable due to the limited number of pediatric Crohn's disease patients in this age group. We are deferring submission of pediatric studies for ages 6 to 17 years for this application because pediatric studies should be delayed until additional safety data have been collected in the adult population. After several years marketing experience in adults the safety profile will be reviewed at that time a final decision will be made regarding waiver or deferral of these studies, based upon the safety findings for these serious and rare safety events. However, due to the requirements the studies in the older age group will be listed as PMCs at this time (see below). These issues were discussed in detail with the Pediatric Division and taken to the PERC on 1/11/2008 who agreed to this approach.

III. Advisory Committee:

On July 31, 2007 a joint Safety (DSaRM) and Gastroenterology (GIDAC) Advisory Committee was held.
For complete details refer to the AC Minutes. The following is an overview of the major topics discussed as summarized by Dr. Hyde.

"The Committee favored approval, but subject to the restrictions that it should only be for patients who had failed other therapies and that it should be subject to a restricted distribution plan like that in effect for MS. They felt that Tysabri should not be used in conjunction with other immunosuppressant drugs; that steroids should be tapered; that treatment should be stopped if Tysabri did not appear to be producing a response or if steroids could not be tapered. The neurologist on the committee recommended a complete neurological evaluation be conducted before treatment was started. The Committee did not feel there was a need to require screening for JCV or monitoring for JCV due the lack of any clear predictive value of JCV test results. The Committee endorsed the idea of collecting additional safety date in a postmarketing safety study."

IV. Labeling Recommendations:

Please see final draft labeling attached to the approval letter. Extensive discussions were conducted internally between the review team, OSE and the Neurology Division in preparation for labeling negotiations with the sponsor. All were in agreement regarding the final draft.

V. Post-Marketing Commitments:

The Applicant had 12 reportable PMC from the 2004 approval. The first two, including the commitment related to accelerated approval have been fulfilled. With the 2006 approval for reintroduction, the Application made a postmarketing commitments to conduct a registry study in MS (TYGRIS study), which is ongoing.

For the Crohn's disease supplement the commitments include pediatric studies and a registry study in Crohn's disease patients designated as TYGRIS-CD. These are summarized in the approval letter as follows:

1. Assess data anticipated from adults in protocol "TYSABRI Observational Study in Safety in CD (Crohn's Disease)" and establish a pediatric study plan that incorporates these new data. These data must be analyzed, to include an assessment of safety, before the required pediatric studies are initiated. The due date for submitting this assessment and pediatric study plan is June 30, 2012.

2. Unless FDA agrees, based on Postmarketing Commitment Number 1 above, that it is not appropriate to conduct a pediatric study in pediatric patients age 12 to 17 years, your deferred pediatric study in pediatric patients age 12 to 17 years required under section 2 of the Pediatric Research Equity Act (PREA) is considered a postmarketing study commitment. The status of this post-marketing study shall be reported annually according to 21 CFR 601.70. This commitment, in combination with the commitment listed as 3 below, are the deferred pediatric studies under PREA for the treatment of Crohn's disease in pediatric patients ages 6 to 17 years.

   The first pediatric study will enroll pediatric patients age 12 to 17 years into four study arms (placebo, 3 mg/kg, 4.5 mg/kg, and 6 mg/kg of TYSABRI administered intravenously every 4 weeks), and evaluate safety, efficacy, and pharmacokinetics of natalizumab.

   Study Start Date: December 31, 2012
   Study Completion Date: April 30, 2014
   Final Report Submission: September 30, 2014

3. Unless FDA agrees, based on Postmarketing Commitment Number 1 above, that it is not appropriate to conduct a pediatric study in pediatric patients age 6 to 11 years, your deferred pediatric study in pediatric patients age 6 to 11 years required under section 2 of the Pediatric Research Equity Act (PREA) is considered a postmarketing study commitment. The status of this post-marketing study shall be reported annually according to 21 CFR 601.70. This commitment in combination with the commitment listed as 2 above are the deferred pediatric studies under PREA for the treatment of Crohn's disease in pediatric patients ages 6 to 17 years.

   The second pediatric study will enroll pediatric patients age 6 to 11 years in a single, open-label arm (dose of TYSABRI will be selected based on results in older pediatric patients), and evaluate safety, pharmacokinetics, and response/remission rates.

Study Start Date: January 31, 2015
Study Completion Date: December 31, 2016
Final Report Submission: June 30, 2017

4. To conduct a prospective, observational study in at least 2000 subjects with Crohn's Disease who are receiving TYSABRI, with each subject followed for at least five years, by completing protocol, "TYSABRI Observational Study in Safety in CD (Crohn's Disease)." You will ensure having at least 1000 patients with two years of TYSABRI treatment, and will increase the total number of patients enrolled beyond 2000 if necessary to achieve this. The final protocol will be submitted by March 31, 2008.

   Study Start Date: June 30, 2008
   Study Patient Accrual Completion Date: June 30, 2012
   Study Completion Date: June 30, 2017
   Final Report Submission: March 31, 2018

LICENSING ACTION RECOMMENDATION

Applicant: BIOGEN, Idec. **STN:** 125104/33

Product:

TYSABRI (natalizumab)

Indication / manufacturer's change :

For inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's Disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF alpha.

■ Approval:
- ☐ Summary Basis For Approval (SBA) included
- ■ Memo of SBA equivalent reviews included
- ☐ Refusal to File: Memo included
- ☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment ☐ Inspection report included

☐ BiMo inspections completed ☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ☐ Categorical Exclusion

■ Review of labeling Date completed 01/11/08 ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: Marlene G. Swider Date: 1/14/08

Product Office's Responsible Division Director(s)*:

Barbara Kellerman PhD (quality reviewer) Date: 1/14/08

Kathleen Clouse, PhD, Dir. DMA Date: 01/14/08

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: _____

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) Marlene G. Swider Date: 1/14/08

Responsible Division Director Jorge Kerrero Date: 1/14 08
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125104/33

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

RECEIVED

FOR FDA USE ONLY

APPLICATION NUMBER

MAY 3 1 2006

CDER/DDR/TBP

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Biogen Idec, Inc.	05/23/2006
TELEPHONE NO. *(Include Area Code)* 617.679.2000	**FACSIMILE (FAX) Number** *(Include Area Code)* 617.679.4459
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 14 Cambridge Center Cambridge, Massachusetts 02134 U.S. License # 1697	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*: 125104/15

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Natalizumab	Tysabri®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
recomb.humanized anti-a4-integrin	BG00002-B

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Liquid	20mg/mL	Intravenous Infusion

(PROPOSED) INDICATION(S) FOR USE: Relapsing forms of Multiple Sclerosis

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
- ☐ NEW DRUG APPLICATION (NDA, 21 CFR 314.50)
- ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
- ☑ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
- ☐ 505 (b)(1)
- ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
- ☐ ORIGINAL APPLICATION
- ☑ AMENDMENT TO A PENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
- ☐ ANNUAL REPORT
- ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
- ☐ EFFICACY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY
- ☐ CBE
- ☐ CBE-30
- ☐ Prior Approval (PA)

REASON FOR SUBMISSION: Final Draft Medication Guide

PROPOSED MARKETING STATUS *(check one)*
- ☑ PRESCRIPTION PRODUCT (Rx)
- ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS
- ☐ PAPER
- ☐ PAPER AND ELECTRONIC
- ☑ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

No changes in establishment information

CDER/DDR

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

BB-IND 6895

MAY 2 4 2006

RECEIVED

This application contains the following items: *(Check all that apply)*	
☑	1. Index
☑	2. Labeling *(check one)* ☑ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
	☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	☐ B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense. U.S. Code, title 18, section 1001.

(b) (6)	TYPED NAME AND TITLE	DATE
	Nadine D. Cohen, Ph.D. Senior Vice President RegulatoryAffairs	05/23/2006

	Telephone Number
14 Cambridge Center Cambridge, Massachusetts 02142	617.679.3783

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

Biogen Idec, Inc.
Attention: Nadine Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

STN	Name of Biological Product
BL 125104/33	Tysabri (Natalizumab)

Reason for the submission: indication for the treatment of Crohn's disease

Date of Supplement: December 14, 2006

Date of Receipt: December 15, 2006

Action Due Date: October 15, 2007

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
http://www.fda.gov/oc/datacouncil/spl.html

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to

http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Marlene Swider, at (301) 796-2104.

Sincerely,

12/28/06

Cristi Stark, M.S.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

FEB 1 8 2007

Biogen Idec, Inc.
Attention: Nadine Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

This letter is in regard to your supplement to your biologics license application STN BL 125104/33 submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated December 14, 2006, for TYSABRI® to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your supplement today. The user fee goal date is October 15, 2007. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified the following potential review issues:

A. Clinical Issues

1. Based upon press reports in the fall of 2006, it appears that the European Medicines Agency (EMEA) has requested you to conduct an additional clinical trial to support your application for the Crohn's disease (CD) indication. Information about this clinical trial has not been provided in your submission. Please confirm that an additional clinical trial was requested by the EMEA, and if so, please state whether or not you plan to conduct the clinical trial. If you are planning to conduct the clinical trial, please provide information such as study objectives, study design, number of patients, enrollment period, endpoints, treatment duration, and study duration.

B. BioPharm Issues

1. Please submit the following datasets to support the population analysis in Report ELN100226-CD901:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

2. Please submit longitudinal PK, efficacy, and safety data from studies CD201, CD202, CD251, CD301, CD303, CD305, CD306, CD307, CD351, CD352, and CD354 in order for us to perform exposure-response modeling.

The longitudinal data (at all available time points) from the above phase II and III studies should be submitted in the following format:

Study number (integer), Patient number (integer), dose group (dose received in mg or mg/kg), Treatment group, Visit number (including dropout visit) (integer), elapsed time since first dose (hr), plasma concentration (CP), Anti-body concentration, antibody positive (0=no,1=yes), CRP concentration (mg/L), baseline CRP concentration (mg/L), use of immunosuppressants at entry into the study (0=no, 1=yes), prior infliximab exposure (0=no, 1=yes), Baseline CDAI score (numeric), CDAI score (numeric), Change in CDAI score from baseline (numeric), Clinical evaluation (0=non-responder, 1=responder), Serious adverse event (0=no, 1=yes), Serious infection (1=yes, 0=no), urinary infection (1=yes, 0=no), herpes simplex (0=no, 1=yes).

Sample of data structure

Patno	Study	Dose	Cp	Anti-body conc	Anti-body positive	Visit	Time	Baseline CRP	Immuno-suppressants (at entry)	Prior Inflix exp	Base CDAI score	CDAI score	Delta CDAI score
1	1	X	0	0	0	0	0	10.1	1	0	220	200	0
1	1	X	15	10	1	1	2.0	10.1	1	0	220	50	-150
2	2	Y	0	0	0	0	0	5.6	0	1	240	300	60
2	2	Y	10	0	0	2	4	5.6	0	1	240	310	70
2	2	Y	30	4	1	3	12	5.6	0	1	240	400	160
3	3	Z	50	3	0	1	7	15.0	1	1	250	250	0
3	3	Z	50	3	0	1	7	15.0	1	1	250	200	-50
4	4	X	0	0	0	0	0	7.0	0	0	235	235	0
4	4	X	20	1	0	1	8	7.0	0	0	235	100	-300
...													

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely,

Julieann DeBeau for Brian Strongin

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Office of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

MAR 27 2007

Biogen Idec, Inc.
Attention: Nadine Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the Patient Insert section(s) for the label of your supplement dated December 14, 2006, for TYSABRI® and have determined that the following information is necessary to take a complete action on your supplement. Please make the following changes to the sections and subsections cited below:

Labeling - Format

1. **HIGHLIGHTS OF PRESCRIBING INFORMATION**

(b) (4)

Limit the length of the **HIGHLIGHTS** to one-half page in two-column format. Your submitted labeling occupies more than one-half for this section.

Reword the second sentence of your first paragraph to read: "See **full prescribing information for Tysabri**."

Include the dosage form and route of administration, "(b) (4)" in bold on the next line under the TYSABRI® (natalixumab) name.

The "**Initial U.S. Approval 2004**," phrase requires bolding.

Within the **Boxed Warning**, please keep bold font but also utilize italics for the "***See full prescribing information for complete boxed warning***" phrase. Also, include the references for first and second paragraph as you did for the third paragraph (i.e., (5.1)).

Use of command language is recommended throughout the label. Please substitute "(b) (4) …" within the **Boxed Warning** with "Monitor patients on TYSABRI®…"

Add a white space line between each major heading.

Changed sections under **RECENT MAJOR CHANGES** must be listed under this heading in Highlights for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period.

Under **INDICATIONS AND USAGE**, please merge first and second sentence to read: (b) (4)" from the second sentence. Also, the "Important Limitations:" subheading should not be bolded.

Include (b) (4) **DOSAGE AND ADMINISTRATION** summary.

Under **DOSAGE FORMS AND STRENGTHS**, substitute "per" for the "/" symbol to read: "300mg per 15 ml vial." FDA has identified instances where the "/" symbol is confused with a number 1. (Refer to the Institute for Safe Medication Practices (ISMP's) web site (http://www.ismp.org/Tools/abbreviationslists.pdf) for list of error-prone abbreviations, symbols, and dose designations.

In the **ADVERSE REACTIONS** last sentences, please delete Biogen and Elan's general web sites and substitute a dedicated adverse event web site if you have one. If not, just delete the current general addresses. Telephone numbers will suffice.

Per 21 CFR 201.56(d)(1), please substitute the (b) (4) heading and summary with the **DRUG INTERACTIONS** and **USE IN SPECIFIC POPULATIONS** headings and summaries. Also, please include the TYSABRI® Pregnancy Exposure Registry telephone number you have in the package insert under the latter section.

Delete the word "**Section**," use capitals for the "**Patient Counseling Information**" and delete (b) (4) "

Add a colon after the word "Revised" of the last line of this section. **NOTE: The revision date at the end of highlights replaces the "revision" or "issued" date at the end of the labeling**. The revision date should not appear in both places. The only exception would be for labeling with an approved patient package insert (PPI) that is a separate document or intended to be separated from the **FULL PRESCRIBING INFORMATION** (FPI). In that case, the revision date can also appear at the end of the PPI. However, a Medication Guide will always have a revision date at the end because it is required by regulation (see 21 CFR Part 208).

2. **FULL PRESCRIBING INFORMATION: CONTENTS***

WARNING – INCREASED RISK OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) title is different from the WARNING title of the **Boxed Warning**. Please select only one and consistently use it throughout the label.

The wording for the headings and subheadings used in this section must match the headings and subheadings used for the FPI section.

For subheading 8.1, delete the parenthesis information: [redacted] (b) (4)

For subheading 17.3, delete the first phrase: [redacted] (b) (4)" to read only "Medication Guide."

[redacted] (b) (4)

Add a horizontal line to divide the **FULL PRESCRIBING INFORMATION: CONTENTS*** and the following section, the FPI, if the increase in font; addition/deletion of headings and summaries; or addition of white space lines preceding each subheading makes the FPI part of the first page. (As it is now, is not needed.)

3. **FULL PRESCRIBING INFORMATION**

All new or modified text in the FPI ***must*** be marked with a vertical line ("margin mark") on the left edge. Your original submission does not include this.

All headings and subheadings must match those in the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and the **FULL PRESCRIBING INFORMATION: CONTENTS*** sections above. Sub-subheadings need to be in italics or underlined instead of bolded (e.g. under section 6.3, underline "CD clinical studies" delete bolding).

FULL PRESCRIBING INFORMATION title should appear outside and in the space preceding the **BOXED WARNING**. It is missing.

BOXED WARNING is missing the "**PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPHATY**" wording. This title must match the one in the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and the **FULL PRESCRIBING INFORMATION: CONTENTS*** Also, the summary within the **BOXED WARNING** needs to be bolded.

Bold all the numbering for subsections throughout the labeling. They are not bolded. (e.g. 2.1, 2.2, 2.3, 5.2, etc.)

The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, "[*see Use in Specific Populations (8.4)*]" not "[see *Pediatric Use (8.4)*]." The cross-reference should be in brackets. Because cross-references

are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]

WARNINGS AND PRECAUTIONS [redacted] (b) (4)

Do not refer to adverse reactions as "adverse events." (Please revise **ADVERSE REACTIONS** summary and the rest of the label accordingly.)

Create a **Clinical Trials Experience** subheading under the **ADVERSE REACTIONS** heading and include under it information from both MS clinical studies and CD clinical studies.

Under the **Post-marketing Experience** subheading of the **ADVERSE REACTIONS** heading, please include the following statement (or appropriate modification): "*The following adverse reactions have been identified during post approval use of TYSABRI®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.*"

Delete (Category C) for the **Pregnancy** subheading title 8.1 of the **USE IN SPECIFIC POPULATIONS** heading and place the following in the text on the next line: "Pregnancy Category C".

We advise addition of the same dosage description: "sterile, colorless, and clear to slightly opalescent concentrate…" from the **DESCRIPTION** summary to the [redacted] (b) (4) to facilitate identification of dosage by health professionals.

PATIENT COUNSELING INFORMATION summary must use command language (e.g. "[redacted] (b) (4)…" should read instead: "Counsel patients to understand the risks…" and "[redacted] (b) (4):" should read instead "INSTRUCT PATIENTS USING TYSABRI TO:").

Finally, at this time, there is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the **PATIENT COUNSELING INFORMATION** section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection and relocate the **17.3 MEDICATION GUIDE** heading title before the I61061-3 Issue date [XXXX] statement on line 644 of your WORD file. However, if you decide to have the PPI or MG attached (intended to be detached) or if it is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section. Be advised though that after June 30, 2007 new ruling will apply. Therefore, FDA recommends attaching the FDA approved labeling to the end of the PLR submissions. (See 21 CFR 201.57(c)(18))

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your supplement is not approvable. Review of your supplement is continuing.

Submit an updated version of the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following web site: http://www.fda.gov/oc/datacouncil/spl.html.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely,

Brian Strongin, R.Ph., M.B.A.

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Office of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

JUN 14 2007

Biogen Idec, Inc.
Attention: Nadine Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the Clinical, Statistical and Safety section(s) of your supplement dated December 14, 2006, for TYSABRI® for use in Crohn's disease (CD) and have determined that the following information is necessary to take a complete action on your supplement:

1. The term "previous medication" is used in all three studies (CD301, CD303, and CD307) and appears to be different from the terms "prior but not concomitant medication" and "prior or concomitant medication" used in Study CD307 only. In Study CD307, the numbers of subjects "previously treated" with medications (Table 15) are different from the sums of the corresponding numbers of subjects who received "prior or concomitant medications" (Table 13) and the corresponding numbers of subjects who received "prior but not concomitant" medications (Table 14). Please explain in detail how each of the three terms is defined, and clarify how the term "previous medication" differs from the other two.

2. The proportion of subjects with previous medication use is summarized in five categories of medications (ASA, immunosuppressants, steroids, anti-TNF, and antibiotics) in Table 10 of Study CD301, Table 6 of Study CD303, and Table 15 of Study CD307. The proportion of subjects with previous medication use for combinations of more than one category of medication is not included in those tables. For each of the studies CD301, CD303, and CD307, please add the following additional categories of previous medications: (1) immunosuppressants or anti-TNF; (2) immunosuppressants and anti-TNF to produce a table like the following:

Subjects who Received Previous Medications for Crohn's Disease – [Study #] - ITT Population			
Previous Medication	Placebo	Natalizumab	Overall
5-ASA Compounds	N(%)	N(%)	N(%)
Steroids	N(%)	N(%)	N(%)
Immunosuppressants	N(%)	N(%)	N(%)
Antibiotics	N(%)	N(%)	N(%)
Anti-TNF	N(%)	N(%)	N(%)
Immunosuppressants or anti-TNF	N(%)	N(%)	N(%)
Immunosuppressants and anti-TNF	N(%)	N(%)	N(%)

Please also submit an electronic dataset that includes each of the fields in the table above by subject identification number and by study number. (Note that one electronic dataset may be submitted that includes the fields from tables in Items 2, 3, 4, 6, and 7 of this Information Request Letter.)

3. The proportion of subjects treated with prior or concomitant medications is summarized by category of medication for Study CD307, but not for Study CD301 or Study CD303. Please provide this summary data for Study CD301 and Study CD303 using the same definition of "prior or concomitant medication" as that used in Study CD307, and in the same manner as in Table 13 of Study CD307, to produce a table like the following for each study:

Subjects who Received Prior or Concomitant Medications for Crohn's Disease – [Study #] - ITT Population			
Prior or Concomitant Medication	Placebo	Natalizumab	Overall
Treatment Naïve	N(%)	N(%)	N(%)
5-ASA Compounds	N(%)	N(%)	N(%)
Steroids	N(%)	N(%)	N(%)
Immunosuppressants	N(%)	N(%)	N(%)
Antibiotics	N(%)	N(%)	N(%)

Please also submit an electronic dataset that includes each of the fields in the table above by subject identification number and by study number.

4. The proportion of subjects treated with prior but not concomitant medications is summarized by category of medication for Study CD307, but not for Study CD301 or Study CD303. Please provide this summary data for Study CD301 and Study CD303 using the same definition of "prior but not concomitant medication" used in Study CD307, and in the same manner as in Table 14 of Study CD307. The proportion of subjects with prior use of more than one category of medication is not included in that table. For each of the studies CD301, CD303, and CD307, please add the following additional categories of prior but not concomitant medications: (1) immunosuppressants or anti-TNF; (2) immunosuppressants and anti-TNF, to produce a table like the following for each study:

Subjects who Received Prior but not Concomitant Medications for Crohn's Disease – [Study #] - ITT Population			
Prior but not Concomitant Medication	Placebo	Natalizumab	Overall
5-ASA Compounds	N(%)	N(%)	N(%)
Steroids	N(%)	N(%)	N(%)
Immunosuppressants	N(%)	N(%)	N(%)
Antibiotics	N(%)	N(%)	N(%)
Anti-TNF	N(%)	N(%)	N(%)
Immunosuppressants or anti-TNF	N(%)	N(%)	N(%)
Immunosuppressants and anti-TNF	N(%)	N(%)	N(%)

Please also submit an electronic dataset that includes each of the fields in the table above by subject identification number and by study number.

5. Inadequate response to a previous medication appears to be defined as the proportion of subjects that discontinued a medication prior to screening for reasons of either (1) adverse event/intolerance to the medication, or (2) unresponsiveness to the medication. The definition of inadequate response to steroids also includes dependence. It is not clear what the highest dose was, or if treatment must have occurred for a particular length of time before the subject was classified as unresponsive or intolerant to that medication. For each of the studies, please state whether the definition of inadequate response used any criteria based on the highest dose and duration of treatment for the previous medication, or describe any other criteria that were used.

6. The proportion of subjects with inadequate response to previous medications is summarized for each of the studies in five categories of medications (ASA, immunosuppressants, steroids, anti-TNF, and antibiotics). The proportion of subjects with inadequate response to previous medications by combinations of more than one category of medication is not included in the tables for those studies. For each of the studies CD301, CD303, and CD307, please add the following additional categories of inadequate response to previous medications: (1) immunosuppressants or anti-TNF, (2) immunosuppressants and anti-TNF; to produce a table like the following for each study:

Subjects with Inadequate Response to Previous Medications for Crohn's Disease – [Study #] - ITT Population			
Inadequate Response to Previous Medication	Placebo	Natalizumab	Overall
5-ASA Compounds	N(%)	N(%)	N(%)
Steroids	N(%)	N(%)	N(%)
Immunosuppressants	N(%)	N(%)	N(%)
Antibiotics	N(%)	N(%)	N(%)
Anti-TNF	N(%)	N(%)	N(%)
Immunosuppressants or anti-TNF	N(%)	N(%)	N(%)
Immunosuppressants and anti-TNF	N(%)	N(%)	N(%)

Please also submit an electronic dataset that includes each of the fields in the table above by subject identification number and by study number.

7. Results of analyses of response to natalizumab in subgroups based on baseline medications, based on prior but not concomitant medications, and based on inadequate response to previous medications are not provided uniformly for each of the studies CD301, CD303, and CD307, or for the population with elevated baseline CRP in the studies CD301 and CD303. (See Section 11.4.2.8.1 of each of the three studies.) In addition, analyses based on combination categories for immunosuppressants and anti-TNFs are not provided. For each of the three studies, and for the population with elevated baseline CRP in each of the studies CD301 and CD303, please provide the proportion of subjects achieving the primary endpoint based on the following subgroups: (1) baseline steroids; (2) baseline immunosuppressants; (3) prior but not concomitant steroids; (4) prior but not concomitant immunosuppressants; (5) prior but not concomitant anti-TNFs; (6) prior but not concomitant immunosuppressants or anti-TNFs; (7) prior but not concomitant immunosuppressants and anti-TNFs; (8) inadequate response to previous steroids; (9) inadequate response to previous immunosuppressants; (10) inadequate response to previous anti-TNFs; (11) inadequate response to previous immunosuppressants or anti-TNFs; (12) inadequate response to previous immunosuppressants and anti-TNFs; to produce a table like the following for each study:

Subgroup Analysis of Proportion of Subjects Meeting Primary Endpoint – [Study# and Population]			
	Natalizumab	Placebo	p-value
Overall	n/N (%)	n/N (%)	p-value
Concomitant:			
Steroids	n/N (%)	n/N (%)	p-value
Immunosuppressants	n/N (%)	n/N (%)	p-value
Prior but not Concomitant:			
Steroids	n/N (%)	n/N (%)	p-value
Immunosuppressants	n/N (%)	n/N (%)	p-value
Anti-TNFs	n/N (%)	n/N (%)	p-value
Immunosuppressants or anti-TNFs	n/N (%)	n/N (%)	p-value
Immunosuppressants and anti-TNFs	n/N (%)	n/N (%)	p-value
Inadequate Response to Previous:			
Steroids	n/N (%)	n/N (%)	p-value
Immunosuppressants	n/N (%)	n/N (%)	p-value
Anti-TNFs	n/N (%)	n/N (%)	p-value
Immunosuppressants or anti-TNFs	n/N (%)	n/N (%)	p-value
Immunosuppressants and anti-TNFs	n/N (%)	n/N (%)	p-value

Please also submit an electronic dataset that includes each of the fields in the table above by subject identification number and by study number. (Note that one electronic dataset may be submitted that includes the fields from tables in Items 2, 3, 4, 6, and 7 of this Information Request Letter.)

8. The study report for CD301 states, "the preparation and administration of study drug infusions were the responsibility of the pharmacist and the Investigator or designee at the site" (Section 9.4.9, Treatment Compliance). Identify the investigational sites for which the

Investigator prepared and administered study drug. Discuss how the study blind was maintained at these sites.

9. Analyses of the response rate versus severity of disease at baseline (based on baseline CDAI) were provided in categories of baseline CDAI of < 330 and ≥ 330, but not across the range of baseline CDAI. For Studies CD301, CD301, and CD307, please provide analyses of response rate by treatment versus quartiles of baseline CDAI for each study, and of response rate by treatment versus baseline CDAI as a continuous variable for each study using a method such as polynomial logistic regression. For Studies CD301 and CD303, please provide these analyses for both the ITT and the high baseline CRP populations for each study.

10. Analyses of the response rate versus baseline CRP were not provided. For Studies CD301, CD303, and CD307, please provide analyses of response rate versus quartiles of baseline CRP for each study, and of response rate versus baseline CRP as a continuous variable for each study using a method such as polynomial logistic regression.

11. The reason for the choice of the CRP cutoff value you have used, 2.87 mg/mL, is not clear. Please provide the rationale for using this cutoff value. In your response, include any statistical analyses and results that may have been used to arrive at this cutoff value definition. Also, please describe the assay method that was used and its sensitivity, state the reference values for each of the laboratories used, and describe any standardization procedures that were used.

12. In Study CD303, the proportion of smokers is not balanced across treatment groups, with approximately 27% smokers in the placebo group and approximately 17% smokers in the natalizumab group. Please analyze the results of this study with stratification based on smoking status.

13. Based on subgroup analyses in Study CD307, subjects with disease confined to the ileum had no significant treatment effect. Please provide your interpretation of this result. In your response, discuss if baseline severity of disease or other covariates may explain this result.

14. The response rates varied by region of the world, with response rates highest in Europe and lowest in North America for both Studies CD303 and CD307, and response rates highest in North America and lowest in "Rest of World" for Study CD301. Please propose an explanation for the variation in response rates by world region for Studies CD301, CD303, and CD307. In your response, discuss if baseline severity of disease, concomitant medication use, prior medication use, or other covariates may explain these results.

15. For logistic regression models that adjusted for factors used to stratify the randomization in Studies CD301, CD303, and CD307, please specify whether these factors were included as main effects only, or as main effects plus treatment interaction terms.

16. For each of the studies CD301, CD303, and CD307, please provide a Cochran-Mantel-Haenszel test of the primary endpoint. Please stratify the tests by the factors that were used

to stratify the randomization. Please include an analysis of the primary efficacy endpoint by estimating the relative risk and the 95% confidence interval for the relative risk.

17. In Study CD301, subjects who demonstrated a clinical response at Week 12 were eligible to participate in Study CD303. These subjects also had the option to participate in the follow-up phase for Study CD301 or enter Study CD351. Provide a descriptive analysis of the subjects in Study CD301 who were eligible to participate in Study CD303, but did not. To help determine whether the participants in Study CD303 are representative of all natalizumab-treated responders, compare the participants and non-participants on important characteristics both at baseline of Study CD301 and at time of candidacy for Study CD303. Comment on the representativeness of the Study CD303 participants.

18. In Table S2-1 in the Summary of Clinical Safety Source Tables, the numbers of subjects taking concomitant medications are listed by particular concomitant medication for the placebo group and the natalizumab group, but not by class of concomitant medication. Please provide a summary table showing the numbers of subjects taking concomitant medications for the placebo group and the natalizumab group, and use the following categories for concomitant medications: (1) monotherapy (defined as taking neither concomitant immunosuppressants nor concomitant steroids), (2) concomitant immunosuppressants but not steroids, (3) concomitant steroids but not immunosuppressants, (4) concomitant immunosuppressants and steroids, (5) concomitant immunosuppressants with or without steroids, and (6) concomitant steroids with or without immunosuppressants.

    For this request and in the following requests define immunosuppressants as any of the following medications: azathioprine, 6-MP, 6-TG, methotrexate, or cyclosporine.

Short-term Placebo-Controlled Treatment Studies of Active CD: Concomitant Medications		
Category	Placebo	Natalizumab
Monotherapy	N(%)	N(%)
Concomitant Immunosuppressants	N(%)	N(%)
Concomitant Steroids	N(%)	N(%)
Concomitant Immunosuppressants and Steroids	N(%)	N(%)
Concomitant Immunosuppressants with or without Steroids	N(%)	N(%)
Concomitant Steroids with or without Immunosuppressants	N(%)	N(%)

19. Analyses of adverse events by concomitant medications are based on the first four of the six categories in the table above. Please add analyses based on the fifth category, concomitant immunosuppressants with or without steroids, and based on the sixth category, concomitant steroids with or without immunosuppressants, to tables for Serious Adverse Events (Table 5-21), Infections (Table 5-22), and Serious Infections (Table 5-23) in the Summary of Clinical Safety.

Short-term Placebo-Controlled Treatment Studies of Active CD: Incidence of [Adverse Event] in Monotherapy and in Combination with Immunosuppressants and Steroids							
Preferred Term	Placebo or Natalizumab	Mono-therapy	Concomitant Immunosupp (but not steroids)	Concomitant Steroids (but not immunosupp)	Concomitant Immunosupp and Steroids	Concomitant Immunosupp with or without Steroids	Concomitant Steroids with or without Immunosupp
a	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

20. In Table S3.1 in the Summary of Clinical Safety Source Tables, the numbers of subjects taking concomitant medications are listed by particular concomitant medication in cohorts based on number of infusions but not by class of concomitant medication. Please provide a summary table showing the numbers of subjects taking concomitant medications by cohorts based on number of infusions, and use the following categories for concomitant medications: (1) monotherapy (defined as taking neither concomitant immunosuppressants nor concomitant steroids), (2) concomitant immunosuppressants but not steroids, (3) concomitant steroids but not immunosuppressants, (4) concomitant immunosuppressants and steroids, (5) concomitant immunosuppressants with or without steroids, and (6) concomitant steroids with or without immunosuppressants.

Short- and Long-Term Dosing in CD: Concomitant Medications						
Category	# Infusions					
	≥ 1	≥ 7	≥ 13	≥ 19	≥ 25	≥ 31
Monotherapy	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Concomitant Immunosuppressants	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Concomitant Steroids	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Concomitant Immunosuppressants and Steroids	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Concomitant Immunosuppressants with or without Steroids	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Concomitant Steroids with or without Immunosuppressants	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

21. Analyses of adverse events by concomitant medications were not provided for the "Short- and long-term dosing in CD" population. Please add analyses based on the six categories of concomitant medications to tables for Infections (Table 2-27) and Serious Infections (Table 2-28) in the Summary of Clinical Safety; and to tables for Upper Respiratory Tract Infections (Table S3.2-4) and Lower Respiratory Tract Infections (Table S3.2-5) in the Summary of Clinical Safety Source Tables. Please add these results in sub-fields within the fields that are categorized by number of infusions (≥ 1, ≥ 7, ≥ 13, ≥ 19, ≥ 25, and ≥ 31) to produce tables like those shown below:

Short- and Long-term Dosing in CD: Incidence of [Adverse Event] in Monotherapy and in Combination with Immunosuppressants and Steroids						
	Subjects Who Received 1 or More Infusions					
Preferred Term	Mono-therapy	Concomitant Immunosupp (but not steroids)	Concomitant Steroids (but not immunosupp)	Concomitant Immunosupp and Steroids	Concomitant Immunosupp with or without Steroids	Concomitant Steroids with or without Immunosupp
a	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

. . . . . .

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. . . . . .

	Subjects Who Received 31 or More Infusions					
Preferred Term	Mono-therapy	Concomitant Immunosupp (but not steroids)	Concomitant Steroids (but not immunosupp)	Concomitant Immunosupp and Steroids	Concomitant Immunosupp with or without Steroids	Concomitant Steroids with or without Immunosupp
a	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

22. In Study CD303, analyses of serious adverse events (in Tables 3.29a, 3.29b, and 3.29c) and infections (in Tables 3.73a, 3.73b, and 3.73c) by concomitant medications were based on the following three categories: (1) monotherapy (defined as taking neither concomitant immunosuppressants nor concomitant steroids), (2) concomitant steroids but not immunosuppressants, and (3) concomitant immunosuppressants but not steroids. Please add analyses based on the following additional categories of concomitant medications: (4) concomitant steroids with or without immunosuppressants, (5) concomitant immunosuppressants with or without steroids, and (6) concomitant steroids and immunosuppressants. Also, in those tables, immunosuppressants were defined as azathioprine, methotrexate, or 6-MP; please analyze the results based on the definition of concomitant immunosuppressants as use of any of the following medications: azathioprine, 6-MP, 6-TG, methotrexate, or cyclosporine.

CD303: Incidence of [Adverse Event] in Monotherapy and in Combination with Immunosuppressants and Steroids							
Preferred Term	Placebo or Natalizumab	Mono-therapy	Concomitant Immunosupp (but not steroids)	Concomitant Steroids (but not immunosupp)	Concomitant Immunosupp and Steroids	Concomitant Immunosupp with or without Steroids	Concomitant Steroids with or without Immunosupp
a	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

23. Although concomitant medications used are summarized by numbers of subjects across studies (see Summary of Clinical Safety Source Tables S2-1 and S3.1), prior medications used are not summarized in a similar way. Please summarize prior medication use in categories as follows: (1) no prior immunosuppressants, steroids, or anti-TNFs, (2) prior steroids (but not immunosuppressants or anti-TNFs), (3) prior immunosuppressants with or without steroids (but not anti-TNFs), and (4) prior anti-TNFs. Please provide this summary for each of the following study populations: (1) short-term placebo-controlled studies of active CD (summarize in placebo and natalizumab groups), and (2) short- and long-term studies in CD (summarize in cohorts based on number of infusions).

Short-term Placebo-Controlled Treatment Studies of Active CD: Prior Medications		
Category	Placebo	Natalizumab
No prior immunosuppressants, steroids, or anti-TNFs	N(%)	N(%)
Prior steroids (but not immunosuppressants or anti-TNFs)	N(%)	N(%)
Prior immunosuppressants (but not anti-TNFs)	N(%)	N(%)
Prior anti-TNFs	N(%)	N(%)

Short- and Long-Term Dosing in CD: Prior Medications						
Category	# Infusions					
	≥ 1	≥ 7	≥ 13	≥ 19	≥ 25	≥ 31
No prior immunosuppressants, steroids, or anti-TNFs	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Prior steroids (but not immunosuppressants or anti-TNFs)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Prior immunosuppressants (but not anti-TNFs)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Prior anti-TNFs	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

24. Although some analyses of adverse events by concomitant medications used are provided (see Tables 5-21, 5-22, and 5-23 in the Summary of Clinical Safety), similar analyses of adverse events by prior medications used are not provided. Please discuss or analyze incidence of infections based on prior medication use in categories as follows: (1) no prior immunosuppressants, steroids, or anti-TNFs, (2) prior steroids (but not immunosuppressants or anti-TNFs), (3) prior immunosuppressants with or without steroids (but not anti-TNFs), and (4) prior anti-TNFs. Please provide these analyses for each of the following study populations: (1) short-term placebo-controlled studies of active CD, (2) short- and long-term studies in CD, and (3) the maintenance study (Study CD303).

Short-term Placebo-Controlled Treatment Studies of Active CD: Incidence of Infections and Prior Medication Use					
Preferred Term	Placebo or Natalizumab	No prior immunosuppressants, steroids, or anti-TNFs	Prior steroids (but not immunosuppressants or anti-TNFs)	Prior immunosuppressants (but not anti-TNFs)	Prior anti-TNFs
a	N (%)	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)	N (%)

Short- and Long-term Dosing in CD: Incidence of Infections and Prior Medication Use				
	Subjects Who Received 1 or More Infusions			
Preferred Term	No prior immunosuppressants, steroids, or anti-TNFs	Prior steroids (but not immunosuppressants or anti-TNFs)	Prior immunosuppressants (but not anti-TNFs)	Prior anti-TNFs
a	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)

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	Subjects Who Received 31 or More Infusions			
Preferred Term	No prior immunosuppressants, steroids, or anti-TNFs	Prior steroids (but not immunosuppressants or anti-TNFs)	Prior immunosuppressants (but not anti-TNFs)	Prior anti-TNFs
a	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)

CD303: Incidence of Infections and Prior Medication Use				
Preferred Term	No prior immunosuppressants, steroids, or anti-TNFs	Prior steroids (but not immunosuppressants or anti-TNFs)	Prior immunosuppressants (but not anti-TNFs)	Prior anti-TNFs
a	N (%)	N (%)	N (%)	N (%)
b	N (%)	N (%)	N (%)	N (%)
c	N (%)	N (%)	N (%)	N (%)
d	N (%)	N (%)	N (%)	N (%)
e	N (%)	N (%)	N (%)	N (%)

25. Section 2.1.5.6 of the Summary of Clinical Safety summarizes the incidence of adverse events related to depression and suicide in multiple sclerosis patients, but does not have corresponding results for CD subjects. Please summarize and discuss the incidence of adverse events related to depression and suicide for both the short-term placebo-controlled CD study population and the short- and long-term dosing in CD population.

26. Estimates of the expected mortality rates for CD patients in the general population, and for a population of CD patients like those exposed to natalizumab in your studies, may provide information that could be of additional help in estimating the relative risk of mortality for CD patients with and without exposure to natalizumab, and may help provide a context for assessing the significance for the CD population of the risk of PML. Please provide age-adjusted mortality rates for a general CD population and for a population comparable to those exposed to natalizumab in CD studies; if possible, the severity of CD should be similar for the comparator group and the natalizumab exposed group. The estimates may be based on data obtained from published literature, established CD databases, or drug development data for natalizumab or other agents.

27. Please provide the definition of Opportunistic Infections (OI) as used in your clinical [741] trials, and confirm whether the same definition is applied to surveillance of OI in the postmarketing setting.

28. In clinical trials of your product, please provide the number of patients and total person-years of exposure to natalizumab for all subjects by indication studied (i.e., multiple sclerosis, Crohn's disease, rheumatoid arthritis, ulcerative colitis, and healthy volunteers).

29. In clinical trials of your product, please provide mean and median months of exposure to steroids, immunosuppressants, and immunomodulators by indication studied (multiple sclerosis, Crohn's disease, rheumatoid arthritis, ulcerative colitis, and healthy volunteers). For multiple sclerosis, please summarize the results in the following categories: (1) steroids, (2) interferons, and (3) non-biologic immunosuppressants or immunomodulators; please state the particular medications that are included in the category of non-biologic immunosuppressants or immunomodulators. For Crohn's disease, please summarize the results in the following categories: (1) steroids, (2) anti-TNFs, and (3) immunosuppressants (defining immunosuppressants as any of the following medications: azathioprine, 6-MP, 6-TG, methotrexate, or cyclosporine). For rheumatoid arthritis, please summarize the results in the following categories: (1) steroids, (2) anti-TNFs, (3) other biologics, and (4) immunosuppressants (please state the particular medications that are included in the category of immunosuppressants for rheumatoid arthritis patients). Please also indicate whether the medication was a prior or concomitant medication, and the particular medication used, to produce tables like those shown below:

Multiple Sclerosis: Months of Exposure (Mean, Median) to Prior or Concomitant Medications		
Medication	Prior	Concomitant
Steroids	Mean, Mdn	Mean, Mdn
Steroid 1	Mean, Mdn	Mean, Mdn
Steroid 2	Mean, Mdn	Mean, Mdn
Steroid 3	Mean, Mdn	Mean, Mdn
Non-Biologic Immunosuppressants or Immunomodulators	Mean, Mdn	Mean, Mdn
Non-Biologic IS/IM 1	Mean, Mdn	Mean, Mdn
Non-Biologic IS/IM 2	Mean, Mdn	Mean, Mdn
Non-Biologic IS/IM 3	Mean, Mdn	Mean, Mdn
Interferons	Mean, Mdn	Mean, Mdn
Interferon 1	Mean, Mdn	Mean, Mdn
Interferon 2	Mean, Mdn	Mean, Mdn
Interferon 3	Mean, Mdn	Mean, Mdn

Crohn's Disease: Months of Exposure (Mean, Median) to Prior or Concomitant Medications		
Medication	Prior	Concomitant
Steroids	Mean, Mdn	Mean, Mdn
Steroid 1	Mean, Mdn	Mean, Mdn
Steroid 2	Mean, Mdn	Mean, Mdn
Steroid 3	Mean, Mdn	Mean, Mdn
Immunosuppressants	Mean, Mdn	Mean, Mdn
Immunosuppressant 1	Mean, Mdn	Mean, Mdn
Immunosuppressant 2	Mean, Mdn	Mean, Mdn
Immunosuppressant 3	Mean, Mdn	Mean, Mdn
Anti-TNFs	Mean, Mdn	Mean, Mdn
Anti-TNF 1	Mean, Mdn	Mean, Mdn
Anti-TNF 2	Mean, Mdn	Mean, Mdn
Anti-TNF 3	Mean, Mdn	Mean, Mdn

Rheumatoid Arthritis: Months of Exposure (Mean, Median) to Prior or Concomitant Medications		
Medication	Prior	Concomitant
Steroids	Mean, Mdn	Mean, Mdn
Steroid 1	Mean, Mdn	Mean, Mdn
Steroid 2	Mean, Mdn	Mean, Mdn
Steroid 3	Mean, Mdn	Mean, Mdn
Immunosuppressants	Mean, Mdn	Mean, Mdn
Immunosuppressant 1	Mean, Mdn	Mean, Mdn
Immunosuppressant 2	Mean, Mdn	Mean, Mdn
Immunosuppressant 3	Mean, Mdn	Mean, Mdn
Anti-TNFs	Mean, Mdn	Mean, Mdn
Anti-TNF 1	Mean, Mdn	Mean, Mdn
Anti-TNF 2	Mean, Mdn	Mean, Mdn
Anti-TNF 3	Mean, Mdn	Mean, Mdn
Other Biologics	Mean, Mdn	Mean, Mdn
Other Biologic 1	Mean, Mdn	Mean, Mdn
Other Biologic 2	Mean, Mdn	Mean, Mdn
Other Biologic 3	Mean, Mdn	Mean, Mdn

For ulcerative colitis, please summarize results by particular immunosuppressant, steroid, or anti-TNF used rather than medication categories, as the number of subjects studied is only approximately ten. For healthy volunteers, please summarize results by particular immunosuppressant, steroid, or anti-TNF used rather than medication categories, as few subjects will have used these medications.

30. In clinical trials of your product, please provide an estimate of PML and other serious OI incidence and rate by indication (based on number of confirmed cases per 1,000 persons/person-years of exposure). For each patient that developed an OI, please indicate whether or not natalizumab was stopped, and whether or not the OI resolved.

31. From the postmarketing experience of your product, please provide the number of patients who have received at least one infusion of Tysabri by indication, and the total person-years exposure, for all patients and by indication.

32. From the postmarketing experience of your product, please provide the mean and median number of infusions, for all patients and by indication.

33. From the postmarketing experience of your product, please provide an estimate of PML and other serious OI incidence and rate by indication (based on number of confirmed cases per 1000 persons/person-years of exposure) for any OI's reported in the postmarketing experience. For each patient that developed an OI, please indicate whether or not natalizumab was stopped, and whether or not the OI resolved.

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a

determination that your supplement is not approvable. Review of the other section(s) of your supplement is continuing.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely,

Joyce A. Korvick, M.D., M.P.H.
Acting Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

OCT 0 1 2007

Biogen Idec, Inc.
Attention: Nadine Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the labeling and RiskMAP for your supplement dated December 14, 2006, for TYSABRI® and have determined that the following information is necessary to take a complete action on your supplement. Please make the following changes to the sections and subsections cited below:

RiskMAP

1)

2)

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely,

Joyce Korvick, MD, MPH
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

OCT 12 2007

Our STN: BL 125104/33

Biogen Idec, Incorporated
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen

Please refer to your supplement to your biologics license application submitted under section 351 of the Public Health Service Act for Tysabri (natalizumab).

We received your September 10, 2007, amendment to this supplement on September 10, 2007, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to January 13, 2008, to provide time for a full review of the amendment.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely, 10/12/07

Joyce Korvick, MD, MPH
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

OCT 29 2007

Biogen Idec, Incorporated
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen

Please refer to your supplement to your biologics license application submitted under section 351 of the Public Health Service Act for Natalizumab.

It has come to our attention that our letter dated October 12, 2007, concerning extension of the user fee goal date, contained an error. Specifically, we stated that because the receipt date of your major amendment concerning your Revised RiskMAP –(TOUCH On-Line) program was within three months of the user fee goal date, we were extending the goal date by three months to January 13, 2008. However, the correct date for this extension is **January 14, 2008** and not January 13, 2008.

We apologize for any confusion that this may have caused.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Marlène G. Swider, at (301) 796-2104.

Sincerely,

Joyce Korvick, MD, MPH
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research