Table 33: Common Adverse Events by Antibody Status, Studies 1801 and 1802[1] Combined

	Natalizumab Antibody Status		
	Negative	Transient Positive	Persistent Positive
N (%)	1084 (100)	51 (100)	75 (100)
Any adverse event	1037 (96)	49 (96)	72 (96)
Fatigue	274 (25)	14 (27)	20 (27)
Nausea	140 (13)	6 (12)	18 (24)
Rigors	22 (2)	1 (2)	17 (23)
Back pain	179 (17)	5 (10)	16 (21)
Arthralgia	179 (17)	9 (18)	14 (19)
Influenza	164 (15)	9 (18)	14 (19)
Urticaria	15 (1)	2 (4)	13 (17)
Myalgia	68 (6)	0 (0)	13 (17)
Diarrhea	128 (12)	4 (8)	12 (16)
Influenza-like illness	120 (11)	10 (20)	11 (15)
Vomiting	61 (6)	2 (4)	10 (13)
Anxiety	77 (7)	5 (10)	9 (12)
Depression	174 (16)	8 (16)	8 (11)
Cough	79 (7)	6 (12)	8 (11)
Muscle spasms	66 (6)	3 (6)	8 (11)
Fall	64 (6)	1 (2)	8 (11)
Flushing	23 (2)	0 (0)	8 (11)
Pruritus	40 (4)	4 (8)	7 (9)
Gastroenteritis, viral	63 (6)	2 (4)	7 (9)
Muscle cramp	55 (5)	0 (0)	7 (9)
Musculoskeletal stiffness	50 (5)	3 (6)	6 (8)
Pharyngolaryngeal pain	56 (5)	1 (2)	6 (8)
Abdominal pain, upper	49 (5)	0 (0)	6 (8)
Peripheral edema	33 (3)	4 (8)	5 (7)
Hypertension	21 (2)	1 (2)	5 (7)
Dyspnea	18 (2)	1 (2)	5 (7)
Tremor	32 (3)	0 (0)	5 (7)
Tachycardia	12 (1)	0 (0)	5 (7)
Sinus congestion	30 (3)	1 (2)	4 (5)
Feeling cold	8 (1)	0 (0)	4 (5)
Feeling hot	11 (1)	3 (6)	3 (4)
Seasonal allergy	35 (3)	2 (4)	3 (4)
Erythema	19 (2)	0 (0)	3 (4)
Abdominal distension	13 (1)	0 (0)	3 (4)
Hypotension	12 (1)	0 (0)	3 (4)
Irritability	11 (1)	0 (0)	3 (4)
Chest discomfort	5 (<1)	0 (0)	3 (4)
Throat irritation	6 (1)	0 (0)	2 (3)

[1] Includes all events, except neurologic events typically associated with multiple sclerosis, which occurred in at least 2 (3%) of subjects who were persistently antibody-positive and which occurred with an incidence at least 2% higher in persistently antibody-positive subjects compared to antibody negative subjects; table also includes some events of interest (e.g., depression) which do not meet these criteria, but are of particular interest because of either the study population or the mechanism of action of natalizumab; above data are derived from analyses by the applicant.

Events that are generally associated with allergic reactions (e.g., rigors and urticaria) are much more common in subjects who are persistently antibody-positive than in subjects who are antibody negative. Antibody status does not have a clear correlation with the rate of infection. Subjects who are antibody-positive have slightly lower rates of depression. However, as for most of the types of events in the above table, the number of events is low, making interpretation difficult.

7.1.10.3 Antibody Status and Efficacy Outcomes

The relationships between relapse rate, MRI findings, and antibody status are shown in Table 34, based on 1-year data provided by the applicant. In this analysis, one fewer subject is characterized as transiently antibody-positive, and one fewer subject is classed as persistently antibody-positive, relative to Table 31, which is based on data submitted as part of the 120-day Safety Update (Amendment 12 to the original application).

Table 34: Primary and Secondary Outcome Measures by Antibody (Ab) Status

	Study 1801				Study 1802			
		Natalizumab			Placebo + Avonex®	Natalizumab + Avonex		
	Placebo	Ab -	Transient antibody +	Persistent antibody +		Ab -	Transient antibody +	Persistent antibody +
N	315	569	19	37	582	514	31	37
Relapse rate	0.698	0.223	0.276	0.462	0.746	0.333	0.420	0.536
Proportion of relapse-free subjects; N (%)	166 (53)	443 (78)	14 (74)	17 (46)	265 (46)	351 (68)	16 (52)	23 (62)
Number of gadolinium-enhancing lesions (mean)	1.2	0.1	0.0	0.6	0.8	0.1	0.1	0.7
Number of new or newly enlarging T2 lesions (mean)	6.1	1.1	0.7	3.3	2.1	0.4	0.7	1.8

For each of the primary and secondary outcome measures, subjects who are antibody-positive appear to have outcomes intermediate between the relatively favorable outcomes in subjects who are antibody negative and the relatively unfavorable outcomes in subjects who received placebo. Subjects with transient antibody positivity tend to have outcomes intermediate between subjects with persistent antibody positivity and subjects who are consistently antibody negative. This indirect correlation between antibody positivity and improvement in outcome is generally consistent across the above outcome measures in both studies.

The applicant provided additional analyses to demonstrate the relationship between antibody status and relapse rate. For subjects who became persistently antibody-positive in Study 1801, the annualized relapse rate following the first appearance of antibody was 0.75, similar to the relapse rate of 0.74 in subjects who received placebo. For subjects who became persistently antibody-positive in Study 1802, the annualized relapse rate following the first appearance of antibody was 0.60, intermediate between the relapse rate of 0.78 in subjects who received placebo and the rate of 0.35 in subjects who remained antibody negative.

Thus, the development of antibodies, particularly persistently-positive antibodies, is strongly associated with a decrease, if not a complete loss, of efficacy of natalizumab. The development of transiently-positive antibodies appears to be associated with a smaller decrease in efficacy than is seen with persistently-positive antibodies. Although this data is sufficient to establish the importance of antibody formation with regard to natalizumab activity, the data are incomplete. Results from long-term exposure of at least two years will be necessary, along with development of a more sensitive assay to detect antibodies, to permit a more complete assessment of the importance of immunogenicity with use of natalizumab.

7.1.11 Human Carcinogenicity

Immunosuppressant drugs such as azathioprine and cyclosporine have been associated with an increased risk of malignancy. By interfering with lymphocyte trafficking, natalizumab has the theoretical potential to impair immune surveillance, thereby increasing the incidence of malignancy. In placebo-controlled MS studies, 7 natalizumab-treated subjects (0.4%) and 10 placebo-group subjects (0.9%) developed malignancies. The rate of malignancy in natalizumab-treated subjects was 0.32 per 100 person years compared to 0.65 per 100 person years in the placebo group. The malignancies are listed in Table 35.

Table 35: Malignancy Incidence in MS Studies*

	Natalizumab	Placebo
Number of subjects (N)	1617	1135
Subjects with a malignancy	7	10
Basal cell carcinoma	3	3
Breast cancer	3	2
Malignant melanoma	1	2
Malignant pleural effusion	0	1
Secretory adenoma of pituitary	0	1
Squamous cell carcinoma of the skin	0	1

* Includes all placebo-controlled MS studies, including Studies 200, 201, 202, 221, 231, 1801, 1802, and 1803 (see Section 4.2, Tables of Clinical Studies).

For the relatively limited duration of clinical exposure in the natalizumab MS development program, natalizumab is not associated with an increase in malignancy. However, the database

(see Section 7.1, Methods and Findings) does not include sufficient numbers of subjects with long-term exposure that would be needed to detect a relatively uncommon event such as malignancy. This issue will need to be reassessed when the applicant submits the final study reports for Studies 1801 and 1802.

7.1.12 Special Safety Studies

No special safety studies were included in the development of this product (see Section 4.2, Tables of Clinical Studies).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Study 231 (see Section 10.1.1, Study 231) is the only placebo-controlled MS study that included administration of natalizumab for at least 3 months with follow-up off medication for at least 3 months. Considering the half-life of natalizumab of approximately 10 days (see Section 5.1, Pharmacokinetics) and the pharmacodynamic effects which can last for several months, follow-up for periods less than 2-3 months may be insufficient to assess drug withdrawal. In Study 231, subjects received 6 infusions of natalizumab, either 3 mg/kg or 6 mg/kg, or placebo over 20 weeks. During the 6-month treatment period, relapses occurred in 38% (27/71) of the subjects who received placebo and in 19% (13/68 in 3 mg/kg group; 14/74 in 6 mg/kg group) of the subjects who received natalizumab. During the follow-up period, relapses occurred in 35% (24/69) of the placebo-treated subjects and in 33% (44/134) of the natalizumab-treated subjects. During the 6-month follow-up, the need for steroids to treat the relapses was similar between the groups (20% natalizumab-treated versus 19% placebo-treated). This study, which provides the best assessment to date of the effect of drug withdrawal in MS subjects, shows no evidence of a rebound increase in relapses following drug withdrawal. Although Study 231 used weight-adjusted dosing, the dosing is similar to the proposed recommended fixed dose of 300 mg.

Study 231 (see Section 9.6.1, Study 231) also provides data on laboratory measures following study agent discontinuation. Increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells (Table 25; Table 26) are reversible, returning to baseline levels usually within 16 weeks after the last dose. However, Study 231 provides evidence that there may be a small rebound decrease (mean decrease $\leq 5\%$ compared to baseline) in some of these laboratory measures, particularly the total WBC and the total lymphocyte count. Although the magnitude of this rebound was small, a few subjects (≤ 4 subjects [6%] in each natalizumab group) had a shift in a specific measure (usually total WBC or total lymphocytes) from normal to low, comparing the values 4 – 7 months following natalizumab discontinuation to the baseline value. The rebound was more prominent in the 6 mg/kg group than in the 3 mg/kg group, and appears to have plateaued by 7 months following the last dose of natalizumab.

Figure 1: Time Course in Changes in Leukocytes, Study 231

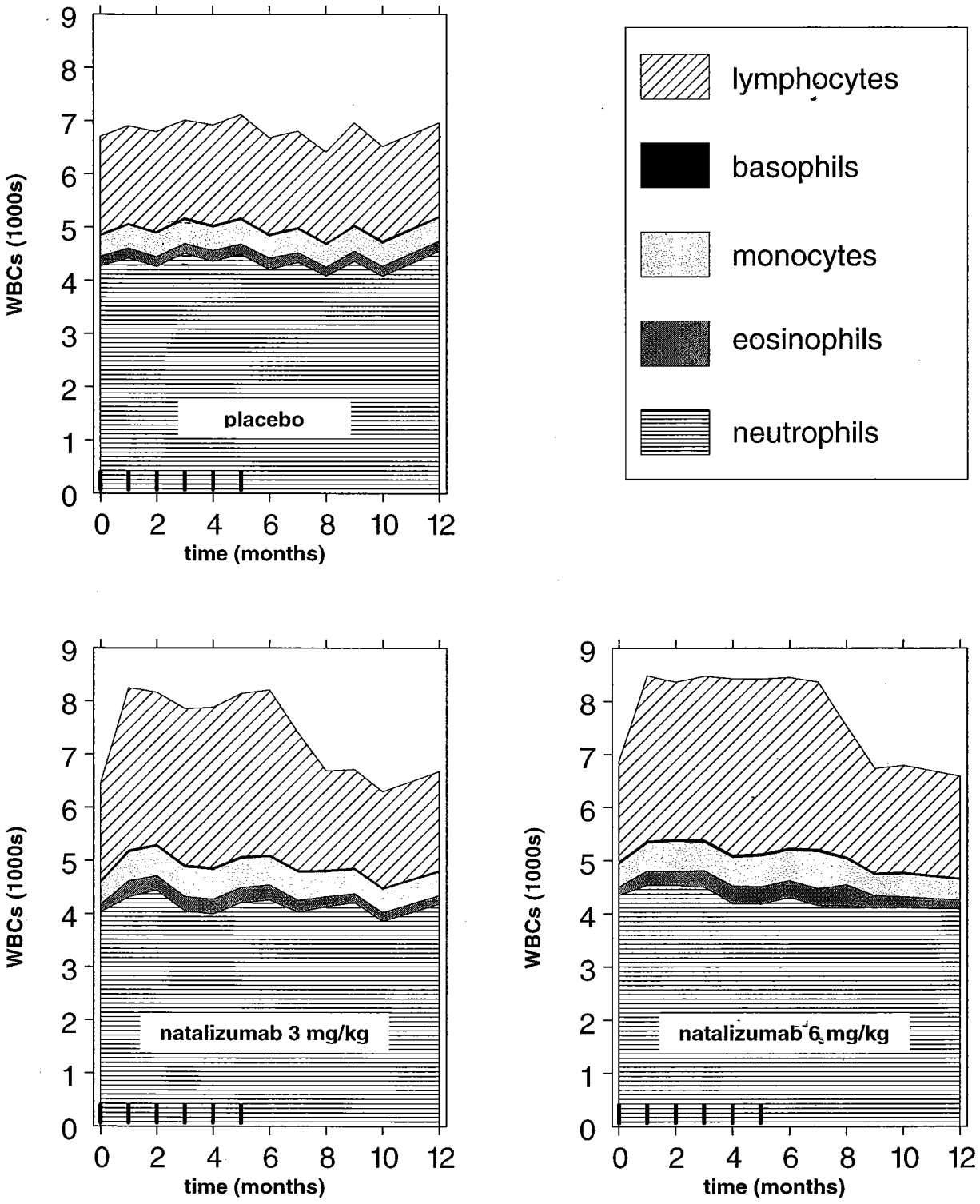

Figure 1 shows the changes in white blood cell counts that occurred with administration and discontinuation of natalizumab in Study 231. Study agent, either natalizumab (bottom panels) or placebo (top panel), was administered every four weeks for a total of six doses, designated by the short vertical hash marks extending up from the x-axis at Months 0-5 on each of the three graphs. In the placebo group, the leukocyte counts show only minor, inconsistent fluctuations. In the two natalizumab groups, the neutrophil counts remain relatively stable during the period of natalizumab administration. However, other leukocyte subsets (particularly the lymphocytes, eosinophils, and monocytes) expand rapidly following the first administration of natalizumab and remain elevated until approximately 2 – 4 months following the last dose of natalizumab. In the 6 mg/kg natalizumab group, the mean total WBC and the total lymphocyte count trend slightly lower at 12 months than at baseline, presenting weak evidence of a possible rebound effect.

Considering the dose-related frequency of this possible rebound, a rebound decrease in leukocytes is most likely to occur in patients with relatively low weight who receive the proposed fixed dose of natalizumab. In addition, the subjects in Study 231 discontinued natalizumab after receiving 6 doses over 20 weeks. Any rebound may be larger in magnitude, and either earlier or later in occurrence, in patients who take natalizumab for longer periods of time prior to discontinuing the drug. The available data are insufficient to confirm the existence of a rebound decrease in these hematology measurements. Additional long-term experience in patients who discontinue taking the 300 mg natalizumab dose will be necessary to confirm the existence of a rebound and to assess the clinical meaningfulness of any possible rebound. However, the data from Study 231 suggests that such rebounds, if they occur, are unlikely to be clinically meaningful.

The two placebo-controlled Phase 3 studies, Studies 1801 and 1802, offer an open-label follow-up study for study completers. Therefore, very few subjects who tolerate natalizumab and do well clinically while on these two studies are expected to actually withdraw from natalizumab. Subjects who discontinue study drug in Studies 1801 and 1802, either due to inability to tolerate the drug or due to adverse events, constitute a select population that will provide only limited information regarding the effect of drug withdrawal.

The potential for abuse has not been specifically studied. However, natalizumab has no known effects likely to present a high potential for abuse.

7.1.14 Human Reproduction and Pregnancy Data

Table 36 summarizes the pregnancy outcomes from all MS and CD studies of natalizumab (see Section 4.2, Tables of Clinical Studies).

Table 36: Pregnancy Outcomes

Number (%)	Multiple Sclerosis		Crohn's Disease	
	Natalizumab	Placebo	Natalizumab	Placebo
Total number of pregnancies	22 (100)	10 (100)	19 (100)	2 (100)
Spontaneous abortions	2 (9)	3 (30)	4 (21)	1 (50)
Elective abortions	9 (41)	3 (30)	4 (21)	0
Live birth	4 (18)	2 (20)	8 (42)	1 (50)
Pregnancy ongoing	7 (32)	2 (20)	3 (16)	0

There were a total of 12 live births with exposure to natalizumab. Of these 12 children, one was born prematurely at week 30 and was healthy. No congenital abnormalities or teratogenic effects have been detected. The rate of spontaneous abortion, including early pregnancy losses (miscarriages), does not exceed the expected rate within the general population of 12-22% (Garcia-Enguidanos et al, 2002). Pending additional data regarding the effects of natalizumab on pregnancy, the applicant recommends that women of childbearing potential use birth control while receiving natalizumab.

7.1.15 Assessment of Effect on Growth

Natalizumab has not been studied in the pediatric population, except in one 5 year-old girl (see Section 4.2, Tables of Clinical Studies, and Section 7.1.1, Deaths). Due to the low incidence of MS in childhood, the applicant does not currently plan to do pediatric studies of natalizumab (see Section 2.5.3, Pediatric Waiver).

7.1.16 Overdose Experience

The highest dose used in the clinical development programs was 6 mg/kg when administered to the heaviest patients (see Section 4.2, Tables of Clinical Studies). No differences in safety profiles were seen between this 6 mg/kg dose and 3 mg/kg in Phase 2 studies. For most patients (i.e., patients weighing between 50 and 100 kg), the proposed recommended natalizumab dose of 300 mg is between 6 and 3 mg/kg, respectively.

7.1.17 Postmarketing Experience

Natalizumab is not approved for use for any indication anywhere in the world. There is no postmarketing experience with natalizumab.

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

A total of 1617 multiple sclerosis patients, including 1216 in Studies 1801 and 1802, have been exposed to natalizumab with a median duration of exposure of 20 months. The total exposure to natalizumab in placebo-controlled MS and CD trials (see Section 4.2, Tables of Clinical Studies) is outlined in Table 19 (see Section 7.1, Methods and Findings). This safety review is based primarily on the experience in Studies 1801 and 1802 (see Section 6.1.3, Study Design), which are the only large, placebo-controlled clinical trials that administered the proposed recommended dose of natalizumab to MS subjects for more than 6 months.

7.2.1.1 Study Type and Design/Patient Enumeration

Table 1 and Table 2 (see Section 4.2, Tables of Clinical Studies) describe the overall clinical development of natalizumab for MS and other indications.

7.2.1.2 Demographics

Considering that MS is largely a disease of Caucasians in their 30s and 40s, demographic groups were reasonably represented, with the exception of patients of African ancestry. These subjects constituted only 2% (22/1216) of the Phase 3 database. Part of this limitation stems from the fact that only 11% and 62% of subjects enrolled in Studies 1801 and 1802, respectively, were from U.S. sites. However, nothing about the biology of MS, its typical co-morbidities, or the biologic actions of natalizumab suggest a particular susceptibility of African Americans, and the data are deemed adequate.

Demographics for Studies 1801 and 1802 are summarized in Table 3 (see Section 6.1.4.1, Baseline Characteristics). As noted above (see Section 6.1.3, Study Design), these two studies provide the primary basis for the safety review.

7.2.1.3 Extent of exposure (dose/duration)

Early clinical development of natalizumab exposed subjects to weight-adjusted dosing ranging from 0.03 – 6 mg/kg (see Section 4.2, Tables of Clinical Studies). However, the majority of these trials do not contribute significantly to either the efficacy or safety database. Studies 1801 and 1802 (see Section 6.1.3, Study Design) are the only large, placebo-controlled clinical trials that administered the proposed recommended dose of natalizumab to MS subjects for more than

6 months. The total exposure to natalizumab in placebo-controlled MS trials is outlined in Table 19 (see Section 7.1, Methods and Findings).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There is no postmarketing experience with natalizumab. The applicant did not submit any secondary source data. This review does not consider any secondary clinical data sources.

7.2.3 Adequacy of Overall Clinical Experience

This application and review rely primarily on Studies 1801 and 1802 for evidence of the safety and efficacy of natalizumab. These two studies provide placebo-controlled experience with natalizumab in 1216 subjects with multiple sclerosis and provide a sufficiently large primary database in this orphan disease (see Section 2, Introduction and Background). The number of subjects in Studies 1801 and 1802 is comparable to, or larger than, the number of subjects evaluated in pivotal clinical trials of currently-approved therapies (Avonex®, Betaseron®, Copaxone®, and Rebif®). However, the assessment of safety in this review is based on a median of 20 months of exposure to natalizumab; this duration of exposure is suboptimal, and a more complete assessment of the safety of natalizumab depends on the completion of Studies 1801 and 1802.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special toxicology studies included immunotoxicology studies, a study in juvenile monkeys, and a study of the interaction of natalizumab and Avonex®. Immunotoxicology studies of a humanized antibody are difficult to interpret because humanized proteins are often immunogenic in non-human species. In Study AN1000226, intravenous natalizumab was generally well-tolerated by juvenile cynomolgus monkeys; this study has limited relevance for the MS population, In Biogen Study #P00002-01-01, the combination of Avonex® and natalizumab was generally well-tolerated by rhesus monkeys. For additional information regarding these preclinical toxicology studies, see the Non-clinical Toxicology review of this application by Dr. Barbara Wilcox.

7.2.5 Adequacy of Routine Clinical Testing

The methods for acquisition of laboratory, vital sign, ECG, immunogenicity, and adverse event data in Studies 1801 and 1802 are described in Sections 7.1.7 (Laboratory Findings), 7.1.8 (Vital Signs), 7.1.9 (Electrocardiograms (ECGs)), 7.1.10 (Immunogenicity), and 7.1.5 (Common Adverse Events). These methods were adequate to assess the safety of natalizumab.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

A discussion of the interaction of natalizumab with interferon β-1a (Avonex®) and with glatiramer acetate (Copaxone) is available in Section 5, Clinical Pharmacology, and in the Clinical Pharmacology review of this application by Dr. Iftekhar Mahmood.

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

The anticipated adverse events for natalizumab, a humanized monoclonal antibody that inhibits the migration of white blood cells, include infections, malignancy, and adverse events related to immunogenicity. The applicant's assessment of these events is considered in Sections 7.1.5 (Common Adverse Events), 7.1.10 (Immunogenicity), and 7.1.11, (Human Carcinogenicity).

The sponsor has not adequately studied the following safety issues:

- The effect of natalizumab on pregnancy outcomes (see Section 7.1.14, Human Reproduction and Pregnancy Data), including the postnatal health status of the children. This issue is of great importance, particularly considering that many patients with MS are women with child-bearing potential.

- The effect of natalizumab on neoantigen immunization and on recall antigen responses. As an immunosuppressant, natalizumab may interfere with the ability to generate a beneficial response to a vaccine, such as the influenza or pneumococcal vaccines. For MS patients with advanced disability, such immunizations are currently incorporated into routine care.

- The effect of immunogenicity on the safety of natalizumab. The current assay for antibodies to natalizumab is relatively insensitive, and a more sensitive assay is necessary (see Section 7.1.10, Immunogenicity) to more fully assess the safety of natalizumab.

See Section 9.3.2, Required Phase 4 Commitments.

7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review is generally very high quality, including two large, multicenter, randomized, double-blind, placebo-controlled, Phase 3 trials (Studies 1801 and 1802). However, this review is based on partial results from these two Phase 3 trials, which are both ongoing.

7.2.9 Additional Submissions, Including Safety Update

The original application was submitted on 5/28/04. The applicant submitted the following amendments with data and analyses relating to the safety of natalizumab:

- Amendment 2 (submitted 7/29/04) contains a final study report for Study 1803 (see Section 9.6.2, Study 1803).

- Amendments 3, 7, 11, 27, 31, 32, 33, 34, and 36 contain safety information (see Section 4.1, Sources of Clinical Data) provided by the applicant in response to CDER information requests.

- Amendment 12 (submitted 9/23/04) contains a 120-day Safety update, which includes Study 1801 safety data through March 1, 2004 and Study 1802 safety data through April 15, 2004 (see Section 7.1, Methods and Findings).

Review of each of these amendments has been incorporated into this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Important adverse events that are likely to be treatment-related include infections, hypersensitivity reactions, depression, menstrual disorders, headache, and fatigue (see Section 7.1.5, Common Adverse Events). Very few of these adverse events were either severe or serious adverse events (see also Section 7.1.4, Other Serious Adverse Events).

7.3.1 Infections

The incidence of urinary tract infections, gastroenteritis, lower respiratory tract infections, vaginitis, and tonsillitis, was increased in subjects who received natalizumab. These infections were generally routine and did not have a complicated course.

7.3.2 Hypersensitivity Reactions

Natalizumab has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) at an incidence of <1%. These reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Many of these reactions are associated with antibodies to natalizumab (see Section 7.1.10, Immunogenicity).

7.3.3 Elevated Liver Function Tests

Currently available interferon beta therapies for MS are associated with liver function abnormalities (see Section 2.2.1, Immune Modulators Approved for Treatment of MS). The

potential for natalizumab to cause liver abnormalities raises the possibility of synergistic hepatotoxicity if natalizumab is co-administered with available agents. However, the safety data suggests that natalizumab alone, and in combination with an interferon beta, causes relatively minor, if any, hepatotoxicity (see Sections 7.1.3.1 Overall profile of dropouts, 7.1.2 Other Serious Adverse Events, and 7.1.7 Laboratory Findings).

7.3.4 Depression

Currently available interferon beta therapies for MS may increase the risk of depression. The potential for natalizumab to cause depression raises the possibility of synergistic toxicity if natalizumab is co-administered with a beta-interferon. There were small trends in favor of depression in natalizumab-treated subjects (versus control subjects), both in Study 1801 and Study 1802 (Table 23). The significance of these trends is magnified by the fact that natalizumab-treated subjects experienced fewer relapses than control subjects. Of note, the increase in the incidence of depression associated with natalizumab was not significantly altered by the co-administration of an interferon-β (Avonex®) (see Section 7.1.5.4, Common adverse event tables).

7.3.5 Menstrual disorders

Natalizumab administration was associated with an increased incidence of menstrual disorders in Studies 1801, 1802, and 1803 (see Section 7.1.5.4, Common adverse event tables, and Table 40). Specific menstrual disorders associated with the use of natalizumab include dysmenorrhea, menstrual irregularities, and amenorrhea.

7.3.6 Other Common Adverse Events

Other common adverse events included headache, fatigue, arthralgia, abdominal discomfort, and syncope. Each of these occurred only slightly more often (absolute increase of 2 - 6%) in the natalizumab groups compared to the placebo groups, and the adverse events were seldom serious (see Section 7.1.5.4, Common adverse event tables, and Section 7.1.4, Other Serious Adverse Events).

Fatigue may be a manifestation of the subject's underlying MS, rather than an effect of natalizumab. The natalizumab group had a higher incidence of fatigue in Study 1801 but a lower incidence of fatigue in Studies 231 (Table 39) and 1802. This lack of reproducibility indicates that the increased incidence of fatigue associated with natalizumab administration in Study 1801 may be a spurious finding. Such comparisons across studies can be informative, but should be viewed with caution.

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

This safety review includes some pooling of MS studies (see Section 7.1.7, Laboratory Findings). However, this review does not pool studies of natalizumab for different indications (i.e., MS and CD). Pooling was also limited to placebo-controlled studies.

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

Subjects in the two Phase 3 studies received a fixed 300 mg dose of natalizumab. Therefore, exposure to natalizumab on a mg/kg basis was inversely related to subject weight. This provided an opportunity to assess the frequencies of adverse events as a function of subject weight, i.e., the dose-dependency of adverse events. The finding of a "dose-response," that is, a higher frequency of adverse events at lower subject weight, suggests (but does not prove) that an adverse event is drug-related.

Using the manual, blinded analysis of the edited line listings for common adverse events, CDER assessed the frequencies of adverse events by subject weight quintile. Of note, some groupings of events were constructed on the basis of common pathophysiologic mechanisms, as well as indistinguishable symptom descriptions (e.g., fatigue and malaise; cold, head cold, URI, etc.).

The numbers displayed in Table 37 represent numbers of subjects with a particular event. Given that the numbers of subjects, and therefore the denominators, in each quintile are approximately equal, higher event numbers in the lower weight quintiles (and lower event numbers in the higher weight quintiles) are indicative of a more persuasive dose-response relation.

For each adverse event or event grouping, the strength of association was assessed using a least-squares approach (i.e., the slope of the relation between numbers of events and numerical quintile). Adverse events (and adverse event groupings) are listed in order of decreasing strength of the "dose-response" relation, within Study 1801.

It is important to recognize that females are over-represented at lower weight quintiles; males are over-represented at upper weight quintiles. Thus, events that tend to be are more common in females, e.g., urinary tract infection, cystitis, etc., as well as those that occur exclusively in females, e.g., vaginitis, dysmenorrhea, etc., appear to show a dose-response. In this case, however, these signals were spurious, in that they largely vanished when data from females were analyzed separately (see Table 37, bottom).

Most concerning regarding the analyses in Table 37 is the strength of the dose-response relation for the 3 upper rows of adverse events. For all 3 of these events/categories ("flu," upper respiratory infection; general infection; headache), the "dose-response" is evident in both Studies 1801 and 1802. Moreover, the "dose-response" is not evident in the control groups. Taken together, these analyses suggest (but do not prove) that the associations between infections and natalizumab, as well as headaches and natalizumab, are causally-related.

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Table 37: Dose-Dependency of Adverse Events – CDER Analysis

	Study 1801										Study 1801									
	Natalizumab					Placebo					Natalizumab + Avonex					Placebo + Avonex				
weight quintile --> (1 = low; 5 = high)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
"flu," URI, cold, head cold, pharyngitis, nasopharyngitis, nasal congestion, sore throat, respiratory tract congestion	87	86	71	59	68	37	39	43	48	54	45	41	41	35	34	46	41	45	44	54
infection	90	100	91	66	77	40	45	52	51	53	47	39	47	33	34	56	42	45	52	56
headache	59	50	44	37	39	27	35	32	34	35	25	20	22	14	16	34	27	30	33	29
urinary tract infection	23	29	21	10	8	14	16	14	7	7	12	11	9	5	4	21	11	11	11	13
MS possible relapses	45	39	40	26	27	18	28	14	24	27	45	39	33	23	25	39	27	32	39	43
migraine	10	9	5	1	3	4	4	4	4	3	3	3	5	3	2	9	3	4	7	9
paraesthesia	30	32	21	21	25	20	22	20	15	22	15	15	13	14	9	24	26	22	24	21
bronchitis, tracheitis, chest cold	16	19	11	10	10	3	8	7	6	6	7	7	7	7	6	9	3	6	7	10
gastroenteritis	12	17	14	5	8	12	9	7	9	14	6	0	5	3	2	12	8	4	10	9
urinary urgency and incontinence	22	27	18	15	18	19	17	16	13	18	8	9	7	7	5	16	19	17	20	19
fatigue or malaise	50	51	40	36	49	31	37	38	37	46	18	19	20	15	15	44	39	38	38	47
cystitis	7	6	5	2	1	1	0	0	0	0	1	4	3	0	0	1	0	0	0	0
cognitive disorders	12	11	10	5	7	9	12	15	16	18	6	6	3	4	8	15	11	14	17	13
abdominal discomfort	18	15	14	12	12	4	7	14	8	9	5	7	6	3	10	7	5	9	7	9
vaginitis	12	6	5	3	6	5	3	6	2	4	5	2	1	1	0	7	4	7	4	6
weakness/fatigue	23	34	24	17	24	21	17	22	21	20	11	16	12	12	15	28	18	21	17	19
influenza	10	15	14	5	8	3	4	1	4	3	7	7	7	2	2	6	1	3	7	2
nausea, vomiting	23	24	23	10	23	14	11	13	12	16	15	11	10	8	7	18	12	15	10	7
infection, bacterial	20	23	23	12	19	11	9	13	11	10	11	14	12	7	9	18	3	8	6	18
constipation	15	9	12	4	11	9	10	16	9	8	8	7	7	3	4	13	10	13	11	8
menstrual irregularity	8	9	5	6	3	4	4	3	1	4	1	1	1	2	2	5	3	1	1	2
impaired mobility, weakness	6	6	4	1	2	3	4	1	2	5	0	1	1	1	5	3	2	2	2	2
tremor	8	6	7	1	4	4	3	9	5	7	2	1	2	3	1	5	4	5	6	3
vertigo	9	16	11	5	8	6	6	8	8	11	3	6	3	5	3	6	8	8	7	4
dysmenorrhoea	6	4	1	0	2	2	2	2	1	2	0	0	0	0	1	5	4	3	4	1
ovarian cysts and pain	6	0	1	0	0	0	1	1	0	2	1	0	0	0	1	2	0	1	0	1
sensory disturbance	9	13	9	3	8	6	2	7	3	6	8	10	6	2	4	8	5	6	11	2
ataxia	3	9	3	3	0	5	6	3	5	4	4	3	3	1	1	5	8	5	7	7
rhinitis, congestion stuffiness	15	26	15	13	16	16	8	8	15	12	2	11	9	12	3	11	9	10	7	7
*** Events and quintiles based on females, only**																				
* vaginitis	8	8	5	2	9	3	4	3	5	5	5	1	1	2	0	6	4	4	8	6
* menstrual irregularity	6	9	5	7	4	2	3	3	4	4	1	0	1	3	2	4	4	1	0	3
* dysmenorrhoea	4	4	3	0	2	1	1	2	3	2	0	0	0	0	1	4	3	4	3	3
* ovarian cysts and pain	4	2	0	1	0	0	1	1	0	2	1	0	0	0	1	2	0	1	0	1

7.4.2.2 Explorations for Time Dependency for Adverse Findings

The applicant provided analyses of the time of occurrence of adverse events relative to the time of administration of the study agent. CDER reviewed this data for Study 1801, Study 1802, and combined results from Studies 1801 and 1802. Hypersensitivity reactions and infusion reactions occurred close to the time of study agent administration. This review did not detect any other clear association between any adverse event and the time of the most recent study agent administration.

7.4.2.3 Explorations for Drug-Demographic Interactions

The study population, like the disease population, is almost exclusively Caucasian; subjects are largely adults in their fourth or fifth decade. Thus, exploratory safety analyses for drug-demographic interactions based on race and/or age are unlikely to be fruitful. Moreover, given the age of the typical MS patient, important co-morbidities that might be expected to impact pharmacokinetics and safety (i.e., diabetes, renal and hepatic insufficiency) are uncommon, making such explorations impracticable.

CDER explored the safety database for drug-gender interactions (Table 38), using the adverse events that appear to constitute a concern, based on the review of common adverse event rates.

There are no trends to suggest a gender-specific susceptibility to adverse events (other than urinary tract infection, which is more common in females).

Table 38: Relation Between Gender and Common Adverse Events

Study 1801

	Females		Males	
	Natalizumab n=449	Placebo n=208	Natalizumab n=178	Placebo n=104
infection	319 (71%)	136 (65.4%)	105 (59%)	64 (61.5%)
infection, bacterial	72 (16%)	37 (17.8%)	25 (14%)	16 (15.4%)
pneumonia	6 (1.3%)	1 (0.5%)	4 (2.2%)	1 (1%)
depression	92 (20.5%)	32 (15.4%)	26 (14.6%)	17 (16.3%)
miscellaneous allergic reaction	21 (4.7%)	3 (1.4%)	3 (1.7%)	1 (1%)
headache	180 (40.1%)	74 (35.6%)	49 (27.5%)	23 (22.1%)
fatigue/malaise	168 (37.4%)	60 (28.8%)	58 (32.6%)	27 (26%)
elevated LFTs	21 (4.7%)	10 (4.8%)	11 (6.2%)	2 (1.9%)
urinary tract infection	82 (18.3%)	35 (16.8%)	9 (5.1%)	6 (5.8%)

Study 1802

	Females		Males	
	Natalizumab + Avonex n=442	Avonex n=420	Natalizumab + Avonex n=147	Avonex n=162
infection	189 (42.8%)	201 (47.9%)	52 (35.4%)	50 (30.9%)
infection, bacterial	47 (10.6%)	43 (10.2%)	7 (4.8%)	10 (6.2%)
pneumonia	6 (1.4%)	4 (1%)	1 (0.7%)	0 (0%)
depression	64 (14.5%)	56 (13.3%)	20 (13.6%)	18 (11.1%)
miscellaneous allergic reaction	12 (2.7%)	22 (5.2%)	3 (2%)	1 (0.6%)
headache	134 (30.3%)	126 (30%)	29 (19.7%)	27 (16.7%)
fatigue/malaise	144 (32.6%)	166 (39.5%)	45 (30.6%)	40 (24.7%)
elevated LFTs	7 (1.6%)	11 (2.6%)	7 (4.8%)	9 (5.6%)
urinary tract infection	57 (12.9%)	63 (15%)	1 (0.7%)	4 (2.5%)