

#### 7.4.2.4 Explorations for Drug-Disease Interactions

The study population consisted almost entirely of patients with relapsing-remitting MS who met McDonald criterion 1 for diagnosis. Additional exploratory safety analyses for a drug – disease interaction are unlikely to be reliable and are not warranted.

#### 7.4.2.5 Explorations for Drug-Drug Interactions

Study 1802 administered the combination of natalizumab and an interferon- $\beta$  to study subjects. The adverse event profile associated with natalizumab in Study 1802 was similar to the adverse event profile of natalizumab in Study 1801 (see Section 7.1.5.4, Common adverse event tables).

Study 1803 administered the combination of natalizumab and glatiramer acetate (Copaxone<sup>®</sup>) to MS subjects. Study 1803 included only 110 subjects randomized equally to two arms, with study agent administration for only 6 months (see Section 10.1.2, Study 1803). This study did not provide evidence of safety concerns beyond those adverse events associated with natalizumab in Studies 1801 and 1802. However, due to the relatively small sample size and brief study duration, Study 1803 provides only limited data regarding the safety of the combination of natalizumab and glatiramer acetate.

Natalizumab is associated with an increased risk of some types of infection (see Section 7.3.1, Infections, and Section 7.1.5.4, Common adverse event tables). Patients with MS often receive short courses of steroids as treatment of relapses. Corticosteroids can increase the risk of infections. The applicant provided several analyses of the incidence of infection for subjects who received natalizumab without any administration of steroids compared to the incidence of infection for subjects who received both natalizumab and at least one course of steroids. These analyses were provided separately for Studies 1801 and 1802, and included analyses for any infection, any infection within 3 months of steroid administration, and any infection within one month of steroid administration. These analyses do not suggest increased risk of infection from the combination of natalizumab with a short (three to five day course) of corticosteroids (see Section 6.1.3.1.1, Study 1801 – Design).

#### 7.4.3 Causality Determination

Adverse events that are most clearly associated with natalizumab administration include hypersensitivity reactions, depression, infections, and menstrual disorders.

- Hypersensitivity reactions. The consistent relationship of hypersensitivity reactions to immunogenicity (see Section 7.1.10, Immunogenicity), and the consistency of these hypersensitivity reactions in the natalizumab groups in Studies 1801 and 1802, provide strong evidence that natalizumab administration is causative.
- Depression. Although the increased incidence of depression associated with natalizumab was small (see Section 7.1.5.4, Common adverse event tables), the consistency of the

association in both Phase 3 studies (1801 and 1802) provides some evidence that natalizumab administration is causative.

- Menstrual irregularities. The consistency of the association of natalizumab with several different types of menstrual disorders (dysmenorrhea, amenorrhea, and menstrual irregularities), in three separate studies (1801, 1802, and 1803) (see Section 7.1.5.4, Common adverse event tables, and Table 40), provides strong evidence that natalizumab administration is causative.
- Infections. Although the increased incidence of infections associated with natalizumab administration in Study 1801 is small, an increase in clinical infections is predicted based on natalizumab's proposed mechanism of action (see Section 2.4, Important Issues With Pharmacologically Related Products). This increased risk of infections is not consistent across studies (see Section 7.1.5.4, Common adverse event tables, Table 23) but there is a dose-response relation for infections that suggests causality (Table 37).
- For other adverse events, including elevations in liver function tests, fatigue, local bleeding, and syncope, the data are weak (very small numbers of adverse events) and/or inconsistent. Strong evidence of natalizumab causation is lacking.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

Study 231 compared administration of two dose levels of natalizumab (3 mg/kg and 6 mg/kg) to placebo in a multicenter, double-blind, randomized, placebo-controlled, 3-arm study (10.1.1, Study 231). Based on the results of Study 231, the sponsor decided that there was no substantial difference in either safety or efficacy between 3 mg/kg and 6 mg/kg of natalizumab. Subsequent clinical studies of natalizumab have administered a fixed dose of 300 mg every 4 weeks.

Exploratory analyses of Studies 1801 and 1802 did not provide substantial evidence that weight-adjusted dosing would provide increased efficacy or safety (see Section 6.1.4.3.1, Primary Endpoint, Subgroup Analyses, and Section 7.4.2.1, Explorations for dose dependency for adverse findings).

The regimen of natalizumab administration every 4 weeks has been used in all large and moderately-sized MS studies of natalizumab, including Studies 231, 1801, 1802, and 1803. This regimen is based on pharmacokinetic and pharmacodynamic studies (see Section 5, Clinical Pharmacology and Dr. Iftekhar Mahmood's Clinical Pharmacology review of this application). However, the sponsor has not provided any substantial clinical trials of alternative dosing regimens.

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## 8.2 Drug-Drug Interactions

In Studies 1 and 2, short-term treatment of relapses with corticosteroids was not associated with an increased rate of infection. The safety and efficacy of natalizumab in combination with other immunosuppressive agents have not been evaluated. Patients receiving these other agents should not receive concurrent therapy with natalizumab because of the possibility of increased risk of infections.

After multiple dosing, interferon  $\beta$ -1a (Avonex<sup>®</sup>) reduced natalizumab's clearance by approximately 30%. Given that the adverse event profiles were similar in Study 1801 (without interferon  $\beta$ -1a) and Study 1802 (with interferon  $\beta$ -1a), the data suggest that natalizumab dose reduction is not necessary to avoid enhanced toxicity during co-administration of an interferon beta. (See Section 5.1, Pharmacokinetics, and Dr. Iftekhar Mahmood's Clinical Pharmacology review of this application.)

Results of studies in multiple sclerosis patients taking natalizumab and concomitant beta-interferon (Avonex<sup>®</sup>) or glatiramer acetate are inconclusive with regard to the need for dose adjustment of the beta-interferon or glatiramer acetate (see Section 5.1, Pharmacokinetics, and Dr. Iftekhar Mahmood's Clinical Pharmacology review of this application).

No data are available on the effects of vaccination in patients receiving natalizumab (see Sections 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, and 9.3.2, Required Phase 4 Commitments).

## 8.3 Special Populations

The sponsor has not adequately studied the safety and efficacy of natalizumab in patients with chronic progressive multiple sclerosis, renal insufficiency, or hepatic insufficiency, in patients aged 65 and over, or in women who are pregnant or nursing (see Sections 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, and 9.3.2, Required Phase 4 Commitments).

Natalizumab should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking natalizumab, discontinuation of natalizumab should be considered. It is not known whether natalizumab is excreted in human milk. Because many drugs and immunoglobulins are excreted in human milk, and because the potential for serious adverse reactions is unknown, a decision should be made whether to discontinue nursing or natalizumab, taking into account the importance of therapy to the mother.

## 8.4 Pediatrics

Safety and effectiveness of natalizumab in pediatric multiple sclerosis patients below the age of 18 have not been studied (see Section 2.5.3, Pediatric Waiver).

## 8.5 Advisory Committee Meeting

This application has not been discussed at a CDER advisory committee meeting.

## 8.6 Literature Review

This review does not include a comprehensive review of the literature on natalizumab.

## 8.7 Postmarketing Risk Management Plan

The applicant did not submit a proposed postmarketing risk management plan.

## 8.8 Other Relevant Materials

Review of this application included consultations from the Office of Drug Safety and the Division of Drug Marketing, Advertising, and Communications (DDMAC).

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

- a. Natalizumab has an acceptable safety profile (see Section 7, Integrated Review of Safety) for the treatment of patients with relapsing forms of MS. This assessment is based on placebo-controlled data from 1617 subjects, primarily in Studies 1801 and 1802, with a median of 20 months of natalizumab exposure.
- b. Natalizumab is effective (see Section 6, Integrated Review of Efficacy) for the treatment of patients with relapsing forms of MS, to reduce the frequency of clinical exacerbations. This assessment is based on effect size, statistical persuasiveness, and substantiation across two adequate, and well-controlled investigations. Natalizumab was associated with a decrease (66% relative reduction, 49% absolute reduction) in the relapse rate in Study 1801, and a decrease (54% relative reduction, 42% absolute reduction) in the relapse rate in Study 1802. Both of these Phase 3 studies are relatively large, multicenter, randomized, double-blind, placebo-controlled studies that provide statistically persuasive evidence of benefit. The consistency of natalizumab's effect across multiple endpoints and multiple subgroups, combined with statistically robust results in two well-designed confirmatory studies, provides compelling evidence of efficacy. The overall assessment is based on data from approximately one year of treatment in Studies 1801 and 1802.
- c. Natalizumab is immunogenic (see Section 7.1.10, Immunogenicity), and the immunogenicity impacts negatively on both the safety and efficacy of natalizumab. The safety and efficacy of natalizumab are uncertain for patients who are persistently antibody-positive.

- d. Adverse events most clearly related to natalizumab administration include hypersensitivity reactions, some infections, menstrual disorders, and depression (see Section 7, Integrated Review of Safety). Most adverse events were mild.
- e. The safety and efficacy of natalizumab beyond 1 year are unknown.
- f. The safety and efficacy of natalizumab have not been established in patients with chronic progressive multiple sclerosis, renal insufficiency, or hepatic insufficiency, in patients aged 65 and over, or in women who are pregnant or nursing.

## 9.2 Recommendation on Regulatory Action

The clinical review recommendation is for accelerated approval of natalizumab for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations. Accelerated approval permits marketing approval based on a surrogate endpoint that is reasonably likely to predict a clinically meaningful benefit.

This recommendation acknowledges that the proposed pivotal studies provide direct evidence of a benefit for only one year of natalizumab administration. The clinical meaningfulness of a decrease in the incidence of relapses at one year is uncertain. Drugs currently approved for this indication have each provided evidence of a benefit at two years in order to gain marketing approval. However, the effect of natalizumab on relapse rate in Study 1801 was approximately twice the effect observed with current first-line drugs for this indication (see Section 2.2.1, Immune Modulators Approved for Treatment of MS). Such comparisons of different agents across studies are problematic, and the public would be best served by direct comparison of natalizumab with available agents. However, the magnitude of natalizumab's effect is sufficient that the effect at one year is reasonably likely to predict a clinical benefit at two years. In this analysis, the effect at one year serves as a surrogate for the effect at two years. This evidence of effectiveness has the limitations of a surrogate, particularly the difficulty in reliably predicting the durability of natalizumab's effect at two years in the ongoing studies. Therefore, completion of the ongoing studies is essential to verify the safety and efficacy of natalizumab.

Accelerated approval requires that the new drug provides evidence of meaningful therapeutic benefit over existing treatments. Many MS patients continue to have exacerbations while taking one of the available first-line MS therapies. None of the currently available therapies have proven efficacy when used as an add-on therapy for these patients. Study 1802, and to a lesser extent Study 1803 (see Section 10.1.2, Study 1803), provide persuasive evidence that natalizumab is effective as an add-on therapy for subjects who continue to have relapses while on a first-line therapy. Therefore, natalizumab has the potential to address an unmet medical need.

The primary safety issue appears to be immunogenicity, which will require further investigation.

The recommended dose of natalizumab is 300 mg IV infusion every four weeks. Natalizumab should be infused over approximately one hour, with observation of the patients during the

infusion and for 1 hour after the infusion is complete. The infusion should be promptly discontinued upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction.

### 9.3 Recommendation on Postmarketing Actions

#### 9.3.1 Risk Management Activity

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

#### 9.3.2 Required Phase 4 Commitments

The following are recommended requests to the applicant for clinical postmarketing commitments. The first recommendation relates to the need to have improved data on the interaction of natalizumab with glatiramer acetate, an available first-line therapy for MS.

1. Please commit to conducting a pharmacokinetic study of at least 6 months duration to assess whether chronic administration of natalizumab in combination with glatiramer acetate results in a drug interaction that suggests the need for a dose adjustment of natalizumab.

The following commitment is an exploration of a potential problem with IgG4 monoclonal antibodies. Because natalizumab is the first IgG4 monoclonal antibody approved for chronic administration, the applicant is requested to explore the existence of this potential problem (see Section 2.4, Important Issues With Pharmacologically Related Products).

2. Please commit to conducting a pharmacokinetic study of the interaction of natalizumab with another IgG4 antibody to assess the generation of dual-specificity antibodies targeting both  $\alpha 4$ -integrin and the target of the other antibody.

The next two recommended commitments are components of the accelerated approval process (see Section 9.2, Recommendation on Regulatory Action).

3. Please commit to verifying that the clinical benefit of reduction in exacerbations is sustained with continued natalizumab administration. This will be accomplished by completing the ongoing studies C-1801 and C-1802 through the planned two years and submitting the results along with appropriate labeling changes.
4. Please commit to further evaluating the safety of natalizumab and the efficacy of natalizumab on physical disability. This will be accomplished by completing the ongoing 2-year studies (C-1801 and C-1802) and submitting the study results, including all safety and efficacy data, for all study subjects through Week 128 or subject withdrawal. Appropriate labeling changes will be proposed as part of this submission.

Many patients with MS are women of child-bearing potential. Therefore, the safety of natalizumab in pregnancy is a critical issue for many MS patients.

5. Please commit to conducting a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to natalizumab to identify the pregnancy outcome and postnatal health status of the children. This commitment includes submitting a revision to the label, once the design of the registry is finalized, that informs patients and physicians of the registry.

The next recommendation is for a postmarketing commitment to assess the mechanism of action of natalizumab (see Section 2.1, Product Information). This commitment reflects the need to have a better understanding of the activity of a new drug for which there is no mechanistically similar drug previously on the market.

6. Please commit to conducting a study to measure the effects of at least a six-month course of natalizumab on immune responses in subjects with relapsing forms of MS that evaluates the effect of natalizumab on percentages of lymphocytes including CD3+, CD4+, CD8+, as well as B and NK cells, and the associated  $\alpha 4$  integrin expression and binding site saturation.

The next two commitments are for postmarketing commitments to explore the effect of natalizumab, as an immunosuppressant, on the response to neoantigens and recall antigens (see Section 8.2, Drug-Drug Interactions).

7. Please commit to conducting a study of the effect of natalizumab on neoantigen immunization with respect to interval from dosing and the potential for induction of tolerance and assessment of tolerance using a series of two booster immunizations post-natalizumab clearance. If such a study provides evidence that natalizumab has an effect on neoantigen immunization, please commit to conducting a study of the effect of natalizumab on patient response to a neovaccination after withdrawal of natalizumab treatment.
8. Please commit to conducting a study of the effect of natalizumab on recall antigen responses in a chronic dosing situation, including the levels of antibody to the recall antigen and the ability of a booster immunization to raise antibody levels.

The following recommendations are for postmarketing commitments to assess the immunogenicity of natalizumab (see Section 7.1.10, Immunogenicity). The available database provides evidence that immunogenicity is an issue that impacts the safety and efficacy of natalizumab. However, the clinical meaningfulness of this immunogenicity has not been adequately established and requires further investigation.

9. Please commit to using new binding and neutralizing assays to conduct a study of the development and general time course of immunogenicity at any level of titer, and the relationship of natalizumab immunogenicity to safety events.

10. Pending the development of a new assay for antibodies to natalizumab, please commit to using your current assay to assess the immunogenicity of natalizumab by conducting a study of patients who are at least three months post-treatment so that no assay interfering natalizumab is present in serum. You will analyze this immunogenicity data with consideration of the reasons for discontinuing natalizumab and the adverse event profile of the subjects.

For CMC postmarketing commitments, see the review of this application by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang. For toxicology postmarketing commitments, see the Non-clinical Toxicology review of this application by Dr. Barbara Wilcox.

#### 9.3.3 Other Phase 4 Requests

There are no additional requests.

### 9.4 Labeling Review

Discussions between the applicant and CDER have resolved all major issues with regard to the label.

The applicant initially proposed the trade name of "Antegren." However, the Division of Medication Errors and Technical Support (DMETS) reviewed the proposal and found a potential for medication errors, particularly the potential for confusion of Antegren with Integrilin and Ativan. The applicant then proposed the trade name of "\_\_\_\_\_." However, DMETS reviewed the new proposal and found a potential for medication errors, particularly the potential for confusion of Antegren with Integrilin. The applicant then proposed, and DMETS approved, the trade name "Tysabri."

### 9.5 Comments to Applicant

None.

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

#### 10.1.1 Study 231

**Title:** A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Safety, Tolerability and Dose Evaluation Study of Intravenous Antegren™ (natalizumab) at Two Dose Levels Using Magnetic Resonance Imaging in Subjects with Multiple Sclerosis

**Objectives:** To assess the effect of natalizumab on brain lesion activity assessed by MRI in subjects with RRMS or SPMS.

**Design:** This was a multicenter (26 centers), double-blind, randomized, placebo-controlled, parallel-group study. Subjects were randomized in a 1:1:1 ratio to placebo, 3 or 6 mg/kg natalizumab IV every 4 weeks for a total of six doses, with follow-up for a total of 12 months.

**Enrollment criteria:** Study inclusion criteria required that subjects have a diagnosis of clinically or laboratory-supported definite relapsing-remitting or secondary-progressive MS; a history of at least 2 MS relapses within the previous 2 years; a baseline EDSS  $\geq 2.0$  and  $\leq 6.5$ ; a minimum of three lesions on T2-weighted MRI of the brain; and no concomitant treatment with immunosuppressant agents.

**Treatment:** Placebo or natalizumab (either 3 mg/kg or 6 mg/kg) IV once every 4 weeks for up to 20 weeks.

**Study Conduct:** 214 subjects were randomized; 213 subjects received at least 1 dose; 195 (92%) of subjects received all 6 doses. Of the 213 who were randomized and dosed, 71 received placebo, 68 received 3 mg/kg natalizumab, and 74 received 6 mg/kg natalizumab.

**Baseline Characteristics:** Females accounted for 65% of the placebo group, 69% of the 3 mg/kg group, and 80% of the 6 mg/kg group. With the exception of gender, the treatment groups were balanced with respect to demography. Age ranged from 22 to 66 years (median 44 years); 152 subjects (71%) were women; 188 subjects (88%) were Caucasian. Weight ranged from 48 to 102 kg (median 69 kg). Treatment groups were balanced with respect to baseline disease characteristics.

**Efficacy Results:** Natalizumab administration was associated with the following:

- a marked reduction in mean number (9.6 in placebo group, 0.6 in 3.0 mg/kg group, 1.2 in 6.0 mg/kg group) of new gadolinium enhancing lesions at 6 months, ( $p < 0.001$ ,

comparing each natalizumab group individually to placebo, Wilcoxon-Mann-Whitney test);

- no effect on EDSS at 6 months;
- significant decrease in proportion of patients with an MS exacerbation (38% placebo, 19% 3 mg/kg, 19% 6 mg/kg;  $p=0.02$ , comparing each natalizumab group to placebo, Fisher's Exact Test).

Safety results: One subject in the placebo group died during the study due to pleural carcinomatosis complicated by hemothorax. Twenty-four subjects experienced serious adverse events: 9 (13%) in the placebo group, 11 (16%) in the 3 mg/kg natalizumab group, and 4 (5%) in the 6 mg/kg natalizumab group. The most common serious adverse events were MS relapses, experienced by 5 subjects (7%) in the placebo group, 4 subjects (6%) in the 3 mg/kg natalizumab group, and no subjects in the 6 mg/kg natalizumab group.

Other serious adverse events were 3 accidental possible overdoses and 3 immune-mediated reactions in the natalizumab groups, (1- anaphylactoid; 1- chest pain, fever, shortness of breath, respiratory infection, lymphadenopathy, otitis media; 1- urticaria and bronchospasm), and 1 immune-mediated reaction in the placebo group (lymphadenopathy, fever, hypersensitivity skin reaction, facial and arm numbness).

The incidence of adverse events that were 5% higher in any natalizumab group compared to placebo is presented in Table 39.

**Table 39: Adverse Events  $\geq$  5% More Common in Any Natalizumab Group**

	Placebo	3 mg/kg	6 mg/kg	Total Natalizumab
No. of subjects dosed, (n, %)	71 (100)	68 (100)	74 (100)	142 (100)
Infection	16 (23)	20 (29)	21 (28)	41 (29)
Accidental injury	14 (20)	13 (19)	20 (27)	33 (23)
Flu syndrome	9 (13)	12 (18)	9 (12)	21 (15)
Rash	6 (8)	10 (15)	11 (15)	21 (15)
Back pain	6 (8)	8 (12)	11 (15)	19 (13)
Sinusitis	5 (7)	10 (15)	6 (8)	16 (11)
Diarrhea	5 (7)	9 (13)	4 (5)	13 (9)
Fever	1 (1)	5 (7)	4 (5)	9 (6)
Urinary incontinence	2 (3)	7 (10)	2 (3)	9 (6)
Leg cramps	1 (1)	4 (6)	4 (5)	8 (6)
Flatulence	0	5 (7)	1 (1)	6 (4)
Alopecia	0	4 (6)	1 (1)	5 (4)

**Immunogenicity:** Seven subjects (10.3%) in the 3 mg/kg natalizumab group, 8 subjects (10.8%) in the 6 mg/kg natalizumab group, and 1 subject (1.4%) in the placebo group had detectable anti-natalizumab antibodies at any time during the study.

**Clinical Pharmacology:** Based on the safety and efficacy results from Study 231, and on the pharmacokinetic assessments, the sponsor decided that natalizumab 3 mg/kg and 6 mg/kg dosing were likely to be equally safe and effective, and that fixed dosing, rather than weight-adjusted dosing, of natalizumab would be appropriate for further clinical development. For a discussion of the clinical pharmacology results of this study, see the Clinical Pharmacology review by Dr. Iftekhar Mahmood.

**Reviewer's comment:** Study 231 provides supportive evidence (to Studies 1801 and 1802) of the efficacy of natalizumab.

#### 10.1.2 Study 1803

**Title:** A Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Safety Study of Natalizumab in Combination with Glatiramer Acetate (GA) in Subjects with Relapsing-Remitting Multiple Sclerosis (MS)

**Objectives:** To assess the safety (including immunogenicity) and pharmacokinetics of natalizumab when administered in combination with GA.

**Design:** This was a multicenter (25 centers), double-blind, randomized, placebo-controlled, parallel-group study. MS patients currently receiving the standard dose and regimen of GA were randomized (1:1) to receive either natalizumab (55 subjects) or placebo (55 subjects) IV every 4 weeks for up to 20 weeks. All subjects continued to receive GA 20 mg SC daily for up to 20 weeks. All subjects had been treated with GA for at least 1 year prior to study entry, and had experienced at least 1 relapse during that time. To preserve blinding, each site had separate treating and evaluating neurologists, with central reading of MRI scans.

**Enrollment criteria:** Study inclusion criteria required that subjects have a diagnosis of RRMS, meet McDonald criteria 1-4, have a baseline EDSS between 0.0 and 5.0, and have experienced at least 1 relapse (while on GA) within the 12 months prior to randomization. Subjects must have received GA and not received any interferon beta for the 12 months prior to randomization.

**Treatment:** 300 mg natalizumab or placebo IV once every 4 weeks for up to 20 weeks. All subjects continued to receive GA 20 mg SC daily for up to 20 weeks.

**Study Conduct:** 110 subjects were randomized and received at least 1 dose; 102 subjects received all 6 doses.

**Baseline Characteristics:** Median age was 42 years; 84% female; 87% Caucasian; 35% subjects had  $\geq 2$  relapses in the year prior to randomization. The two groups were generally well

matched; however, the natalizumab group had greater MRI activity at baseline than the placebo group (31% active scans vs. 22%).

Study results are presented in Table 40. The only serious adverse event in the natalizumab group was an elective right hip surgery for treatment of arthritis. The two serious adverse events in the placebo group were an MS relapse and an anaphylactic reaction to GA. There were no hypersensitivity reactions observed with natalizumab infusions.

<b>Table 40: Study 1803 Results</b>	<b>Natalizumab + GA N = 55</b>	<b>Placebo + GA N = 55</b>
Relapse rate (mean, annualized)	0.349	0.649
Proportion of subjects with relapse (n, %)	8 (15)	14 (25)
0 – 1 New gadolinium-enhancing lesions <sup>1</sup> (n, %)	47 (85)	37 (68)
0 – 1 New active lesions <sup>1</sup> (n, %)	45 (82)	35 (64)
Serious adverse events (n, %)	1 (2)	2 (5)
Any adverse events (n, %)	50 (91)	51 (93)
Infections (n, %)	33 (60)	36 (65)
Headache	17 (31)	15 (27)
Back pain	9 (16)	4 (7)
Fatigue	8 (15)	6 (11)
Flushing	6 (11)	1 (2)
Menstrual disorders (n / female N, %)	5 / 50 (10)	3 / 42 (7)
Depression (n, %)	3 (5)	2 (4)

<sup>1</sup> MRI evaluations were performed every 4 weeks. Values provided are cumulative for all study visits. The number of new active lesions at each visit was calculated as the sum of the gadolinium-enhancing lesions and the non-enhancing new or newly enlarging T2 lesions.

**Immunogenicity:** Five subjects (9%) who received natalizumab were persistently antibody-positive, compared to 26% of subjects who were antibody-positive at any time post-baseline. The presence of serum antibodies to natalizumab appeared to be associated with a higher incidence of certain infusion-related adverse events (e.g., flushing, pyrexia, rigors), and MS relapse.

**Reviewer's comment:** This study provides modest evidence of the safety of the co-administration of natalizumab and GA. The study also provides supportive evidence (to Study 1802) that natalizumab will be beneficial as an add-on therapy for patients who have a relapse while receiving a non-interferon therapy for MS. However, because of the short duration of this study, further study would be necessary to confirm the efficacy and safety of natalizumab as an add-on agent for subjects who have a relapse while receiving GA. The study is insufficient to assess whether the co-administration of natalizumab and GA warrants a dose adjustment for either natalizumab or GA (see Clinical Pharmacology review by Dr. Iftexhar Mahmood).

### 10.1.3 Amendments to Protocols for Studies 1801 and 1802

#### Study 1801 Protocol Amendments

- 1) Initial protocol submitted on September 5, 2001.
- 2) Protocol amendment submitted on January 11, 2002. This amendment contained modifications to the eligibility criteria and modified the treatment of relapses.
- 3) Protocol amendment submitted on September 15, 2003. This amendment rank prioritized the secondary endpoints.
- 4) Final protocol submitted on September 15, 2003.

#### Study 1802 Protocol Amendments

- 1) Initial protocol submitted on January 11, 2002.
- 2) Protocol amendment submitted on September 4, 2002. This amendment contained modifications to the eligibility criteria and rank prioritized the secondary endpoints.
- 3) Protocol amendment submitted on September 16, 2003. This amendment contained several minor revisions to the protocol.
- 4) Final protocol submitted on September 16, 2003.

## 10.2 Line-by-Line Labeling Review

The applicant submitted a draft label that was revised during discussions between the applicant and CDER. After extensive revisions, the proposed label contains an accurate presentation of the known safety and efficacy of natalizumab. The label also provides appropriate directions for the use of natalizumab.

**Appears This Way  
On Original**

### 10.3 McDonald Diagnostic Criteria for MS

See McDonald et al, 2001.

Clinical Presentation	Additional data needed for MS Diagnosis
1 – Two or more attacks; objective evidence of 2 or more lesions	None
2 – Two or more attacks; objective evidence of 1 lesion	Dissemination in space, demonstrated by: <ul style="list-style-type: none"> <li>• MRI*, or</li> <li>• <math>\geq 2</math> lesions on MRI + positive cerebrospinal fluid (CSF)**, or</li> <li>• await clinical attack</li> </ul>
3 – One attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by: <ul style="list-style-type: none"> <li>• MRI***, or</li> <li>• second clinical attack</li> </ul>
4 – One attack; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: <ul style="list-style-type: none"> <li>• MRI*, or</li> <li>• <math>\geq 2</math> lesions on MRI + positive CSF**, or</li> <li>• await clinical attack,</li> </ul> and Dissemination in time, demonstrated by: <ul style="list-style-type: none"> <li>• MRI***, or</li> <li>• second clinical attack</li> </ul>

\*MRI must have any three of the following:

- 1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions if there is no gadolinium-enhancing lesion
- $\geq 1$  infratentorial lesion
- $\geq 1$  juxtacortical lesion
- $\geq 3$  periventricular lesions

\*\*Positive CSF determined by oligoclonal bands detected by established methods different from any such bands in serum or by a raised Immunoglobulin G (IgG) index.

\*\*\*MRI must meet the following criteria for dissemination of lesions in time:

- 1) If a first scan occurs 3 months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T2 hyperintense or gadolinium-enhancing lesion at this time then fulfills the criterion for dissemination in time.
- 2) If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new

gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T2 hyperintense lesion or an enhancing lesion will suffice.

#### **10.4 Kurtzke Expanded Disability Status Scale**

The Expanded Disability Status Scale (EDSS) provides a disability score based on assessment of seven Functional Systems (Pyramidal, Cerebellar, Brain Stem, Sensory, Bowel and Bladder, Visual, and Mental) and ambulation. Functional System (FS) scores are subjective, based on the neurologic examination and/or symptoms. For each FS, a score of 0 is normal, with higher scores, up to a maximum of 5 or 6, indicating increasing dysfunction. EDSS scores from 0-10 are described below:

- 0.0 - Normal neurologic exam [all grade 0 in all FS scores]
- 1.0 - No disability, minimal signs in one FS (i.e., grade 1)
- 1.5 - No disability, minimal signs in more than one FS (more than one grade 1)
- 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1)
- 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1)
- 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory
- 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two grade 3 (others 0 or 1) of 5 grade 2 (others 0 or 1)
- 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps and the patient should be able to walk > 500 meters without assistance or rest
- 4.5 - Fully ambulatory without aid, up and about much of the day, may otherwise require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps and walks > 300 meters without assistance or rest.
- 5.0 - Ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provision).
- 5.5 - Ambulatory without aid or rest for 100 meters; disability severe enough to preclude full daily activities (e.g., to work a full day without special provision).

6.0 - Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk 100 meters with or without resting.

6.5 - Constant bilateral assistance (canes, crutches, or braces) required to walk 20 meters without resting.

7.0 - Unable to walk at least 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair about 12 hours a day.

7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer; wheels self but unable to carry on in wheelchair a full day.

8.0 - Essentially restricted to chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms.

8.5 - Essentially restricted to bed most of day; has some effective use of arm(s); retains some self-care functions

9.0 - Helpless bed patient; can communicate and eat.

9.5 - Totally helpless bed patient; unable to communicate effectively or eat or swallow

10.0 - Death due to MS.

**Appears This Way  
On Original**

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