U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	STN BL 125104 / 15
Drug Name:	Tysabri® (Natalizumab)
Indication(s):	Multiple Sclerosis
Applicant:	Biogen Idec
Date(s):	Date of Submission: September 26, 2005
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Table of Contents

1. EXECUTIVE SUMMARY

This sBLA of natalizumab contains clinical data in support of a modification to the previously approved indication for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The original indication was based on results achieved after approximately one year of treatment in then ongoing trials C-1801 and C-1802; both are two year studies in design. On 28 February 2005, when Study 1801 had been completed and Study 1802 was near its completion, Biogen Idec suspended natalizumab dosing based on 2 serious adverse event reports of progressive multiple leukoencephalopathy (PML) in natalizumab studies. This sBLA contains clinical efficacy and safety results from the completion of the second year of these two clinical studies.

1.1 Conclusions and Recommendations

The two studies, C-1801 and C-1802, have shown that natalizumab administered as monthly IV infusion, taken alone or with Avonex, is efficacious in treating relapse-remitting MS patients.

The estimated hazard ratio of disability progression for patients treated with natalizumab (natalizumab+Avonex in C-1802) versus patients treated with placebo (placebo+Avonex in C-1802) was 0.58 and 0.76 in studies C-1801 and C-1802, respectively. Due to a large number of subjects completed the study without disability progression in both studies, the median time to disability progression could not be estimated.

The annual relapse rate, which the initial approval of natalizumab was based on, maintained statistical significance in the treatment difference at the end of 2 years for both studies.

1.2 Brief Overview of Clinical Studies

The submission included two pivotal efficacy studies of natalizumab, C-1801 and C-1802. Study C-1801 is a monotherapy study in previously untreated patients. In C-1802 natalizumab was administered as an add-on therapy to Avonex to patients who had been treated with Avonex for at least one year. Other features in design of the two studies are similar. Both studies were multicenter, randomized, double-blind, placebo-controlled and parallel-group trials in patients with relapsing remitting multiple sclerosis (RRMS). Patients received either 300 mg of natalizumab or placebo by IV infusion every 4 weeks for up to 116 weeks. All patients in C-1802 received weekly IM injections of 30 µg Avonex in addition to the treatment of natalizumab or placebo IV infusions.

The studies have two sets of endpoints, one set to be determined after a mean of 1 year of follow-up and a second set to be determined after 2 years. The primary endpoint after 1 year was the annualized relapse rate and the primary endpoint after 2 years was the time to onset of a sustained progression in disability.

A total of 942 subjects (627 in natalizumab and 315 in placebo group) were randomized in C-1801 and 1171 subjects were randomized in C-1802 (589 in natalizumab and 582 in natalizumab + Avonex).

1.3 Statistical Issues and Findings

The two studies (C-1801 and C-1802) have demonstrated that natalizumab, used alone or as an add-on therapy to Avonex, was effective in the treatment of relapsing remitting MS patients. Efficacy results from analyses of time to disability progression (primary endpoint at 2 years) and annualized relapse rate (primary endpoint at 1 year analyzed at 2 years) are summarized in Table 1.

In Study C-1801 the proportion of patients who had sustained disability progression during the 2-year period was .27 for patients treated with placebo and .17 for patients treated with natalizumab. The estimated hazard ratio of disability progression for subjects receiving natalizumab versus subjects receiving placebo was 0.58 (95% CI: 0.43, 0.77). In C-1802, the same proportion was .27 for patients treated with placebo + Avonex and .22 for patients treated with natalizumab + Avonex. The same hazard ratio was 0.76 (95% CI: 0.61, 0.96).

Annual relapse rates at 2 years for the two studies were similar to the ones at one year, which the original approval was based on. The significance of the treatment difference achieved at the end of one year was maintained at the end of the two years.

Table 1 Summary of Efficacy Results for C-1801 and C-1802

	C-1801		**C-1802**	
	Placebo (n=315)	**Natalizumab (n=627)**	**Placebo + Avonex (n=582)**	**Natalizumab + Avonex (n=589)**
Time to Disability Progression				
Number (%) progressed	84 (26.7%)	104 (17.6%)	156 (26.8%)	129 (22.9%)
Number (%) censored	231 (73.3%)	523 (83.4%)	426 (73.2%)	460 (78.1%)
Censor (%) by Week 108	29 (9.2%)	46 (7.3%)	78 (13.4%)	54 (9.2%)
Hazard ratio (Nat vs. plb)		0.58		0.76
p-value		0.0002		0.0238
Annual Relapse Rate				
Unadjusted - 2 year	0.61	0.21	0.70	0.31
Adjusted - 2 year	0.73	0.24	0.75	0.34
p-value		<.001		<.001

The fluctuation of EDSS score between screening visit and baseline visit raises the concern of the interpretation of the results, since the primary efficacy endpoint of time to disability progression is based on changes in EDSS from baseline. My main concern is for Study C-1802 where the treatment difference in time to disability progression is small. About 40% of the

subjects in Study C-1802 had different EDSS scores between screening and baseline. Table 2 presents some preliminary results, pending verification or confirmation by the sponsor, from C-1802. Among the subjects who progressed, about 25% of them would not have met the criteria of disability progression had their baseline EDSS scores not lowered from screening visit. For example, 32 of the 129 subjects in natalizumab + Avonex group and 40 of the 156 subjects from placebo + Avonex group would not have met the criteria of progression if their post-drug EDSS scores were compared to screening EDSS score instead of baseline EDSS score. On the other hand, subjects who had completed the study without disability progression might have met the criteria of disability progression had their EDSS scores not raised from baseline from screening visit. While I understand that such fluctuation might not be avoidable, such fluctuation would add difficulty in interpretation of efficacy results, particularly in Study C-1802, because of high censoring rate, small treatment difference, and insignificant treatment difference in efficacy evaluable population (p=0.346).

Table 2 Disability Progression with Difference in Screening and Baseline EDSS Scores - C-1802

	Natlizumab + Avonex	Placebo + Avonex
Total # of subjects	589	582
# subjects progressed	129	156
EDSS increase from Screening to Baseline:		
0.5 point	79	85
1.0 point	43	44
1.5 point	8	12
2.0 point	7	5
2.5 point	4	1
3.0 point	1	0
If screening visit was used instead of baseline		
# would not progress	32	40
# would progress in a later date	5	12
# would progress on the same date	10	6

2. INTRODUCTION

This sBLA contains clinical data in support of a modification to the previously approved indication for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The original indication was based on results achieved after approximately one year of treatment in ongoing trials of two years in duration. This sBLA contains clinical efficacy and safety results from the completion of the second year of clinical studies C-1801 and C-1802.

2.1 Overview

The submission included two pivotal efficacy studies of natalizumab, C-1801 and C-1802. Study C-1801 is a monotherapy study in previously untreated patients. In Study C-1802 natalizumab was administered as an add-on therapy to Avonex to patients who had been treated with Avonex for at least one year.

The two studies were similar in design except that C-1801 was a monotherapy study in previously untreated patients while in C-1802 natalizumab was used as an add-on therapy to patients previously treated with Avonex. Both studies were multicenter, randomized, double-blind, placebo-controlled and parallel-group trials in patients with relapsing remitting multiple sclerosis (RRMS). Patients received either 300 mg of natalizumab or placebo by IV infusion every 4 weeks for up to 116 weeks. In C-1802, all patients received weekly IM injections of 30 µg Avonex in addition to the treatment of natalizumab or placebo IV infusions.

The studies have two sets of endpoints, one set to be determined after a mean of 1 year of follow-up and a second set to be determined after 2 years. The primary endpoint was the annualized relapse rate after 1 year and the time to onset of a sustained progression in disability after 2 years. Hochberg procedure for multiple comparisons was used for the evaluation of the primary endpoints. For 2 endpoints, the Hochberg procedure results in the following rule: if the maximum of the 2 p-values is ≤ 0.05, then both endpoints are considered statistically significant, otherwise the minimum p-value must be ≤ 0.025 to be considered statistically significant. Since the treatment effect in relapse rate resulted in a p-value of less than .025 at one year in both studies, natalizumab was approved for that indication. The current submission is to demonstrate the effect on slowing disability progression, and the treatment effect is to be determined based on .05 significance level by Hochberg procedure.

A total of 942 subjects (627 in natalizumab and 315 in placebo group) were randomized in C-1801 and 1171 subjects (589 in natalizumab + Avonex and 582 in placebo + Avonex) were randomized in C-1802.

2.2 Data Sources

All document reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for the submission is listed below:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The evaluation of efficacy includes two pivotal studies: C-1801 and C-1802. The two studies had similar design except that C-1801 is a monotherapy study while C-1802 is an add-on study to the standard regimen of AVONEX.

3.1.1 Study Objectives

Studies 1801 and 1802 had 2 sets of objectives, 1 set at 1 year and the other set at 2 years.

The primary objective at 1 year was to determine whether natalizumab, when compared with placebo (used alone in C-1801 and added to the standard regimen of AVONEX in C-1802) was effective in reducing the rate of clinical relapses at 1 year.

The primary objective at 2 years was to determine whether natalizumab, when compared with placebo (used alone in C-1801 and added to the standard regimen of AVONEX in C-1802), was effective in slowing the progression of disability at 2 years, as measured by at least a 1.0 point increase on the Expanded Disability Status Scale (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.

3.1.2 Study Design

Studies C-1801 and C-1802 were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in subjects with relapsing-remitting MS. Nine hundred forty-two (942) subjects were randomized in a 2:1 allocation in C-1801 and 1171 subjects were randomized in 1:1 allocation in C-1802 to receive either 300 mg of natalizumab or placebo by IV infusion every 4 weeks for up to 116 weeks. In C-1802, subjects received either 300 mg of natalizumab or placebo in addition to 30 µg of AVONEX by IM injection weekly.

The two studies were designed with 2 sets of objectives and endpoints for 1-year and 2-year. The primary endpoint for the first year was the annualized relapse rate. The primary endpoint for the second year was time to sustained progression of disability, as determined by meeting the criteria of increase in EDSS.

All study management, investigational site personnel, investigators, and subjects directly involved in Studies C-1801 or C-1802 were to remain blinded to subject treatment assignments until the conclusion of the 2-year study. To protect the integrity of the blind, the analysis team who conducted the 1-year analyses was not involved in the conduct of the second year of the

study or in any data review of the 2-year data prior to the unblinding at 2 years. Members of the Advisory Committee were blinded to subject treatment assignments.

On 28 February 2005, when C-1801 had been completed and C-1802 was near its completion, Biogen Idec suspended natalizumab dosing based on 2 serious adverse event reports of progressive multiple leukoencephalopathy (PML) in natalizumab studies. Any remaining dosing visits (Week 116) were cancelled and all subjects were evaluated for signs and symptoms of PML.

3.1.3 Efficacy Variables

Primary Efficacy Variables

Each of the two studies includes 2 primary endpoints; relapse rate analyzed at 1 year and disability progression analyzed at 2 years.

Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist. The subject must have had objective signs on the Examining Neurologist's examination confirming the event. New or recurrent neurological symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were to be considered part of the same relapse and were not to be treated with IVMP.

Progression of disability was defined as at least a 1.0 point increase on the EDSS from baseline if baseline EDSS $\geq$ 1.0 or at least a 1.5 point increase on the EDSS from baseline if baseline EDSS=0. Such increase has to be sustained for 12 weeks.

Secondary Efficacy Variables

The secondary endpoints were rank prioritized in order of importance. A closed testing procedure was used such that if statistical significance was not achieved for an endpoint, all endpoint(s) of a lower rank were not considered statistically significant.

At 1 year, to determine whether natalizumab is effective in:

- reducing the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans;
- reducing the number of gadolinium- enhancing lesions on brain MRI scans; and
- increasing the proportion of relapse- free subjects.

At 2 years, to determine whether natalizumab is effective in:

- reducing the rate of clinical relapses
- attenuating the increase in T2 hyperintense lesion volume on brain MRI scans
- attenuating the increase in T1 hypointense lesion number on brain MRI scans, and

• slowing the progression of disability, as determined by the change in the MSFC in each treatment group. The MSFC consisted of the Timed 25- Foot Walk, 9HPT, and PASAT 3.

3.1.4 Statistical Analysis Methods

Poisson regression model was to be used for the 1-year primary endpoint of relapse rate, and Cox proportional hazard model was to be used for the 2-year primary endpoint of time to disability progression.

For the primary efficacy analyses, the model for each endpoint was to include a term for treatment group and for the baseline value of that endpoint. In addition, up to 4 baseline factors were to be included in the model if there was a statistical association between the factor and the outcome. These 4 baseline factors were: baseline EDSS (EDSS $\leq$ 3.5 versus EDSS > 3.5), number of T2 lesions (T2 lesions < 9 versus T2 lesions $\geq$ 9), presence of gadolinium-enhancing lesions (lesions present versus lesions absent), and age (age < 40 years versus age $\geq$ 40 years). A backward stepwise selection procedure was to be used to select which of the 4 factors to include in the model. Initially, the model was to be fit with the baseline value of the endpoint, treatment group, and all 4 factors. The factor with the highest p-value > 0.10 was to be removed from the model and the model was to be refit with the remaining factors. This process would continue until the model included the baseline value of the endpoint, treatment group, and any remaining factors that were statistically significant (p-value $\leq$ 0.10).

The Hochberg procedure was to be used to control the experiment-wise alpha level at 0.05 for the multiple primary endpoint analyses. For 2 endpoints, the Hochberg procedure results in the following rule: if the maximum of the 2 p-values is $\leq$ 0.05, then both endpoints are considered statistically significant, otherwise the minimum p-value must be $\leq$ 0.025 to be considered statistically significant. Since treatment effect for the relapse rate reached 0.025 significance level at one year for both studies, the significance level to be reached for the 2-year endpoint is 0.05 for both studies.

3.1.5 Disposition of Subjects

A total of 942 subjects were enrolled into the C-1801 in 99 centers in North America, Europe, Australia, Turkey, and New Zealand. Of the 942 subjects enrolled, 315 were randomized to receive placebo and 627 were randomized to receive natalizumab. All but 3 subjects randomized to placebo received at least 1 dose of study drug. A total of 118 subjects (13%) discontinued study drug and a total of 86 subjects (9%) withdrew from the study. Note that a subject discontinued study drug could stay in the study until the completion of the study. Table 2 presents the subject disposition.

In Study -1802, site number 473 in Austria was closed due to protocol noncompliance and the data was excluded from all summaries and analyses. The site enrolled 25 subjects, the first in

November 2002, and was asked to stop dosing in February 2003. When it was formally closed in June 2003, the site's subjects had received a maximum of four infusions.

The remaining 123 investigators in North America, Europe, and Israel enrolled a total of 1171 subjects, of those 582 were randomized to receive AVONEX plus placebo and 589 were randomized to receive AVONEX plus natalizumab. A total of 229 subjects (20%) discontinued study drug, and 168 subjects (14%) withdrew from the study.

Table 3 Disposition of Subjects for C-1801 and C-1802 (Source: Table 10.1-1 in sponsor's study reports)

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

3.1.6 Demographic Characteristics of Subjects

Baseline demography was balanced between the groups with the exception of gender in C-1801, where a slightly higher proportion of women received natalizumab than placebo (Table 3).

In C-1801, the study population comprised 660 women (70%) and 282 men (30%), aged between 18 and 50 years (median 37 years), of whom 899 (95%) were white. In C-1802, the study population comprised 862 women (74%) and 309 men (26%), in the age range of 18 to 55 years (median 39 years), of whom 1092 (93%) were white.

Table 4 Demographic Characteristics of Subjects for C-1801 and C-1802 (Source: Table 10.2-1 of sponsor's study reports)

	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex	Natalizumab + Avonex
Number randomized	315	627	582	589
Age (years)				
Mean (SD)	36.7 (7.8)	35.6 (8.5)	39.1 (7.6)	38.8 (7.7)
Median	37.0	36.0	39.0	39.0
Gender				
Male	104 (33%)	178 (28%)	162 (28%)	147 (25%)
Female	211 (67%)	449 (72%)	420 (72%)	442 (75%)
Race				
White	296 (94%)	603 (96%)	542 (93%)	550 (93%)
Black	6 (2%)	4 (1%)	22 (4%)	17 (3%)
Hispanic	6 (2%)	7 (1%)	9 (2%)	13 (2%)
Other	7 (2%)	13 (2%)	9 (2%)	9 (2%)

3.1.7 Baseline Disease Characteristics

Table 4 presents a summary of disease history of subjects for the two studies.

A total of 901 subjects (96%) in C-1801 and 1160 subjects (99%) in C-1802 were diagnosed based on 2 or more relapses and 1 or more objective lesions clinically or on MRI.

MS disease history at screening was similar between the two treatment groups in both studies. Time since onset of MS symptoms (total disease duration) ranged from 0 to 34 years (median 5 years) in C-1801 and ranged from 1 to 34 years (median 7 years) in C-1802. Time since diagnosis ranged from 0 to 24 years (median 2 years) for C-1801 and ranged from 0 to 30 years (median 4 years) for C-1802. The number of subjects who reported to have had at least 2 MS relapses in the year prior to entry was 382 (41%) in C-1801 and 421 (36%) in C-1802.

Treatment groups were similar with respect to the EDSS at baseline, which ranged from 0 to 6 (medians of 2 in C-1801 and 2.5 in C-1802). Ninety-five percent (95%) of subjects in C-1801 and 89% of subjects in C-1802 had 9 or more T2 hyperintense lesions at baseline.

Table 5 Summary of Disease History for C-1801 and C-1802 (Source: Tables 10.3-1, 10.3-2, 10.3-3 and 10.3-4 of sponsor's study reports)

	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex	Natalizumab + Avonex
Number randomized	315	627	582	589
McDonald criteria				
1 (a)	261 (83%)	528 (84%)	532 (91%)	538 (91%)
2 (b)	40 (13%)	72 (11%)	44 (8%)	46 (8%)
3 (c)	14 (4%)	27 (4%)	6 (1%)	5 (1%)
Time since 1st symptom				
Median	6.0	5.0	8.0	7.0
Min, max	0, 33	0, 34	1, 34	1, 34
Time since diagnose				
Median	2.0	2.0	5.0	4.0
Min, max	0, 23	0, 24	0, 30	0, 27
Relapses within past year				
0	6 (2%)	6 (<1%)	1 (<1%)	0
1	180 (57%)	368 (59%)	357 (61%)	390 (66%)
2	102 (32%)	197 (31%)	174 (30%)	153 (26%)
3	20 (6%)	43 (7%)	39 (7%)	32 (5%)
≥ 4	7 (2%)	13 (2%)	11 (2%)	12 (2%)
EDSS score				
Median	2.0	2.0	2.5	2.0
Min, max	0, 6	0, 6	0, 5.5	0, 6
MRI T2 hyperintense lesions				
<9	15 (5%)	29 (5%)	52 (9%)	67 (11%)
≥9	299 (95%)	597 (95%)	528 (91%)	519 (88%)

a. 2 or more relapses, 2 or more objective lesions.
b. 2 or more relapses, 1 objective lesion
c. 1 relapse, 1 or 2 objective lesions

In C-1801, 90% of subjects in the placebo group and 93% in the natalizumab group were followed for more than 108 weeks. In C-1802, 86% of subjects in the AVONEX plus placebo group and 89% in the AVONEX plus natalizumab group were followed for more than 108 weeks.

Of the 939 subjects dosed in C-1801, 786 (84%) received all 30 infusions. Of the 1171 subjects dosed in C-1802, 822 (69%) received all 30 infusions; a slightly higher proportion of these were in the Avonex plus natalizumab group than in the Avonex plus placebo group. The following table presents the study drug exposure.

Table 6 Study Drug Exposure in C-1801 and C-1802 (Source: Table 10.5-1 of sponsor's study reports)

	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex	Natalizumab + Avonex
Number randomized	315	627	582	589
Number of infusion received				
0	3 (<1%)	0	0	0
1-6	13 (4%)	29 (5%)	32 (5%)	30 (5%)
7-12	11 (3%)	11 (2%)	29 (5%)	23 (4%)
13-18	6 (2%)	18 (3%)	32 (5%)	17 (3%)
19-25	10 (3%)	10 (2%)	21 (4%)	19 (3%)
26-29	15 (5%)	30 (5%)	73 (13%)	73 (12%)
30	257 (82%)	528 (84%)	395 (68%)	427 (72%)
≥31	0	1 (<1%)	0	0

3.1.8 Efficacy Results Reported by the Sponsor - Study C-1801

3.1.8.1 Primary Endpoint at 2 Years - Disability Progression

Time to disability progression, the primary endpoint at 2 years, was compared between treatment groups using a Cox proportional hazards model. The backward selection procedure resulted in a model included treatment group, baseline EDSS score and age group (< 40 vs. ≥ 40). Subjects who did not have disease progression and had taken alternative MS medications were censored at the time that they took the alternative MS medications. Confirmation of disease progression, however, may have occurred after alternative medications were taken. A total of 77 subjects added rescue medication, with the most common treatment being Avonex (31 subjects).

Results from the analysis of time-to-sustained progression of disability at 2 years are shown in Table 6 and Figure 1. The Kaplan- Meier estimate of percentage of subjects progressing by 2 years in the placebo group was 29% compared to 17% for the group that received 300 mg natalizumab. The hazard ratio obtained from Cox model was 0.58 (95% CI: 0.43, 0.77) indicating a 42% reduction in the risk of disability progression following treatment with natalizumab. The comparison between treatment groups was highly statistically significant ($p < 0.001$).

The analyses were also carried out for the efficacy evaluable population (patients who had fewer than 26 infusions were excluded) and the population including progressions confirmed during a relapse. The analyses resulted hazard ratios of 0.59 and 0.54 for the efficacy evaluable population and population including progressions confirmed during a relapse, respectively. The p-values for the two analyses are both < .001.

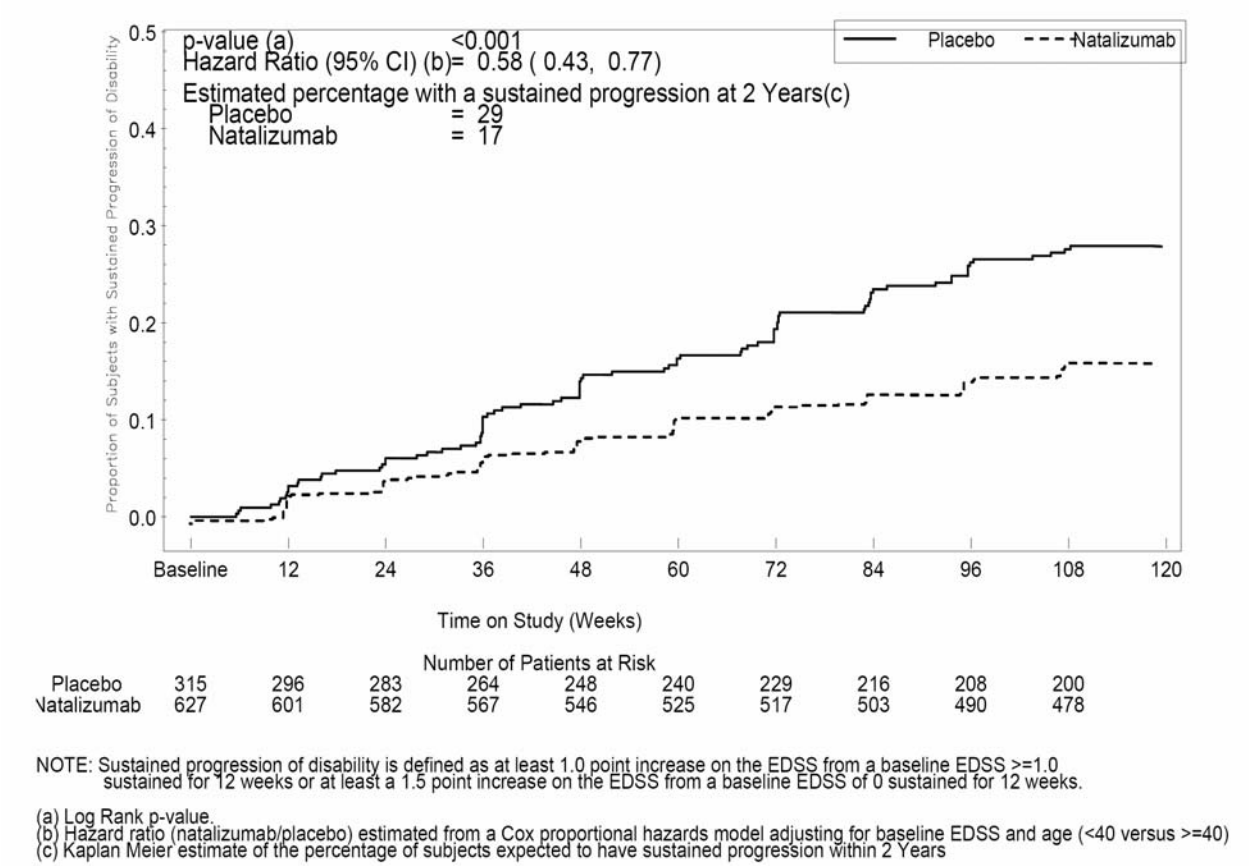
Table 7 Time to Sustained Progression of Disability at 2 Years for C-1801 (Source: Table 11.4.1 of sponsor's study report)

	Placebo	Natalizumab	p-value (a)
Number of subjects randomized	315 (100)	627 (100)	
Number of subjects progressed regardless of length of follow-up	84 (27)	104 (17)	
Time (yr) to progression (b)			
25th percentile	1.8	.	
50th percentile (Median)	.	.	
Mean and 95% CI	1.78 (1.72,1.84)	1.90 (1.87,1.94)	
Estimated proportion of subjects with progression at 2-years (b)	0.29	0.17	
Hazard ratio (Natalizumab/Placebo) and 95% CI	0.58 (0.43, 0.77)		<0.001

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

(a) P-value assessing the difference between the treatment groups, from Cox Proportional Hazards model, adjusted for baseline EDSS values and age (<40 versus >=40).

(b) Estimated time to progression and proportion of subjects with progression based on the Kaplan-Meier product limit method.



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

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

Figure 1 Time to Sustained Progression of Disability for C-1801 (Source: Figure 11.4-2 of sponsor's study report)

3.1.8.2 Annualized Relapse Rate over Two Years

Annualized relapse rate was the highest ranked secondary endpoint at 2 years. Annualized relapse rate was .611 for the placebo group compared to a rate of 0.210 for the group that received 300 mg natalizumab. Adjusting by the Poisson model, the estimated annual relapse rate was .733 for the placebo group and .235 for the natalizumab group, with treatment difference of .320 (C.I.: (.256, .399); p<.001). In both treatment groups, the relapse rate over 2 years was lower than that over 1 year, which had estimated relapse rate of .805 and .261 for the placebo group and natalizumab group, respectively.

3.1.9 Efficacy Results Reported by the Sponsor - Study C-1802

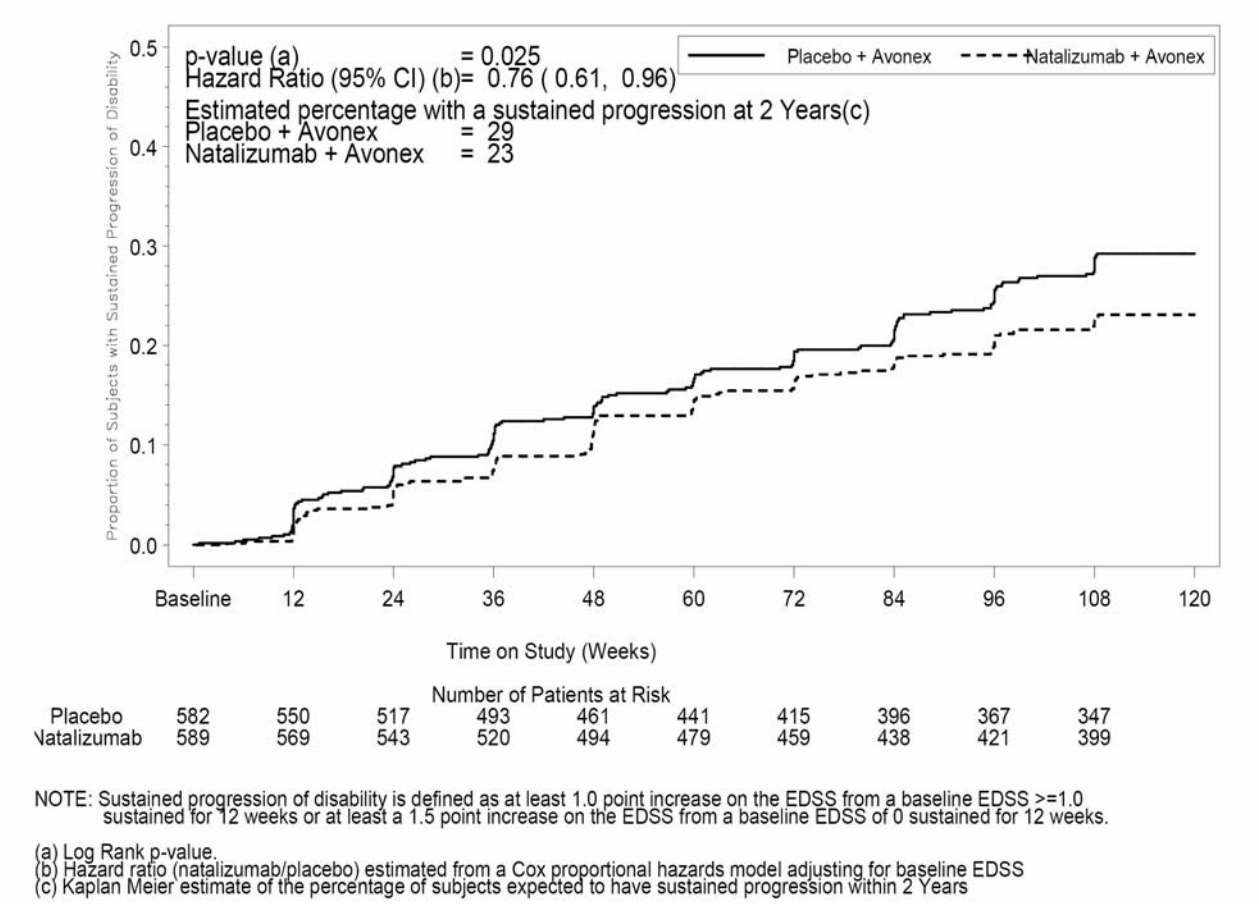
3.1.9.1 Primary Endpoint at 2 Years - Disability Progression

The primary endpoint at 2 years was the time to sustained disability progression. The treatment groups were compared using a Cox proportional hazards model. The Cox model included treatment and baseline EDSS score as all other 4 factors were excluded by the backward selection procedure. Subjects were censored if they did not have protocol-defined disease progression and had taken alternative MS medications. A total of 62 subjects added rescue medication to study drug in association with disease progression, with the most common treatment being Rebif (20 subjects).

The Kaplan- Meier estimate of percentage of subjects progressing by 2 years in the Avonex plus natalizumab group was 23% compared to 29% for the group that received AVONEX plus placebo (Figure 2 and Table 7). The hazard ratio obtained from the Cox model was 0.76 (95% CI: 0.61, 0.96) indicating a 24% reduction in the risk of disability progression following treatment with AVONEX plus natalizumab. The comparison between treatment groups was statistically significant (p= 0.024).

The analysis of time to sustained progression of disability at 2 years was also carried out for the efficacy evaluable population and the population that including progression confirmed during a relapse. The hazard ratio was 0.88 (95% CI: 0.68, 1.15; p= 0.346) for the efficacy evaluable population and was 0.75 (95% C.I.: 0.50, 0.94; p=0.013) for the population including progression confirmed during a relapse.

A smaller reduction in the risk of disability progression was observed in efficacy evaluable population. The sponsor stated that one factor contributing to this result involves the subjects in the AVONEX plus placebo arm who discontinued study drug due to disease activity. The loss of these subjects left a higher proportion of stable subjects in the AVONEX plus placebo group, lowering the rate of disability progression in this group, thereby minimizing the differences compared to the AVONEX plus natalizumab group.



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

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

Figure 2 Time to Sustained Progression of Disability for C-1802 (Source: Figure 11.4-2 of sponsor's study report)

Table 8 Time to Sustained Progression of Disabiltiy for C-1802 (Source: Table 14.1-1 of sponsor's study report)

	Placebo + Avonex	Natalizumab + Avonex	p-value (a)
Number of subjects randomized	582 (100)	589 (100)	
Number of subjects progressed regardless of length of follow-up	156 (27)	129 (22)	
Time (yr) to progression (b)			
25th percentile	1.8	.	
50th percentile (Median)	.	.	
Mean and 95% CI	1.78 (1.73,1.82)	1.83 (1.79,1.88)	
Estimated proportion of subjects with progression at 2-years (b)	0.29	0.23	
Hazard ratio (Natalizumab/Placebo) and 95% CI	0.76 (0.61, 0.96)		0.024

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

(a) P-value assessing the difference between the treatment groups, from Cox Proportional Hazards model, adjusted for baseline EDSS values.

(b) Estimated time to progression and proportion of subjects with progression based on the Kaplan-Meier product limit method.

3.1.9.2 Annualized Relapse Rate over Two Years

Unadjusted annualized relapse rate was .698 in the placebo + Avonex group and .310 in the natalizumab + Avonex group. The estimated annual relapse rate from the Poisson model was .749 for the Placebo + Anonex group and .336 for the natalizumab + Avonex group, resulting a treatment difference of .448 (95% CI: .382, .525; p<.001). The relapse rate over 2 years was slightly lower than that over 1 year, which was estimated as .759 for the Avonex plus placebo group and .353 for the Avonex plus natalizumab group.

3.1.10 Reviewer's Analysis Results

This reviewer conducted efficacy analysis independently based on protocol specified statistical methods. The results obtained agree with the ones obtained by the sponsor. The following table summarizes the efficacy results for the two studies.

The analysis confirmed sponsor's results that treatment difference for the primary efficacy endpoint of time to disability progression achieved statistical significance in both studies.

The analyses of both 1-year and 2-year primary efficacy endpoints used backward selection for factors to be included in their corresponding analysis models. Such backward selection procedure might inflate the Type-I error. The review performed analyses by including in the model with varies subsets of factors from the 4 factors specified. The results from the analyses of both 1-year and 2-year primary endpoints were similar in both studies: treatment difference remained significant and p-values were virtually unchanged.

The effect on delaying the disability progression needs to be interpreted cautiously since the majority of subjects completed the participating study without disability progression. In addition, the treatment difference in time to sustained progression of disability is small in C-1802, and the robust of the results is in question. The difference in time to sustained progression of disability did not reach statistical significance in the efficacy evaluable population in C-1802.

The treatment difference in relapse rate that achieved statistical significance at one-year point was maintained at the end of two years. The relapse rate at the end of 2 years was slightly lower than the one at the end of 1 year for both studies.

Table 9 Summary of Efficacy Results for C-1801 and C-1802

	C-1801		**C-1802**	
	Placebo (n=315)	**Natalizumab (n=627)**	**Placebo + Avonex (n=582)**	**Natalizumab + Avonex (n=589)**
Time to Disability Progression				
Number (%) progressed	84 (26.7%)	104 (17.6%)	156 (26.8%)	129 (22.9%)
Number (%) censored	231 (73.3%)	523 (83.4%)	426 (73.2%)	460 (78.1%)
Hazard ratio (Nat vs. plb)		0.58		0.76
p-value		0.0002		0.0238
Annual Relapse Rate				
Unadjusted - 1 year	0.67	0.24	0.75	0.35
Adjusted - 1 year	0.78	0.27	0.82	0.38
Unadjusted - 2 year	0.61	0.21	0.70	0.31
Adjusted - 2 year	0.73	0.24	0.75	0.34
p-value at 2 year		<.001		<.001

3.2 Evaluation of Safety

Refer to Clinical Review by Dr. Susan McDermott for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Time to disability progression, the primary efficacy variable, was analyzed by subgroups of gender and age, and results are presented in Table 8. The majority of subjects (over 90%) are White, and analysis by Race was not performed.

Females comprised of about 70% of the subjects. The observed treatment difference is larger among the female subjects than among the male subjects, and in subjects younger than 40 years of age than in older subjects. In Study C-1802, treatment difference in males is minimal.

Table 10 Time to Sustained Progression of Disability by Gender and Age for C-1801 and C-1802 (Source: Reviewer's analysis)

	Study 1801		**Study 1802**	
	Placebo	Natalizumab	Placebo + Avonex	Natalizumab + Avonex
Gender				
Male				
# progressed	24	29	50	40
# censored (%)	80 (76.92%)	149 (83.71%)	112 (69.14%)	107 (72.79%)
25th percentile[1]	censored	censored	1.82 year	1.83 year
Hazard Ratio (p)		.681 (p=.1656)		.902 (p=.6266)
Female				
# progressed	60	75	106	89
# censored (%)	151 (71.56%)	374 (83.30%)	314 (74.76%)	353 (79.86%)
25th percentile[1]	1.65 year	censored	1.85 year	censored
Hazard Ratio (p)		.536 (p=.0003)		.729 (p=.0278)
Age (year)				
< 40				
# progressed	50	51	83	63
# censored (%)	138 (73.40%)	348 (87.22%)	212 (71.86%)	241 (79.28%)
25th percentile[1]	1.76 year	censored	1.82 year	censored
Hazard Ratio (p)		.421 (p<.0001)		.702 (p=.0346)

≥ 40				
# progressed	34	53	73	66
# censored (%)	93 (73.23%)	175 (76.75%)	214 (74.56%)	219 (76.84%)
25th percentile[1]	1.80 year	censored	1.84 year	censored
Hazard Ratio (p)		.844 (p=.4402)		.843 (p=.3149)

1. Median time to progression was censored. 25th percentile of time to progression was censored as indicated.

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

About 40% of the subjects in Study C-1802 had different EDSS scores between screening and baseline. Among the subjects who progressed, about 25% of them would not have met the criteria of disability progression had their baseline EDSS scores not lowered from screening visit. On the other hand, subjects who had completed the study without disability progression might have met the criteria of disability progression had their EDSS scores not raised from baseline from screening visit. Such fluctuation would add difficulty in interpretation of efficacy results, particularly in Study C-1802, because of high censoring rate, small treatment difference, and insignificant treatment difference in efficacy evaluable population (p=0.346).

The analyses of both 1-year and 2-year primary efficacy endpoints used backward selection for factors to be included in their corresponding analysis models. Such backward selection procedure might inflate the Type-I error. Sensitivity analyses were performed by including in the model with varies subsets of factors from the 4 factors specified. The results from the analyses of both 1-year and 2-year primary endpoints were basically unchanged in varies models for both studies.

5.2 Conclusions and Recommendations

The two studies, C-1801 and C-1802, have shown that natalizumab administered as monthly IV infusion, taken alone or with Avonex, is efficacious in treating relapse-remitting MS patients.

The estimated hazard ratio of disability progression for patients treated with natalizumab (natalizumab+Avonex in C-1802) versus patients treated with placebo (placebo+Avonex in C-1802) was 0.58 and 0.76 in studies C-1801 and C-1802, respectively. Due to a large number of subjects completing the study without disability progression in both studies, the median time to disability progression could not be estimated.

The annual relapse rate, which the initial approval of natalizumab was based on, maintained statistical significance in the treatment difference at the end of 2 years for both studies.