0.370) compared to placebo. Clearly, therefore, the sponsor's decision to exclude data from Site —— would not importantly affect the overall study results, and CDER excluded these data as well.

Subject #146-105 (Study 1802): This subject (in the placebo group) was initially reported by the applicant to have had a first relapse on ———— and a second relapse on ———— and the sponsor included both relapses in the primary analysis. However, after a review of the available data, the sponsor assessed the ——— "relapse" as a continuation of the ——— relapse. Only the ———— relapse and not the ———— "relapse" is included in CDER analyses. This results in a minor discrepancy between the results of the applicant's analyses and CDER analyses.

Use of alternative MS treatment: As noted above, CDER included all time on study for these subjects, irrespective of the initiation of treatment with alternative MS treatment.

6.1.4.5.2.2 Financial conflicts of interest

CDER conducted analyses of the primary endpoint excluding data from all sites with reported financial conflicts of interest. This included 6 sites in Study 1801 that enrolled 16 subjects into the placebo group and 30 subjects into the natalizumab group, as well as 12 sites in Study 1802 that enrolled 76 subjects into the placebo + Avonex® group and 79 subjects into the natalizumab + Avonex® group. In the sites with no reported financial conflicts of interest, treatment with natalizumab resulted in a 67% decrease in annualized relapse rate (0.735 vs. 0.246) compared to placebo (Study 1801). Treatment with natalizumab + Avonex® resulted in a 55% decrease in annualized relapse rate (0.756 vs. 0.340) compared to placebo + Avonex® in Study 1802. Thus, if there were investigator biases at these sites, due to financial or other conflicts of interest, as well as unblinding, they would not have importantly affected the overall study results.

6.1.4.5.2.3 Relapses by Severity

Natalizumab appears to decrease the rate of severe relapses and relapses treated with steroids, proportionate to the overall decrease in relapse rate (Table 7; Table 8). Natalizumab administration in Study 1802 is also associated with a proportionate decrease in the number of serious relapses. However, the number of serious relapses is very low, so the strength of this observation is limited.

Table 7: Mean Annualized Relapse Rate, by Severity, Study 1801*

Study 1801	Number of relapses		Relapse rates (mean annualized)		
	Placebo N = 315	Natalizumab N = 627	Placebo N = 315	Natalizumab N = 627	% change
All relapses	235 (100)	165 (100)	0.735	0.250	66% decrease
Serious relapses*	4 (2%)	9 (5%)	0.012	0.013	8% increase
Severe relapses*	15 (6%)	10 (6%)	0.047	0.014	70% decrease
Relapses treated with steroids*	168 (71%)	105 (64%)	0.542	0.158	71% decrease

* Percentages represent percent of all relapses.

Only 2 relapses, one in each 1801 study group, resulted in discontinuation of study agent.

Table 8: Mean Annualized Relapse Rate, by Severity, Study 1802[1]

Study 1802	Number of relapses		Relapse rates (mean annualized)		
	Placebo N = 582	Natalizumab N = 589	Placebo N = 582	Natalizumab N = 589	% change
All relapses[2]	478 (100)	225 (100)	0.780	0.357	54% decrease
Serious relapses[2]	7 (1%)	1 (0.4%)	0.011	0.001	91% decrease
Severe relapses[2]	34 (7%)	19 (8%)	0.057	0.030	47% decrease
Relapses treated with steroids[2]	397 (83%)	156 (69%)	0.645	0.243	62% decrease

[1] Excludes site 473 data
[2] Percentages represent percent of all relapses.

Ten relapses, 9 in the placebo + Avonex® group and 1 in the natalizumab + Avonex® group, resulted in discontinuation of study agent.

The slightly higher rate of steroid use in the placebo groups, compared to the natalizumab groups, is difficult to interpret, but may suggest that relapses were more severe in the placebo group. The higher use of steroids in the placebo group could also reflect investigator bias, if the Treating Neurologist were able to ascertain or guess a subject's treatment assignment and expected that subjects receiving placebo were more likely to need steroids. If steroids have any effect on the incidence of a subsequent relapse, the higher rate of steroid use in the placebo group might bias the overall study results. However, such a bias would favor the placebo group, leading to an underestimate of the benefit of natalizumab.

Table 9: Distribution of Relapse Severity, Studies 1801 and 1802

Relapses	Study 1801		Study 1802	
	Placebo	Natalizumab	Placebo + Avonex®	Natalizumab + Avonex®
Total number*	235 (100%)	165 (100%)	478 (100%)	225 (100%)
Severe relapses*	15 (6%)	10 (6%)	34 (7%)	19 (8%)
Moderate relapses*	112 (48%)	77 (47%)	309 (65%)	133 (59%)
Mild relapses*	108 (46%)	78 (47%)	135 (28%)	73 (32%)

* Percentages represent percent of all relapses.

The distributions of relapse severities (Table 9) were strikingly similar between the natalizumab and control groups; this was true in both studies. Thus, the decrease in relapse rate associated with natalizumab is not accompanied by a shift to milder or more severe relapses. Additional analyses examined the frequency of relapses requiring steroids and the proportion of subjects

who had severe relapses in each of the two Phase 3 studies; these analyses are presented in Table 10. The numbers of subjects with serious relapses were too small for meaningful analysis.

Table 10: Numbers of Subjects with Severe Relapses and Relapses Requiring Steroids

	Placebo	Natalizumab	Relative risk[1] (95% CI)	Decreased risk of relapse associated with natalizumab	
				Absolute	Relative
Severe relapses					
Study 1801	12 / 315 (3.8%)	9 / 627 (1.4%)	0.38 (0.16, 0.88)	2.4%	62%
Study 1802	30 / 582 (5%)	17 / 589 (3%)	0.56 (0.31, 1.00)	2.3%	44%
Relapses requiring steroids					
Study 1801	105 / 315 (33%)	88 / 627 (14%)	0.42 (0.33, 0.54)	19%	58%
Study 1802	256 / 582 (44%)	129 / 589 (22%)	0.50 (0.42, 0.59)	22%	50%

[1] Relative risk of being severe relapse-free or steroid-treated relapse-free, comparing natalizumab group to placebo group. Subjects with no relapses prior to alternative MS drug or prior to dropping out of the study were all considered to have no relapses.

Note the analyses presented in Table 10 support the consistency of natalizumab's effect.

6.1.4.5.3 Primary Endpoint, Subgroup Analyses

Results of subgroup analyses are shown in (Table 11).

Table 11: Primary Efficacy Endpoint, Annualized Relapse Rate - Subgroup Analysis

	Study 1801					Study 1802				
	Natalizumab		Placebo			Natalizumab		Placebo		
	n	relapse rate	n	relapse rate	reduction (%)	n	relapse rate	n	relapse rate	reduction (%)
Overall	627	0.25	315	0.735	66.0%	245	0.253	265	0.687	63.2%
Gender										
male	178	0.247	104	0.713	65.4%	147	0.326	162	0.789	58.7%
female	449	0.251	211	0.746	66.4%	442	0.367	420	0.776	52.7%
Race										
Caucasian	602	0.25	296	0.724	65.5%	551	0.355	542	0.759	53.2%
African descent	5	0.187	6	0.776	75.9%	17	0.451	22	0.712	36.7%
Asian	3	0	3	1.72	100.0%	2	2.182	4	1.251	-74.4%
Hispanic	8	0.303	6	0.911	66.7%	12	0.121	9	1.332	90.9%
Age										
≤ 37 yrs (median)	345	0.239	165	0.911	73.8%					
> 37 yrs (median)	282	0.262	150	0.543	51.7%					
≤ 39 yrs (median)						303	0.357	295	0.917	61.1%
> 39 yrs (median)						286	0.357	287	0.639	44.1%
Weight (kilograms)										
< 50	16	0.183	14	0.776	76.4%	20	0.482	16	1.293	62.7%
50 - 59.9	134	0.289	55	1.176	75.4%	124	0.349	117	0.813	57.1%
60 - 69.9	172	0.216	83	0.74	70.8%	143	0.424	149	0.716	40.8%
70 - 79.9	140	0.26	68	0.632	58.9%	122	0.276	123	0.759	63.6%
80 - 89.9	76	0.239	51	0.486	50.8%	90	0.304	79	0.878	65.4%
90 - 99.9	46	0.33	29	0.75	56.0%	40	0.451	48	0.596	24.3%
100 - 109.9	20	0.273	7	0.373	26.8%	24	0.293	26	0.628	53.3%
110 - 150	22	0.116	7	0.369	68.6%	20	0.522	19	0.96	45.6%
Region										
United States	71	0.24	37	0.555	56.8%	363	0.312	361	0.729	57.2%
Not USA	556	0.251	278	0.759	66.9%	226	0.429	221	0.862	50.2%

The treatment effect of natalizumab is generally robust across all subgroups. It is consistent in both genders. Numbers of minority subjects were too small to reliably assess differences; however, the effect trended in favor of natalizumab in subjects of African and Hispanic descent. There were only 6 Asian subjects in each study, a number too small to interpret the apparent diametrically opposed outcomes in the two studies. Of note, race information is missing or classified as "Other" for 13 subjects in 1801, 12 subjects in 1802.

In general, MS relapse rates were lower for older subjects. This tendency may be related to changes in immune response with aging, and there is the possibility that older MS subjects may be less likely to derive benefit from immune-modifying therapies. The tendency for older subjects to have lower relapse rates is seen in data from the placebo groups in both studies. In natalizumab groups of both studies, however, annualized relapse rates were virtually the same in younger and older subjects. Thus, natalizumab treatment was associated with a greater treatment

effect in younger subjects in both studies. Nevertheless, the treatment effect appears to be fairly impressive, even in older subjects (52% and 44% relative reductions in annualized relapse rates in Studies 1801 and 1802, respectively).

Data from Study 1801 tends to show a slightly greater treatment effect in individuals of lower weight; however, there was a trend in the opposite direction in Study 1802 (see Section 2.5.1, Fixed Dosing Regimen). Specifically, in Study 1801, there was a 73% reduction in annualized relapse rate in natalizumab-treated subjects weighing under 70 kg (70 kg was close to median weight in both studies), and a 56% reduction in annualized relapse rate in natalizumab-treated subjects weighing ≥ 70kg. In Study 1802, the corresponding percent reductions were 50% and 57%. Thus, the trends in Studies 1801 and 1802 were directionally opposite, and there is no clear signal to suggest that subjects of greater weight were inadequately dosed.

The activity of natalizumab is generally consistent within and outside the U.S.

Table 12 shows the annualized relapse rates for disease-related subgroups. There is no consistent relationship between baseline disability, as measured on the EDSS, and the percent reduction in annualized relapse rate associated with the use of natalizumab. There is a direct correlation between the pre-study relapse rate (over either 1 year or 3 years) and the on-study relapse rate. This is true both in subjects who received natalizumab, and those who did not. Nevertheless, the percent reduction in relapse rate associated with natalizumab is relatively consistent across pre-study relapse rate categories.

The McDonald criteria (see Section 10.3, McDonald Diagnostic Criteria for MS) use various measures to assess whether or not a patient has MS. The two Phase 3 studies enrolled primarily subjects with McDonald category 1 data in support of the diagnosis. However, in spite of relatively small enrollment numbers for subjects who met diagnostic criteria other than category 1 evidence, the two studies suggest that the effect of natalizumab is present of subjects with category 2 evidence, and perhaps subjects with category 3 evidence, of MS. The sample numbers are too small to assess the natalizumab effect, if any, in subjects with McDonald criteria category 4 evidence of MS.

Table 12: Primary Efficacy Endpoint, Annualized Relapse Rate – MS-Related Subgroups

	Study 1801					Study 1802				
	Natalizumab		Placebo			Natalizumab		Placebo		
	n	relapse rate	n	relapse rate	reduction (%)	n	relapse rate	n	relapse rate	reduction (%)
Overall	627	0.25	315	0.735	66.0%	245	0.253	265	0.687	63.2%
Baseline EDSS										
0	31	0.215	18	0.879	75.5%	24	0.068	19	0.659	89.7%
1	72	0.227	35	0.344	34.0%	45	0.212	35	0.79	73.2%
1.5	107	0.199	59	0.656	69.7%	101	0.305	108	0.733	58.4%
2	129	0.23	59	0.767	70.0%	130	0.383	124	0.796	51.9%
2.5	79	0.23	44	0.738	68.8%	83	0.441	79	0.641	31.2%
3	82	0.261	30	0.714	63.4%	76	0.362	63	0.847	57.3%
3.5	48	0.233	33	0.754	69.1%	49	0.331	64	0.921	64.1%
4	37	0.368	16	0.742	50.4%	42	0.442	48	0.746	40.8%
4.5	23	0.406	12	1.549	73.8%	26	0.579	23	0.887	34.7%
5 to 6	19	0.461	9	1.18	60.9%	13	0.33	19	0.875	62.3%
Number of Relapses in Year Prior to Enrollment										
0	6	0.167	6	0.722	76.9%	0	-	1	0	
1	368	0.219	180	0.623	64.8%	390	0.317	357	0.677	53.2%
2	197	0.287	102	0.74	61.2%	153	0.415	174	0.892	53.5%
3	43	0.284	20	1.65	82.8%	32	0.585	39	1.15	49.1%
≥ 4	13	0.468	7	0.94	50.2%	12	0.345	11	1.099	68.6%
Number of Relapses in 3 Years Prior to Enrollment										
1	105	0.155	49	0.421	63.2%	70	0.178	70	0.405	56.0%
2	206	0.17	125	0.607	72.0%	156	0.236	163	0.607	61.1%
3	168	0.304	82	0.77	60.5%	169	0.366	149	0.776	52.8%
4	79	0.345	32	1.16	70.3%	91	0.425	92	0.93	54.3%
≥ 5	69	0.389	27	1.29	69.8%	100	0.602	108	1.16	48.1%
Baseline McDonald Criteria Classification										
1	528	0.246	261	0.783	68.6%	538	0.367	532	0.789	53.5%
2	72	0.292	40	0.58	49.7%	46	0.266	44	0.752	64.6%
3	18	0.164	10	0.301	45.5%	3	0.217	3	0.334	35.0%
4	9	0.311	4	0.251	-23.9%	2	0	3	0	0.0%
Received Approved Alternative MS Drug Prior to Enrollment *										
Yes	48	0.461	26	0.936	50.7%	80	0.429	75	0.785	45.4%
No	579	0.232	289	0.717	67.6%	509	0.345	507	0.779	55.7%
Number of Baseline Gadolinium-enhancing Lesions										
0	311	0.234	172	0.57	58.9%	393	0.377	374	0.616	38.8%
1	117	0.22	52	0.74	70.3%	101	0.349	107	0.951	63.3%
2	63	0.272	26	0.783	65.3%	32	0.239	32	0.938	74.5%
3	38	0.276	18	0.566	51.2%	20	0.285	27	1.07	73.4%
4 to 9	63	0.282	30	1.27	77.8%	35	0.303	35	1.578	80.8%
10 to 98	35	0.36	17	1.56	76.9%	8	0.335	7	1.083	69.1%
Number of Baseline T2 Hyperintense Lesions										
< 9	31	0.363	16	0.563	35.5%	68	0.476	52	0.556	14.4%
≥ 9	596	0.244	299	0.745	67.2%	521	0.341	530	0.802	57.5%

* For Study 1801, the term "Approved Alternative MS Drug" in the above table refers to either glatiramer acetate or any beta interferon. For Study 1802, all subjects received Avonex® prior to the study, and the term "Approved Alternative MS Drug" in this table refers to either glatiramer acetate or any beta interferon other than Avonex®.

In general, subjects who had previously taken an alternative MS drug experienced higher relapse rates than subjects who had never taken an alternative MS drug. This is expected, given that patients with more active disease would be more likely to utilize a treatment for their MS than subjects with relatively inactive disease. However, the percent reduction in relapse rate was similar for these two groups of subjects.

In the placebo groups of both studies, there were trends toward higher relapse rates in subjects who had higher baseline numbers of gadolinium-enhancing lesions on MRI. Of note, however, the percent reduction in relapse rate associated with natalizumab administration tended to increase in subjects with higher numbers of baseline gadolinium-enhancing lesions, particularly in study 1802. Thus, the data do not suggest waning of natalizumab's treatment effect with greater baseline MRI activity.

In both studies, the natalizumab treatment effect was less robust in subjects with <9 (versus ≥9) baseline numbers of T2 hyperintense lesions. There were trends in favor of lower relapse rates in the placebo groups, as well as higher relapse rates in the natalizumab groups. However, only ~5% and ~10% of subjects in Studies 1801 and 1802, respectively, had <9 baseline T2 lesions at baseline, so some measure of caution is called for in interpreting these results.

Table 13 provides annualized relapse rates for each center that enrolled ≥ 20 subjects. There was a wide range in the percent reduction in annualized relapse rate. However, consistent with the robust natalizumab treatment effect observed across both studies, all but one of these larger enrolling sites showed a trend in favor of natalizumab.

Table 13: Primary Efficacy Endpoint, Annualized Relapse Rate, by Study Center

	Study 1801					Study 1802				
	Natalizumab		Placebo			Natalizumab		Placebo		
	n	relapse rate	n	relapse rate	reduction (%)	n	relapse rate	n	relapse rate	reduction (%)
Overall	627	0.25	315	0.735	66.0%	245	0.253	265	0.687	63.2%
Individual Large (≥ 20 Subjects) Centers										
1801 Site Number										
108	21	0.178	11	0.551	67.7%					
313	14	0.406	7	1.654	75.5%					
322	13	0.562	7	0.628	10.5%					
402	14	0.205	7	1.645	87.5%					
403	13	0.63	7	1.171	46.2%					
405	13	0	7	0.266	100.0%					
407	13	0.067	7	0	-100.0%					
440	14	0.133	6	0.655	79.7%					
443	13	0.15	7	0.563	73.4%					
446	13	0.21	7	0.263	20.2%					
449	14	0	7	0.125	100.0%					
1802 Site Number										
125						12	0.235	12	0.463	49.2%
142						10	0.141	10	0.238	40.8%
151						13	0.265	14	1.352	80.4%
156						12	0.205	11	0.471	56.5%
168						15	0.133	16	0.937	85.8%
170						15	0.213	16	0.637	66.6%
176						10	0.581	10	0.777	25.2%
197						11	0.514	12	1.105	53.5%
952						10	0.636	10	0.824	22.8%

6.1.4.6 Efficacy Results – Secondary Endpoints

The secondary endpoints were rank prioritized in the order presented below. If statistical significance ($p < 0.05$) was not achieved for any secondary endpoint, all secondary endpoints of a lower rank were not considered statistically significant. Analysis of all MRI scans was performed at a central facility that was blinded to treatment assignment.

6.1.4.6.1 New or Newly-enlarging T2 Hyperintense Lesions

This secondary endpoint was prespecified as the reduction in the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, comparing the natalizumab group to the

placebo group, using a pre-specified logit regression, adjusted for baseline number of T2 lesions (<9 versus ≥9 lesions).

Table 14 includes only those subjects who had year 1 gadolinium-enhancing MRI data available.

Table 14: Number of New or Newly-Enlarging T2 Hyperintense Lesions on Year 1 MRI*

	Study 1801		Study 1802	
	Placebo N = 293	Natalizumab N = 600	Placebo N = 485	Natalizumab N = 505
0	70 (24%)	376 (63%)	230 (47%)	392 (78%)
1	41 (14%)	112 (19%)	70 (14%)	69 (14%)
2	23 (8%)	40 (7%)	61 (13%)	24 (5%)
3	24 (8%)	30 (5%)	39 (8%)	10 (2%)
4-9	71 (24%)	34 (6%)	55 (11%)	8 (2%)
10-98	64 (22%)	8 (1%)	30 (6%)	2 (<1%)

* Missing data omitted from analyses.

Considering subjects with available 1 year MRI data, natalizumab treatment was associated with absolute increases of 39% and 31% in the percentage of subjects with no new or newly-enlarging T2-hyperintense lesions in Studies 1801 and 1802, respectively (Table 14).

Subjects who are missing MRI data are likely to be a biased population. Therefore, the above analyses, which exclude these subjects, may over-represent the relative number of subjects in each group with a good outcome (i.e., a low number of new or newly-enlarging T2-hyperintense lesions).

Applicant's analysis: In Study 1801, Year 1 T2 MRI data are missing for 49 subjects: 22 in the placebo group and 27 in the natalizumab group. The mean number of new or newly-enlarging T2 hyperintense lesions at Year 1 was 2.85 for all subjects with Year 1 MRI data. This value was rounded to 3 and imputed as the number of new or newly enlarging T2 hyperintense lesions at Year 1 for all subjects who did not have a Year 1 MRI.

In Study 1802, Year 1 T2 MRI data is missing for 181 subjects: 97 in the placebo group and 84 in the natalizumab group. The mean number of new or newly-enlarging T2 hyperintense lesions at Year 1 was 1.30 for all subjects with Year 1 MRI data. This value was rounded to 1 and imputed as the number of new or newly enlarging T2 hyperintense lesions at Year 1 for all subjects who did not have a Year 1 MRI.

Using the above imputation for Study 1801, treatment with natalizumab resulted in an 80% reduction in the mean number of new or newly-enlarging T2-hyperintense lesions (6.1 vs. 1.2, $p<0.001$, Table 15). Using the above imputation for Study 1802, treatment with natalizumab resulted in a 76% reduction in the mean number of new or newly-enlarging T2-hyperintense lesions (2.1 vs. 0.5, $p<0.001$, Table 15). Because the numbers of lesions are not normally

distributed (see Table 14), the median values and the distributions of subjects may be more representative of natalizumab activity than the mean values.

Table 15: 1 Year New or Newly-Enlarging T2-Hyperintense Lesions

	Study 1801		Study 1802	
	Placebo N = 315	Natalizumab N = 627	Placebo + Avonex® N = 582	Natalizumab + Avonex® N = 589
Median	3	0	1	0
Range				
Mean	6.1	1.2	2.1	0.5
Standard Deviation	8.89	4.66	3.67	1.13

6.1.4.6.2 Gadolinium-Enhancing Lesions

This secondary endpoint was prespecified as the reduction in the number of gadolinium-enhancing lesions on brain MRI scans, comparing the natalizumab group to the placebo group, using a pre-specified logit regression, adjusted for baseline number of gadolinium-enhancing lesions. For this analysis, missing values were imputed using the mean number of gadolinium-enhancing lesions in the study population.

Applicant's analyses: In Study 1801, there was a 92% reduction in the mean number of Gd-enhancing lesions (1.2 vs. 0.1, $p<0.001$). In Study 1802, there was an 88% reduction in the mean number of Gd-enhancing lesions (0.8 vs. 0.1, $p<0.001$; Table 16).

Table 16: Summary of 1 Year Gadolinium-Enhancing Lesions

	Study 1801		Study 1802	
	Placebo N = 315	Natalizumab N = 627	Placebo N = 582	Natalizumab N = 589
Median	0	0	0	0
Range				
Mean	1.25	0.12	0.77	0.13
Standard Deviation	3.18	1.33	2.47	0.39

Because the numbers of lesions are not normally distributed (see Table 17), the median values and distributions of subjects may be more representative of natalizumab activity than the mean values. Table 17 includes only those subjects who had Year 1 gadolinium-enhancing MRI data available.

Table 17: Number of Gadolinium-Enhancing Lesions on Year 1 MRI

	Study 1801		Study 1802	
	Placebo N = 292	Natalizumab N = 600	Placebo N = 483	Natalizumab N = 504
0	192 (66%)	577 (96%)	343 (71%)	479 (95%)
1	41 (14%)	17 (3%)	71 (15%)	18 (4%)
2	15 (5%)	4 (1%)	27 (6%)	3 (1%)
3	8 (3%)	0 (0%)	13 (3%)	2 (<1%)
4-9	27 (9%)	1 (<1%)	21 (4%)	2 (<1%)
10-43	9 (3%)	1 (<1%)	8 (2%)	0 (0%)

In Study 1801, a single subject (subject #124-006) with — gadolinium-enhancing lesions accounted for 50% of the 64 total gadolinium-enhancing lesions in all 600 natalizumab group subjects. Subject 124-006 is a 50 year-old woman who received 7 doses of natalizumab. She did not receive any natalizumab doses after Week 24, so she was off natalizumab for approximately 6 months before she had the MRI that showed — gadolinium-enhancing lesions.

In subjects with 1 year MRI data available regarding the number of gadolinium-enhancing lesions (Table 17), natalizumab treatment resulted in a 30% absolute increase (45 % relative increase) in the percent of Study 1801 subjects with no gadolinium-enhancing lesions, and a 24% absolute increase (34 % relative increase) in the percent of Study 1802 subjects with no gadolinium-enhancing lesions. Most striking is the fact that 96% of natalizumab-treated subjects in Study 1801 had no gadolinium-enhancing lesions at one year, and this finding was precisely recapitulated in Study 1802.

Subjects who are missing MRI data are likely to be a biased population. Therefore, the above analyses, which exclude these subjects, may over-represent the relative number of subjects in each group with a good outcome (i.e., a low number of gadolinium-enhancing lesions).

In Study 1801, Year 1 MRI data regarding gadolinium-enhancing lesions are missing for 50 subjects: 23 in the placebo group and 27 in the natalizumab group. The mean number of gadolinium-enhancing lesions at Year 1 was 0.50 for all subjects with Year 1 MRI data. This value was imputed as the number of gadolinium-enhancing lesions at Year 1 for all Study 1801 subjects who did not have data regarding gadolinium-enhancing lesions at Year 1.

In Study 1802, Year 1 MRI data regarding gadolinium-enhancing lesions are missing for 184 subjects: 99 in the placebo group and 85 in the natalizumab group. The mean number of gadolinium-enhancing lesions at Year 1 was 0.45 for all subjects with Year 1 MRI data. This value was imputed as the number of gadolinium-enhancing lesions at Year 1 for all Study 1802 subjects who did not have data regarding gadolinium-enhancing lesions at Year 1.

6.1.4.6.3 Proportion of Subjects Relapse-Free

This secondary endpoint was prespecified as the increase in the proportion of relapse-free subjects, comparing the natalizumab group to the placebo group, using a pre-specified logistic regression adjusted for the number of relapses in the one year prior to study entry. For this analysis, a subject was considered to have relapsed if either the subject withdrew from the study and did not experience a relapse prior to withdrawal, or the subject took alternative MS medications and did not experience a relapse.

Applicant's analyses: In Study 1801, natalizumab was associated with a 43% relative (23% absolute) increase in the proportion of relapse-free subjects (76% vs. 53%, p<0.001). There are 32 subjects (13 subjects in the placebo group; 19 subjects in the natalizumab group) for whom relapse information is unknown, either because they left the study prior to having a relapse or because they started an alternative MS drug prior to having a relapse. In the applicant's analysis, all of these subjects are considered to have relapsed.

Table 18: Proportion of Subjects Relapse-Free

	Study 1801			Study 1802		
	Placebo N = 315	Natalizumab N = 627	Relative risk[0] (95% CI)	Placebo + Avonex® N = 582	Natalizumab + Avonex® N = 589	Relative risk[0] (95% CI)
Number relapse-free[1]	166 (53%)	474 (76%)	1.43 (1.28, 1.61)	265 (46%)	392 (67%)	1.46 (1.32, 1.62)
Number relapse-free[2]	N = 302 166 (55%)	N = 608 474 (78%)	1.42 (1.27, 1.58)	N = 563 265 (47%)	N = 569 392 (69%)	1.46 (1.32, 1.62)
Number relapse-free[3]	N =299 171 (57%)	N = 597 452 (76%)	1.32 (1.19, 1.48)	N =582 284 (49%)	N = 589 392 (67%)	1.36 (1.23, 1.51)

[0] Relative risk of being relapse-free, comparing natalizumab group to placebo group
[1] Analysis with subjects of unknown status (including 13 placebo group and 19 natalizumab group subjects in Study 1801, 19 placebo group and 20 natalizumab group subjects in Study 1802) as having relapses (i.e., applicant's analysis)
[2] Analysis with subjects of unknown status excluded from the analysis
[3] Analysis with subjects of unknown status, using a worst-case possibility, counting placebo group subjects as not having a relapse and natalizumab group subjects as having a relapse; this analysis excluded data from all sites with a known conflict of interest (results in excluding 16 placebo subjects and 30 natalizumab subjects from the analysis).

Reviewer's comment: The analyses in Table 18 indicate that the benefit seen with natalizumab is a robust effect that is not dependent on the method for imputation of missing data.

6.1.5 Clinical Microbiology

Natalizumab is not an antimicrobial. Therefore, this section is not applicable to this review.

6.1.6 Efficacy Conclusions

Analyses of the primary and secondary endpoints provide statistically strong and consistent support for the efficacy of natalizumab. Subgroup and sensitivity analyses also support the existence of a favorable treatment effect of natalizumab.

Natalizumab appears to be effective in decreasing the relapse rate at one year in subjects with active relapsing-remitting MS. Natalizumab is effective when administered as monotherapy and when administered as add-on therapy to a beta-interferon for subjects who have continued to relapse while taking Avonex®.

For other MS products, FDA has required two-year data to support an indication for decreasing the frequency of clinical relapses. A salutary effect on relapse rate at one year is not a validated surrogate for benefit at two years. However, the apparent treatment effect of natalizumab with respect to relapse rate at one year is unprecedented in the MS field, and its magnitude is reasonably likely to predict clinically meaningful effectiveness at two years. If, in fact, the benefit on clinical relapses is shown to be durable through two years, the product may be substantially more efficacious than currently approved MS therapies (see Section 2.2, Currently Available Treatment for Indications).

It is possible, however, that the magnitude of natalizumab's effect on relapse rate, when assessed through one year, may substantially overestimate natalizumab's benefit on relapse rate through two years, as well as its risks. In particular, the treatment effect appears to wane with the development of anti-natalizumab antibodies, which may increase with time (see Section 7.1.10, Table 34). Therefore, the final two-year results of the two Phase 3 studies (Studies 1801 and 1802) are critical for a more complete characterization of the risk benefit relation (see Section 9.3.2, Required Phase 4 Commitments).

The effect of natalizumab as an add-on therapy appears to represent a significant advance over currently available first-line MS treatments (the interferon betas and glatiramer acetate), none of which have proven efficacy as add-on therapy to one another (see Section 2.2, Currently Available Treatment for Indications). Therefore, natalizumab has the potential to address an unmet medical need by providing a benefit when added to an existing therapy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

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. Table 19 includes the data from a 120-day safety update (Amendment 12 to the original BLA application), which includes Study 1801 safety data through March 1, 2004 and Study 1802 safety data through April 15, 2004.

The table highlights the limited duration of exposure to natalizumab in CD placebo-controlled trials, relative to the MS trials. Study CD303 is a moderately-sized (428 subjects), placebo-controlled study of administration of the proposed recommended natalizumab dose for up to 48 weeks in subjects with CD. Study CD303 is ongoing and therefore provides limited data for this review. The open-label experience in CD includes exposure of 1098 subjects to natalizumab, but includes only 382 subjects with at least one year of exposure to natalizumab. The placebo-controlled experience in normal volunteers is limited to the 35 subjects in Study 101. Phase 1 and Phase 2 studies of natalizumab in MS were generally small, brief in duration, and/or used weight-adjusted natalizumab dosing (see Section 4.2, Tables of Clinical Studies). For these reasons, the studies in CD, ulcerative colitis (a single open-label study in 10 subjects), and normal volunteers, as well as the Phase 1 and Phase 2 MS studies, do not contribute substantially to the safety database, and are not considered in detail in this review.

Table 19: Total Exposure to Natalizumab in Placebo-Controlled Trials

	Multiple Sclerosis			Crohn's Disease		
	Total	Natalizumab	Placebo	Total	Natalizumab	Placebo
Total N	2752	1617	1135	1178	922	256
Duration of Exposure (weeks)						
1 to <12	376	247	129	1178	922	256
12 to <24	114	63	51	0	0	0
24 to <52	331	184	147	0	0	0
52 to <116	1924	1119	805	0	0	0
≥ 116	7	4	3	0	0	0

Thus, 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 (300 mg IV every 4 weeks) to MS subjects for more than 6 months. Study 1801 compared natalizumab monotherapy (627 subjects) to placebo (315 subjects) and is highlighted in this safety review. Study 1802 included administration of natalizumab (582 subjects) or placebo (589 subjects) to subjects who also received Avonex® 30 µg IM once a week. Because all subjects in Study 1802 received background administration of Avonex®, Study 1802 provides a less clear assessment of the

safety of natalizumab, compared to Study 1801. **Thus, the Study 1801 data were primarily used to assess the incidence of adverse events against a placebo background.**

For ongoing studies, including MS trials 1801, 1802, and 1808, and CD trials CD303, CD351, and CD352, this review considers safety data through cut-off dates ranging from March 1st to April 30th, 2004.

7.1.1 Deaths

There have been nine deaths in the natalizumab development program. The causes of death are summarized below:

- Three subjects receiving placebo in MS trials
  1. 66 year-old woman – pleural carcinomatosis complicated by hemothorax and myocardial infarction, Study 231
  2. 47 year-old woman – sudden death, presumed cardiac arrhythmia, Study 1802
  3. 23 year-old woman – sudden death, unexplained, Study 1802
- Two subjects receiving natalizumab in MS trials
  1. 49 year-old woman – violent death (homicide or suicide; police investigation in progress), Study 1801
  2. 5 year-old girl – respiratory distress secondary to progressive MS, Study 1804; At age 18 months, while recovering from a fever and upper respiratory infection, the subject developed a right hemiparesis. Subsequent exacerbations included transverse myelitis, truncal ataxia, bilateral optic neuritis, and left hemiparesis. She did not tolerate cyclophosphamide and did not responded adequately to steroids, intravenous immunoglobulin, and a beta-interferon. The sponsor initiated a single-subject study in order to provide her with open-label natalizumab. She received a total of ten weight-adjusted (3 mg/kg – 6 mg/kg) infusions of natalizumab. She received her last natalizumab infusion on ——— However, due to continued progression of her MS, natalizumab administration was discontinued. She was subsequently treated with mitoxantrone and daclizumab. In ——— she was blind as a result of MS and had a white blood cell count of 500/mm^3. She died in ——— with cause of death listed as MS and post-infectious encephalitis.
- Four subjects receiving natalizumab in CD trials
  1. 42 year-old man – carbon monoxide poisoning, described by the applicant as "work-related … [and] accidental," Study 301
  2. 49 year-old woman – progression of CD and nephrotic syndrome, complicated by peritonitis and sepsis, Study 301
  3. 60 year-old man – malignant astrocytoma, Study 351
  4. 73 year-old man – perforated duodenal ulcer with peritonitis and pulmonary aspergillosis, Study 351

The deaths in MS trials do not provide a clear safety signal, although the possibility of a suicide in a Study 1801 subject who received natalizumab is of concern. The deaths in CD trials are of concern, particularly because a mechanistic relationship to natalizumab is plausible for the two

subjects who developed infections and the one subject who developed a malignancy (see Section 2.4, Important Issues With Pharmacologically Related Products).

7.1.2 Non-Fatal Serious Adverse Events

Table 20 provides the applicant's analysis of serious adverse events from all placebo-controlled trials in MS and CD. Note that with the exception of hypersensitivity and anaphylactoid reactions, no safety signal emerges.

In its examination of the adverse event listings, CDER found a number of events that had been divided into multiple categories, making their detection difficult (e.g., "pneumonia," "lobar pneumonia," "atypical pneumonia," etc.). Thus, CDER performed a manual, blinded analysis of the adverse event listings in the safety "as treated" population. This involved tabulation of 31,278 lines of adverse event data for Studies 1801 and 1802. Adverse events which occurred prior to the first administration of study agent were not considered in this analysis.

Table 21 summarizes CDER's analysis, which includes all serious adverse events with an incidence >0.5% in the natalizumab group in Studies 1801 and 1802 (see Section 2.4, Important Issues With Pharmacologically Related Products). Note that the numbers can not be compared to the applicant's analyses in Table 20, because the applicant has combined Studies 1801 and 1802 with other MS studies under the "Multiple Sclerosis" columns (left).

Table 20: Percent of Subjects with Serious Adverse Events in Placebo-Controlled Trials; Includes All Serious Adverse Events With Incidence ≥ 1% In Natalizumab Group, And Selected Serious Adverse Events of Interest (From Applicant's Analysis)

(%)	Multiple Sclerosis[1]		Crohn's Disease[2]	
	Natalizumab N = 1617	Placebo N = 1135	Natalizumab N = 922	Placebo N = 256
Any serious adverse event	12.5	15.2	17.4	17.2
Infections and infestations	1.8	1.6	2.8	3.1
Neoplasms	0.6	1.2	0.9	0.4
Hypersensitivity / Anaphylactoid	0.7	0.2	0.5	0.4
Depression / Suicide attempt	0.6	0.7	0.2	0.8
Cardiac disorders	<0.1	0.4	0.5	0

[1] Placebo-controlled MS trials includes studies 200, 202, 221, 201, 231, 1801, 1802, and 1803
[2] Placebo-controlled CD studies include CD — , CD202, and CD301

Table 21: CDER Analysis of Serious Adverse Events, >0.5% Incidence in Study 1801, Greater Frequency in Natalizumab Group Than Placebo Group

	Study 1801		Study 1802	
	Natalizumab n = 627	Placebo n = 315	Natalizumab + Avonex n = 601	Placebo + Avonex n = 595
Infection	13 (2.1%)	4 (1.3%)	11 (1.8%)	7 (1.2%)
Allergic reaction	8 (1.3%)	1 (0.3%)	2 (0.3%)	3 (0.5%)
Anaphylaxis	3 (0.5%)	0 (0%)	1 (0.2%)	1 (0.2%)
Cholelithiasis	5 (0.8%)	1 (0.3%)	2 (0.3%)	0 (0%)
Depression	5 (0.8%)	3 (1.0%)	2 (0.3%)	1 (0.2%)
Suicidal Ideation or Attempt	3 (0.5%)	1 (0.3%)	0 (0%)	1 (0.2%)
Neoplasm	4 (0.6%)	1 (0.3%)	3 (0.5%)	5 (0.8%)
Urinary Tract Infection	4 (0.6%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
Pneumonia	4 (0.6%)	0 (0%)	1 (0.2%)	1 (0.2%)

Notable serious adverse events, more frequent in the natalizumab group, were infection (including pneumonia and urinary tract infection), allergic reaction, anaphylaxis, and cholelithiasis.

Of note, the majority of subjects were exposed to the study agent for less than 13 months. The total number of adverse events per subject will increase with the two-year exposure in the two Phase 3 studies. Therefore, the final study reports for those studies will provide a more complete picture of the adverse event profile.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile of Dropouts

The total number of dropouts (approximately 4% in Study 1801 and 6% in Study 1802) at one year is well within the range of other large MS trials (

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Table 22). MS patients now have several available treatment options (see Section 2.2, Immune Modulators Approved for Treatment of MS). Study subjects in current trials may be less tolerant of adverse events or perceived lack of efficacy than during previous trials when treatment options were more limited. Dropouts due to lack of efficacy were more common in the placebo group in each study, consistent with natalizumab's association with decreased relapse rate. Dropouts due to adverse events were similar in the two groups in each study. However, dropouts due to allergic reactions (including hypersensitivity reactions and urticaria) were more common in the natalizumab group in Study 1801, consistent with clinically important immunogenicity of natalizumab (See Section 7.1.10, Immunogenicity).

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Table 22: Dropouts from Pivotal Clinical Trials (CDER Analysis)**

	Study 1801		Study 1802	
	Natalizumab N = 627	Placebo N = 315	Natalizumab + Avonex N = 589	Placebo + Avonex N = 582
Total withdrawals from study (%)	**21 (3)**	**18 (6)**	**29 (5)**	**41 (7)**
Withdrew consent prior to the first administration of study drug.	0	3	0	0
Risk of adverse event	1	0	0	1
Lack of efficacy and/or decision to take alternative MS therapy	1	4	5	17
Subject moved from area	1	1	4	1
Study procedures burdensome	0	1	3	6
Pregnancy or unwilling to practice contraception	3	1	4	3
Personal reasons or reason not specified	1	0	2	4
Lost to follow-up	0	2	2	2
Noncompliance	1	0	1	1
Total study withdrawals due to adverse events* (%)	**13 (2)**	**6 (2)**	**8 (<1)**	**6 (<1)**
Urticaria	4	2	0	0
Hypersensitivity reactions (includes anaphylaxis and anaphylactoid reactions)	2	0	0	0
Abdominal pain	1	0	0	0
Adverse drug reaction, not otherwise specified	1	0	0	0
Conjunctivitis, night sweats, arthralgia, and headache	1	0	0	0
Alcohol poisoning	1	0	0	0
Cough	1	0	0	0
Allergic dermatitis	1	0	0	0
Overdose, not otherwise specified	1	0	0	0
Depression or suicidal ideation	1	0	2	1
Ulcerative colitis	0	1	0	0
Elevated liver function tests	0	1	1	0
Multiple sclerosis	0	1	1	1
Musculoskeletal stiffness	0	1	0	0
Rash, not otherwise specified	0	1	0	0
Diarrhea	0	0	2	0
Headache	0	0	1	0
Herpes zoster	0	0	1	0
Nasopharyngitis	0	0	1	0
Peripheral edema	0	0	1	0
Pain in extremity	0	0	1	0
Fever	0	0	1	0
Syncope	0	0	1	0
Breast cancer	0	0	0	1
Death, presumed cardiac etiology	0	0	0	1
Increased flu-like symptoms	0	0	0	1
Molluscum contagiosum	0	0	0	1

* Some subjects cited more than one adverse event as reason for withdrawal from the study.
** Includes only dropouts through the date of the 1-year analysis (see Section 6.1.2, General Discussion of Endpoints).

7.1.3.2 Adverse Events Associated With Dropouts

In the two Phase 3 MS studies, the most common adverse events associated with dropping out of the study or discontinuing study medication were urticaria, anaphylaxis, and hypersensitivity reactions (see Section 7.1.10, Immunogenicity), and depression or suicidal ideation. Each of these types of events occurred more frequently in subjects who received natalizumab (see Section 7.1.5, Common Adverse Events).

7.1.3.3 Other Significant Adverse Events

All significant adverse events are listed as either serious adverse events (see Section 7.1.2, Other Serious Adverse Events), or reasons for discontinuation of treatment (see Section 7.1.3.1, Overall profile of dropouts). Significant laboratory abnormalities are discussed in Section 7.1.7.3, Standard analyses and explorations of laboratory data).

7.1.4 Other Search Strategies

On request of CDER, the applicant provided tables listing the frequency of adverse events relative to the time of study agent infusion. The objective of this analysis was to look for distribution patterns that differed between the two arms of the studies. For example, events that relate to a relatively high concentration of natalizumab might be more likely to cluster in the natalizumab group, but not in the placebo group, in the first few days following study agent administration. Similarly, CDER reviewed data for Studies 1801 and 1802, separately and combined. CDER did not identify any clear difference in the pattern of distribution of events.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting Adverse Events Data in The Development Program

The applicant's approach to eliciting adverse event data was the same in Studies 1801 and 1802, the two pivotal studies.

An adverse event was defined as any untoward medical occurrence experienced by a subject. An adverse event could be any sign (including an abnormal laboratory result that the investigator determined was clinically significant), symptom, or diagnosis/disease that was unfavorable or unintended, that appeared or worsened in a subject. All adverse events reported by the subject or observed by investigational site personnel from the start of study drug treatment until (and including) the subject's last follow-up visit were recorded in the subject's case report form (CRF). Laboratory values that were deemed clinically significant were recorded as adverse

events. Adverse events were to be recorded regardless of relationship to study drug. Adverse events reported solely at the screening visit (prior to administration of the test agent) were not included in the analyses.

Overdose and pregnancy were not considered adverse events, although the applicant did collect this information. However, if there were subsequent adverse events as a result of overdose or pregnancy, these subsequent events were to be reported on the adverse event form.

Adverse Events were classified as serious if they met any of the following criteria (in accordance with 21 CFR Part 312.32).

- Any death.
- Any life-threatening event, i.e., an event that placed the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (does not include an event that, had it occurred in a more severe form, might have caused death).
- Any event that required or prolonged in-patient hospitalization.
- Any event that resulted in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a subject who was participating in this study and received study drug.
- Other medically important events that in the opinion of the investigator jeopardized the subject or required intervention to prevent one of the other outcomes listed in the definition above.
- A new diagnosis of cancer.

Monitoring and recording of adverse events were performed at each study visit after randomization. This included Study Drug Administration Visits (SDAVs) at baseline (Week 0) and every 4 weeks (+/- 3 days) through Week 116, Unscheduled Clinical Evaluation Visits (CEVs) to assess possible relapses, an End-of-Study visit at Week 120, and a post-treatment visit at Week 128. For subjects who discontinued study agent administration, telephone contacts every four weeks to monitor adverse events replaced the SDAVs. For subjects who dropped out of the study, adverse events were recorded at a premature study withdrawal visit. Additional information regarding the assessments at each visit is provided in Section 6.1.3.1.4, Study 1801 – Study Procedures).

7.1.5.2 Appropriateness of Adverse Event Categorization and Preferred Terms

The applicant provided COSTART and MedDRA terms for all adverse events in the two Phase 3 MS trials. CDER initially disagreed with the applicant on the classification of some adverse

events. CDER reviewed the primary symptom for each adverse event and classified each adverse event as deemed appropriate, with no consideration for the COSTART and MedDRA classification provided by the applicant. CDER did not conduct any formal assessment of the extent of disagreement between the applicant's classification and CDER's classification of adverse events. However, CDER and the applicant resolved all substantial disagreements through extensive discussion and cooperative review of the safety database. Examples of initial disagreements included: separation of loss of consciousness from syncope (CDER considered both together), separation of "lobar pneumonia," "bronchial pneumonia," and "atypical pneumonia," (CDER considered all as "pneumonia"), etc. Agreement was reached to use gender-specific denominators for gender-related adverse events, e.g., gynecologic events.

7.1.5.3 Incidence of Common Adverse Events

This safety review is based on CDER's independent classification of adverse events. For reasons discussed previously (see Section 7.1, Methods and Findings), the adverse event tables in the next section consider only adverse events from Studies 1801 and 1802.

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7.1.5.4 Common Adverse Event Tables

Table 23 summarizes CDER's analyses of common adverse events from Studies 1801 and 1802, based on a blinded classification of the 31,278 line listings. The table includes events with a frequency of ≥2% in study 1801.

Table 23: Common Adverse Events With Incidence of ≥ 2% in Natalizumab Group of Study 1801

	Study 1801		Study 1802	
	Natalizumab n=627	Placebo n=315	Natalizumab + Avonex n=601	Placebo + Avonex n=595
infection	424 (67.6)	198 (62.9)	236 (39.3)	242 (40.7)
headache	206 (32.9)	92 (29.2)	147 (24.5)	142 (23.9)
fatigue or malaise	149 (23.8)	57 (18.1)	105 (17.5)	114 (19.2)
depression	106 (16.9)	43 (13.7)	65 (10.8)	53 (8.9)
arthritis/arthralgia	105 (16.7)	38 (12.1)	85 (14.1)	75 (12.6)
sleep disorder	90 (14.4)	38 (12.1)	73 (12.1)	63 (10.6)
urinary tract infection	89 (14.2)	38 (12.1)	55 (9.2)	66 (11.1)
rhinitis, congestion stuffiness	80 (12.8)	36 (11.4)	54 (9)	41 (6.9)
abdominal discomfort	70 (11.2)	31 (9.8)	39 (6.5)	36 (6.1)
rash	58 (9.3)	22 (7)	36 (6)	39 (6.6)
gastroenteritis	55 (8.8)	16 (5.1)	51 (8.5)	42 (7.1)
urinary urgency and incontinence	53 (8.5)	15 (4.8)	43 (7.2)	37 (6.2)
infection, viral	51 (8.1)	22 (7)	47 (7.8)	46 (7.7)
* vaginitis	32 (7.1)	8 (3.8)	20 (4.5)	28 (6.7)
* menstrual irregularities	30 (6.7)	7 (3.4)	15 (3.4)	9 (2.1)
GOT/GPT/GGT	30 (4.8)	10 (3.2)	14 (2.3)	20 (3.4)
dematitis	27 (4.3)	9 (2.9)	23 (3.8)	11 (1.8)
pruritus	25 (4)	6 (1.9)	19 (3.2)	17 (2.9)
allergic reaction	23 (3.7)	4 (1.3)	14 (2.3)	18 (3)
rigors	17 (2.7)	3 (1)	15 (2.5)	2 (0.3)
bleeding	17 (2.7)	5 (1.6)	8 (1.3)	7 (1.2)
* dysmenorrhoea	11 (2.4)	1 (0.5)	8 (1.8)	16 (3.8)
neuralgia	10 (1.6)	1 (0.3)	7 (1.2)	5 (0.8)
* amenorrhea	8 (1.8)	0 (0)	0 (0)	4 (1.0)

* percentage based on female n

Table 24includes all severe adverse events with incidence of at least 0.6% in the natalizumab group in Study 1801 (see Section 2.4, Important Issues With Pharmacologically Related Products). The most concerning signal is infection, although most were mild and resolved either spontaneously or to usual antibiotic intervention. The incidence of severe adverse events was generally low in this study, for an MS population.

Table 24: Severe Adverse Events with Incidence ≥ 0.6% in Natalizumab Group (Study 1801)

	Study 1801		Study 1802	
	Natalizumab n = 627	Placebo n = 315	Natalizumab + Avonex n = 601	Placebo + Avonex n = 595
infection	22 (3.5%)	8 (2.5%)	35 (5.8%)	29 (4.9%)
fatigue or malaise	19 (3%)	9 (2.9%)	22 (3.7%)	23 (3.9%)
MS possible relapses	19 (3%)	23 (7.3%)	10 (1.7%)	31 (5.2%)
headache	12 (1.9%)	11 (3.5%)	21 (3.5%)	16 (2.7%)
muscle cramp, spasm, stiffness, tightness, heaviness	9 (1.4%)	7 (2.2%)	12 (2%)	20 (3.4%)
mood or emotional disorders	8 (1.3%)	5 (1.6%)	12 (2%)	5 (0.8%)
back strain/ache	7 (1.1%)	3 (1%)	3 (0.5%)	12 (2%)
pain in extremity	6 (1%)	2 (0.6%)	6 (1%)	9 (1.5%)
infection, bacterial	5 (0.8%)	3 (1%)	4 (0.7%)	3 (0.5%)
sleep disorder	5 (0.8%)	1 (0.3%)	2 (0.3%)	3 (0.5%)
Arthritis/arthralgai	5 (0.8%)	2 (0.6%)	6 (1%)	2 (0.3%)
miscellaneous allergic reaction	4 (0.6%)	1 (0.3%)	0 (0%)	2 (0.3%)
anaphylaxis /anaphylactoid	4 (0.6%)	0 (0%)	0 (0%)	1 (0.2%)
migraine	4 (0.6%)	3 (1%)	5 (0.8%)	11 (1.8%)
neoplasm	4 (0.6%)	0 (0%)	1 (0.2%)	2 (0.3%)
urinary tract infection	4 (0.6%)	1 (0.3%)	7 (1.2%)	4 (0.7%)
depression	4 (0.6%)	2 (0.6%)	10 (1.7%)	3 (0.5%)
anxiety	4 (0.6%)	2 (0.6%)	1 (0.2%)	0 (0%)

The incidence of Avonex® injection site reactions, including bruising, pain, and erythema, was approximately 3% in each study group of Study 1802. This low incidence probably reflects the study eligibility requirement that all subjects must have received Avonex® for at least one year prior to enrollment. MS patients who had Avonex® injection site reactions after prolonged exposure would most likely have discontinued Avonex® and been ineligible for Study 1802.

7.1.5.5 Common and Drug-Related Adverse Events

See Table 23 and Table 24.

Adverse events that were more common in the natalizumab group include infection (including pneumonia), headache, fatigue or malaise, depression, other mood or emotional disorders, arthritis/arthralgia, rhinitis and nasal congestion, ear and hearing disorders, abdominal

discomfort, gastroenteritis, menstrual disorders (including menstrual irregularities, dysmenorrhea, and amenorrhea), dermatitis, bleeding (including epistaxis), urticaria, and hypersensitivity reactions (including anaphylaxis and anaphylactoid reactions). Most of these adverse events occurred with an incidence only slightly (i.e., 1-3%) higher in the natalizumab group than the placebo group in one or both of the two Phase 3 MS studies.

Of the many possible sites for infection, the most consistent site for an increased risk of infection associated with natalizumab was the gastrointestinal tract, with increased incidence of gastroenteritis in the natalizumab group in both studies. This is consistent with the proposed mechanism of action of natalizumab (see Section 2.1, Product Information), which binds to α4-integrins. The α4β7 integrin, which is expressed on lymphocytes with a tropism for the gastrointestinal tract, binds to the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Natalizumab may block this interaction by binding to the α4 subunit, preventing the lymphocytes from reaching their normal targets in the gastrointestinal parenchyma. However, the clinical assessment of infection as the etiology of gastroenteritis can be difficult; therefore, this correlation of the proposed mechanism of action with the adverse event profile may be a spurious finding.

Infusion reactions were defined as adverse events that started within two hours after the initiation of the study drug infusion. In Study 1801, infusion reactions occurred in 20% of the natalizumab group subjects and 15% of the placebo group subjects. In Study 1802, infusion reactions occurred in 21% of the natalizumab group subjects and 16% of the placebo group subjects. The most common infusion reactions were headache, nausea, flushing, erythema, fatigue, dizziness, urticaria, pruritus, rigors, and chest tightness or pain. Headache occurred in 3-4% of subjects in Studies 1801 and 1802; all other infusion site reactions occurred in no more than 1% of subjects in either treatment group in either study. Infusion reactions that were classified as severe or serious included hypersensitivity reactions, dizziness, flushing, and headache; each of these severe or serious infusion reactions had an incidence <0.5%, except for hypersensitivity reactions, which occurred in the natalizumab groups with an incidence of 1%.

There were 4 malignancies reported in the natalizumab group in Study 1801 (0.6%) and 1 malignancy reported in the placebo group (0.3%). In Study 1802, there were 3 and 4 malignancies reported in the natalizumab + Avonex® and placebo + Avonex® groups, for rates of 0.5% and 0.7%, respectively. Overall, there was no clear association between natalizumab administration and malignancy.

7.1.5.6 Additional Analyses and Explorations

Additional exploratory analyses of the adverse events that appeared to be drug-related centered on the issue of immunogenicity (see Section 7.1.10, Immunogenicity).

7.1.6 Less Common Adverse Events

7.1.6.1 Uncommon Adverse events

CDER review of uncommon adverse events in the entire safety database did not identify additional safety concerns.

7.1.6.2 Progression of Disability

The two primary clinical manifestations of multiple sclerosis are relapses and progression of disability (see Section 2, Introduction and Background). CDER expressed concern that natalizumab might produce a favorable effect on relapse frequency while having an adverse effect on progression of disability. However, progression of disability is the primary endpoint for the two-year analysis (see Section 6.1.2, General Discussion of Endpoints). In order to prevent any unblinding that might create bias in the study personnel, the applicant did not conduct any analyses of disability progression as part of the 1 year analyses in the original submission of this BLA. For the purpose of this BLA review, CDER viewed the progression of disability as solely a safety issue, and not as an efficacy parameter. CDER evaluated minimal information on disability in order to obtain some reassurance that natalizumab was not associated with an adverse effect on progression of disability. This information is viewed as safety data and does not impact the alpha allotment for the primary endpoint of progression of disability at two years (see Section 6.1.2, General Discussion of Endpoints). The limited data on disability did not reveal any apparent acceleration of disability in the natalizumab group.

7.1.7 Laboratory Findings

7.1.7.1 Overview of Laboratory Testing in the Development Program

For reasons discussed previously (see Section 7.1, Methods and Findings), this review focuses on laboratory testing in Studies 1801 and 1802. These two Phase 3 MS studies included the following laboratory studies.

1) Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen, creatinine, and bicarbonate at Screening, at Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and at premature study withdrawal visits.

2) Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, total leukocyte (WBC) count (with differential), and platelet count at Screening, at Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and at premature study withdrawal visits.

3) Urinalysis: color, specific gravity, pH, protein, glucose, blood, and ketones at Screening, at Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, and at premature study withdrawal visits.

7.1.7.2 Selection of Studies and Analyses for Drug-Control Comparisons of Laboratory Values

This review focuses on Studies 1801 and 1802, which provide the only substantial database on natalizumab exposure for at least 12 months. For further discussion of the selection of these two studies for analysis, see Section 7.1, Methods and Findings).

7.1.7.3 Standard Analyses and Explorations of Laboratory Data

Natalizumab binds to the α4 subunit of the α4β1 integrin that is highly expressed on the surface of all leukocytes, with the exception of neutrophils (see Section 2.1, Product Information). Therefore, the following analyses focus on hematologic measures.

7.1.7.3.1 Analyses Focused on Measures of Central Tendency

The applicant provided an analysis of laboratory measures based on central tendency, combining data from all placebo-controlled MS studies, including Studies 200, 202, 221, 201, 231, 1801, 1802, and 1803.

Table 25: Hematology Laboratory Measures, Baseline and Week 48 (mean)		
Laboratory Measure	Natalizumab	Placebo
WBC (x 10^9/L)		
Baseline (n)	6.9 (1573)	6.8 (1112)
Week 48 (n)	**8.5** (1184)	6.8 (819)
Lymphocytes (x 10^9/L)		
Baseline (n)	2.0 (1573)	2.0 (1112)
Week 48 (n)	**3.3** (1182)	1.9 (818)
Neutrophils (x 10^9/L)		
Baseline (n)	4.3 (1573)	4.3 (1112)
Week 48 (n)	4.3 (1182)	4.3 (818)
Monocytes (x 10^9/L)		
Baseline (n)	0.39 (1573)	0.38 (1112)
Week 48 (n)	**0.49** (1182)	0.40 (818)
Eosinophils (x 10^9/L)		
Baseline (n)	0.13 (1573)	0.13 (1112)
Week 48 (n)	**0.24** (1182)	0.13 (818)
Basophils (x 10^9/L)		
Baseline (n)	0.046 (1573)	0.046 (1112)
Week 48 (n)	**0.064** (1182)	0.045 (818)
RBC (x 10^{12}/L)		
Baseline (n)	4.6 (1573)	4.6 (1112)
Week 48 (n)	4.6 (1184)	4.7 (819)
Hemoglobin (g/dL)		
Baseline (n)	13.9 (1573)	14.0 (1112)
Week 48 (n)	13.5 (1184)	13.9 (819)
Hematocrit (%)		
Baseline (n)	41.7 (1564)	41.8 (1108)
Week 48 (n)	40.4 (1180)	41.9 (814)
MCV (x 10^{15} L)		
Baseline (n)	90.7 (1564)	90.5 (1108)
Week 48 (n)	89.0 (1180)	89.8 (814)
Platelets (x 10^9/L)		
Baseline (n)	271 (1565)	268 (1107)
Week 48 (n)	261 (1175)	267 (811)

As expected, considering its mechanism of action, natalizumab administration is associated with increases in total white blood cells, lymphocytes, monocytes, eosinophils, and basophils (**bold font**). These increases in non-neutrophil WBCs are associated with a decrease in the percent of neutrophils in the total WBC, although natalizumab is not associated with a change in the

absolute neutrophil count. Natalizumab is associated with small mean decreases in hemoglobin, hematocrit, MCV, and platelets (Table 25). No changes are apparent in the placebo subjects.

7.1.7.3.2 Analyses Focused on Outliers or Shifts From Normal to Abnormal

Table 26: Laboratory Measures – Shifts to Abnormal (% of Subjects), 1-Year Analysis

	Study 1801				Study 1802 (All + Avonex)			
	Shift to Low		Shift to High		Shift to Low		Shift to High	
	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo
Hematology								
WBC	<1	2	38	15	2	9	26	7
Neutrophils	3	3	17	16	9	12	12	10
Lymphocytes	<1	<1	38	3	<1	6	29	1
Monocytes	<1	2	6	2	1	3	9	1
Eosinophils	0	0	13	4	0	0	10	2
Basophils	0	0	5	1	0	0	5	<1
RBC	23	8	0	<1	25	12	0	12
MCV	3	4	3	8	4	4	4	4
MCH	1	2	<1	<1	2	3	<1	3
MCHC	4	6	0	<1	3	5	0	5
Hemoglobin	8	3	0	1	12	7	0	7
Hematocrit	10	3	<1	<1	13	5	<1	5
Platelets	1	2	6	5	2	<1	3	<1
Chemistry								
BUN	0	0	2	3	<1	0	3	5
Creatinine	<1	<1	<1	<1	0	0	<1	<1
Bicarbonate	4	4	<1	0	3	4	<1	0
Chloride	0	0	3	2	0	<1	3	3
Potassium	<1	<1	1	2	1	1	<1	<1
Sodium	<1	<1	2	1	<1	<1	2	<1
Alkaline Phosphatase	2	<1	2	3	1	2	4	3
ALT	<1	<1	14	14	<1	0	18	19
AST	<1	<1	7	7	<1	<1	12	9
Bilirubin	3	7	5	7	12	14	3	1
GGT	2	<1	6	5	1	<1	9	10
LDH	0	0	5	2	0	<1	3	2

Urinanalysis

	Shift to High /Positive		Shift to High /Positive	
	Natalizumab	Placebo	Natalizumab	Placebo
Color	<1	0	<1	<1
Occult Blood	27	29	24	23
Glucose	2	3	<1	1
Ketones	2	2	3	2
pH	<1	0	<1	<1
Protein	6	4	4	4
Specific	3	3	4	4

The applicant provided laboratory data for approximately 300 subjects in the Study 1801 placebo group, for approximately 600 subjects in the Study 1801 natalizumab group, and for approximately 560 subjects in each Study 1802 treatment group. The exact number of subjects with data from each test varies slightly for the different laboratory tests, but the approximations given above are within 10% of the exact number for all laboratory studies presented in Table 26.

The increases in total WBC and in total lymphocytes are sufficient to be elevated outside of the normal range in 38% of subjects in Study 1801, the most reliable data to assess the safety of natalizumab alone. The increases in monocytes, basophils, and eosinophils were more modest, affecting 6%, 5%, and 13% of natalizumab-treated subjects in Study 1801, and similar percentages in Study 1802 (Table 26).

Natalizumab was associated with an increased risk of developing a decreased hematocrit, decreased hemoglobin, and especially reduced RBCs. There was no consistent effect on platelet count.

Natalizumab may be associated with a slightly increased risk of an elevation in serum sodium (2% of subjects, versus ≤1% in controls). Natalizumab does not appear to be associated with any other disturbance of serum electrolytes, BUN, or creatinine.

In this analysis, natalizumab alone does not appear to increase the risk of elevation of liver function tests to outside of the normal range. However, when natalizumab was combined with Avonex® in Study 1802, natalizumab administration appeared to slightly increase the risk of an elevation in selected liver function studies (aspartate transaminase and bilirubin), compared to Avonex® plus placebo.

Compared to placebo, natalizumab was associated with an increase in the incidence of proteinuria in Study 1801; however, this was not observed in Study 1802. No other changes in urinary measures were apparent.

7.1.7.3.3 Marked Outliers and Dropouts for Laboratory Abnormalities

Table 27: Elevations of Liver Function Tests

	Study 1801		Study 1802	
	Natalizumab	Placebo	Natalizumab + Avonex®	Placebo + Avonex®
Resulted in dropout from study	0	1	1	0
Resulted in discontinuation of study agent (but not study participation)	0	0	0	1
Serious adverse event	1	1	1	2

No other routine laboratory measure was associated with a discontinuation of study agent administration and/or study participation. However, one natalizumab group subject in Study 1802 discontinued study agent administration due to an elevation in pancreatic enzymes.

7.1.7.4 Additional Analyses and Explorations

In combined data from all placebo-controlled MS studies, 77 (5%) of 1617 subjects who received natalizumab developed abnormal levels of nucleated red blood cells, in contrast to an elevation of nucleated red blood cells in only 1 of 1135 subjects who received placebo. A similar pattern was seen in the placebo-controlled studies in Crohn's disease.

The sponsor notes that the α4 integrin, α4β1, is involved in the retention of hematopoietic progenitor cells in the bone marrow (see Papayannopoulou, 1993, and Papayannopoulou, 2001, in References). Maturing RBCs express both β1 and β2 integrins which are involved in anchoring the RBC in the marrow. The binding of natalizumab to these maturing RBCs or nucleated RBCs (nRBCs) could enhance their exit from the marrow.

One subject in Study 221 had nRBCs of 13% (relative to 100 WBCs counted/high powered field) following a single dose of natalizumab. The hemoglobin remained stable. In the remaining subjects, nRBCs were detected usually on a single occasion, ranged between 1-4% and were transient. Only 6 of 77 subjects (8%) with detectable nRBCs at any timepoint had hemoglobin levels that dipped below the lower limit of normal. One subject was anemic at baseline with a low MCV, consistent with an iron deficiency type anemia, and remained anemic throughout the study, with hemoglobin ranging from 9.1 – 9.7 g/dL. Another subject was also anemic at baseline with a low MCV, but by Week 24 when nRBCs were noted, the hemoglobin had corrected to 11.3 g/dL. A third subject had nRBCs at Week 48, with a hemoglobin of 10.9 g/dL, which corrected to 11.4 g/dL by Week 60. In the remaining 3 subjects with nRBCs and a low hemoglobin, the finding of low hemoglobin occurred only once. Thus, the appearance of elevated levels of nucleated RBCs is clearly associated with natalizumab, but is of unclear clinical significance.

7.1.7.5 Special Assessments

Several available treatments for MS (all three β-interferons and glatiramer acetate) have been associated with a risk of hepatotoxicity. The data provided in this submission suggests that natalizumab, when administered in combination with a β-interferon, may minimally increase the risk of hepatotoxicity, compared to the risk with the β-interferon alone, as evidenced by the increased frequency of elevated liver function tests reported as adverse events (Table 23) and the shifts in liver function tests noted it Study 1802 (Table 26). This issue will warrant consideration by physicians who plan to co-administer natalizumab and one of these other MS therapies, or any known hepatotoxic agent. This issue will also warrant careful review when final study reports for Studies 1801 and 1802 become available.

7.1.8 Vital Signs

7.1.8.1 Overview of Vital Signs Testing in the Development Program

For reasons discussed previously (see Section 7.1, Methods and Findings), this review focuses on measurements of vital signs (temperature, pulse, systolic blood pressure, and diastolic blood pressure) in Studies 1801 and 1802, but also considers data from all placebo-controlled MS studies. The two Phase 3 MS studies included measurements of vital signs at all study drug administration visits (every four weeks through Week 116; see Section 6.1.3.1.4, Study 1801 – Study Procedures) within 1 hour prior to infusion of study drug and within 1 hour post-infusion. Subjects were required to sit quietly for 5 minutes prior to assessment of pulse and blood pressure. In addition, Studies 1801 and 1802 included physical examinations, including measurements of vital signs, at Screening, at Weeks 52, 104, and 120, and at premature study withdrawal visits.

7.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

This review focuses on Studies 1801 and 1802, which provide the only substantial database on natalizumab exposure for at least 12 months. For further discussion of the selection of these two studies for analysis, see Section 7.1, Methods and Findings). The analysis of the effect of natalizumab on vital signs focuses on shifts from normal to abnormal.

7.1.8.3 Standard Analyses and Explorations of Vital Signs Data

7.1.8.3.1 Analyses Focused on Outliers or Shifts From Normal to Abnormal

For the placebo-controlled studies (including Studies 1801 and 1802), vital sign abnormalities were defined as outlined in Table 28.

Table 28: Vital Sign Abnormalities: Definitions		
Vital Sign	Protocol Criteria	Post-hoc Criteria[1]
Temperature	>38 °C and an increase from pre-dosing of at least 1 °C	Same as Protocol Criteria
Pulse	>120 beats per minute and an increase from pre-dosing of more than 20 beats per minute, or <50 beats per minute and a decrease from pre-dosing of more than 20 beats per minute	>120 beats per minute and an increase from pre-dosing of more than 10 beats per minute, or <50 beats per minute and a decrease from pre-dosing of more than 10 beats per minute
Systolic Blood Pressure	>180 mmHg and an increase from pre-dosing of more than 40 mmHg, or <90 mmHg and a decrease from pre-dosing of more than 30 mmHg	>180 mmHg and an increase from pre-dosing of more than 10 mmHg, or <90 mmHg and a decrease from pre-dosing of more than 10 mmHg
Diastolic Blood Pressure	>105 mmHg and an increase from pre-dosing of more than 30 mmHg, or <50 mmHg and a decrease from pre-dosing of more than 20 mmHg	>105 mmHg and an increase from pre-dosing of more than 10 mmHg, or <50 mmHg and a decrease from pre-dosing of more than 10 mmHg

[1] Post-hoc criteria were requested by CDER as a sensitivity analysis.

7.1.8.3.1.1 Acute (Post-Infusion) Changes in Vitals Signs

Table 29 summarizes the incidence of vital sign abnormalities observed within an hour post-infusion. Table 29 illustrates that, using the more stringent sensitivity criteria (Table 28, right column), there were no trends apparent to suggest hemodynamically important changes.

Table 29: Incidence of Post-Infusion Vital Sign Abnormalities: All MS Studies			
Vital Sign	Protocol Criteria	All MS Studies[1]	
		Natalizumab	Placebo
Temperature	>38 °C and an increase from pre-dosing of at least 1 °C	11/1442 (0.8%)	9/1030 (0.9%)
Pulse	>120 beats per minute and an increase from pre-dosing of more than 20 beats per minute, or	1/1615 (0.1%)	3/1135 (0.3%)
	<50 beats per minute and a decrease from pre-dosing of more than 20 beats per minute	11/1615 (0.7%)	6/1135 (0.5%)
Systolic Blood Pressure	>180 mmHg and an increase from pre-dosing of more than 40 mmHg, or	0/1615 (0%)	1/1135 (0.1%)
	<90 mmHg and a decrease from pre-dosing of more than 30 mmHg	6/1615 (0.4%)	9/1135 (0.8%)
Diastolic Blood Pressure	>105 mmHg and an increase from pre-dosing of more than 30 mmHg, or	8/1615 (0.5%)	7/1135 (0.6%)
	<50 mmHg and a decrease from pre-dosing of more than 20 mmHg	26/1615 (1.6%)	15/1135 (1.3%)
Respiration	<10 or >24 per minute	1/142 (0.1%)	0/71 (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). Entries are numbers of subjects meeting criterion / number of subjects being evaluated (%) at infusion visits.

Assessed one hour post-infusion, very few subjects in Study 1801 or 1802 exhibited abnormalities of vital signs

7.1.8.3.1.2 Chronic Abnormalities in Vital Signs

Based on the protocol-specified definitions of vital sign abnormalities, very few vital sign readings in Studies 1801 or 1802 were categorized as abnormal. (The protocol-defined definitions were relatively insensitive to change). Results based on the more sensitive post-hoc definitions are shown in Table 30. Though abnormal vital signs are relatively infrequent, there are clear trends (in both studies) towards greater frequencies of abnormally high, rather than abnormally low, blood pressure measurements (i.e., frequency of hypertension >> hypotension). Similar trends are evident in assessments of pulse (tachycardia >> bradycardia). Given that these trends are evident in both the natalizumab- and placebo-treated groups, they do not suggest chronic changes in vital signs related to natalizumab.

Table 30: Incidence of Post-Baseline Abnormalities in Vital Signs, Sensitivity Analysis: Studies 1801 and 1802[1]

		Study 1801		Study 1802	
Vital Sign	**Protocol Criteria**	**Natalizumab**	**Placebo**	**Natalizumab + Avonex®**	**Placebo + Avonex®**
Temperature	>38 °C and an increase from pre-dosing of at least 1 °C	1/627 (0.2%)	0/312 (0%)	11/589 (1.9%)	6/582 (1.0%)
Pulse	>120 beats per minute and an increase from pre-dosing of more than 10 beats per minute	14/627 (2.2%)	6/312 (1.9%)	12/589 (2.0%)	22/582 (3.8%)
	<50 beats per minute and a decrease from pre-dosing of more than 10 beats per minute	1/627 (0.2%)	2/312 (0.6%)	2/589 (0.3%)	4/582 (0.7%)
Systolic BP	>180 mmHg and an increase from pre-dosing of more than 10 mmHg	37/627 (5.9%)	23/312 (7.4%)	49/589 (8.3%)	37/582 (6.4%)
	<90 mmHg and a decrease from pre-dosing of more than 10 mmHg	1/627 (0.2%)	3/312 (1.0%)	4/589 (0.7%)	1/582 (0.2%)
Diastolic BP	>105 mmHg and an increase from pre-dosing of more than 10 mmHg	36/627 (5.7%)	17/312 (5.4%)	28/589 (4.8%)	26/582 (4.5%)
	<50 mmHg and a decrease from pre-dosing of more than 10 mmHg	7/627 (1.1%)	9/312 (2.9%)	13/589 (2.2%)	13/582 (2.2%)

[1] Based on assessments of vital signs during routine visits at Weeks 52, 104, 120, and at premature withdrawal visits. These values do not include abnormalities recorded immediately post-infusion (see Table 29). Number evaluated is the number of subjects who had a baseline measurement and at least one post-baseline measurement of that vital sign. Numbers in parentheses are percentages based on the number of subjects evaluated.

7.1.8.3.2 Marked Outliers and Dropouts for Vital Sign Abnormalities

In Study 1801, no vital sign abnormality was designated as a serious adverse event, and no vital sign abnormality was the primary reason for discontinuing study medication or dropping out of the study.

In Study 1802, one subject in the placebo plus Avonex® group developed a hypertensive crisis which was classified as a serious adverse event. However, no subject in the natalizumab plus Avonex® group had a vital sign abnormality that was classified as a serious adverse event. No vital sign abnormality was the primary reason for dropping out of the study. In the natalizumab

plus Avonex® group, three subjects discontinued study medication due to tachycardia, and one subject discontinued study medication due to hypotension. In the placebo plus Avonex® group, one subject discontinued study medication due to hypertensive crisis, and one subject discontinued study medication due to tachycardia.

7.1.8.4 Additional Analyses and Explorations

No additional analyses and explorations are indicated. Overall, natalizumab-induced changes in vital signs, either during the two hours after the initiation of natalizumab administration or during routine monitoring as part of scheduled physical examinations, were uncommon and/or mild.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG Testing in the Development Program, Including Brief Review of Preclinical Results

In Elan Study #723-013-98, 32 cynomolgous monkeys received intravenous natalizumab, including 10 monkeys that received the highest dose of 60 mg/kg, every week for up to 26 weeks. In ——————— Study #1164-87, 40 rhesus monkeys received natalizumab, including 20 monkeys that received the highest dose of 60 mg/kg, every week for 4 weeks. In Elan Study #309-011-00, 22 juvenile cynomolgus monkeys received intravenous natalizumab, including 10 monkeys that received the highest dose of 60 mg/kg, every week for up to 6 months. The monkeys in all three studies were monitored with ECGs, which did not reveal any treatment-related abnormalities. Also, no cardiac toxicity was noted on necropsy. For additional information regarding the preclinical assessments of cardiotoxicity, see the Non-clinical Toxicology review by Dr. Barbara Wilcox.

The clinical development program included electrocardiographic monitoring, but did not include systematic assessment for prolongation of the QT interval. The two Phase 3 MS studies which form the basis for this application did not include routine ECGs as part of the monitoring of study subjects. ECG data were evaluated in the Phase 1 and 2 studies..

Of note, prolongation of the QT interval, torsades de pointes, and sudden death have not been associated with other monoclonal antibodies.

7.1.9.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

In Study 101, 35 normal volunteers were randomized to receive a single administration of natalizumab (26 subjects) or placebo (9 subjects). Natalizumab doses ranged from 0.03 mg/kg to 3 mg/kg. The study included serial electrocardiograms through Day 92 post-administration of study agent. The applicant reports that there were no clinically significant ECG abnormalities.

In Study 200, 28 subjects were randomized to receive a single IV dose of either natalizumab (21 subjects) or placebo (7 subjects). This was a dose-escalation study with weight-adjusted dosing. ECG monitoring was included in the study; no ECG abnormalities were noted.

Study 224 also included routine ECG monitoring for 38 subjects who received either 3 mg/kg or 6 mg/kg every 4 weeks for at least 3 months. The applicant reports that analysis of ECG data did not raise any safety concerns.

Study 202 included routine ECG monitoring for subjects who received a single administration of either 1 mg/kg natalizumab (57 subjects), 3 mg/kg natalizumab (60 subjects), or placebo (63 subjects). The applicant reports that there were no clinically important differences among the groups in ECG parameters.

Study 231 administered natalizumab (3 mg/kg, 6 mg/kg, or placebo) to 213 MS subjects every 4 weeks for 20 weeks. The study included routine monitoring of ECGs. The applicant reports that there were no clinically significant differences between the groups in ECG parameters.

In Study 1806, a single IV administration of natalizumab, either one of two formulations, was administered to 86 normal volunteers. There were no clinically significant abnormalities in ECG results following dosing with either of two formulations of natalizumab.

7.1.9.3 Standard Analyses and Explorations of ECG Data

The electrocardiogram database was not sufficient to support meaningful exploratory analyses. In placebo-controlled MS studies, there were four subjects with cardiac events (including two myocardial infarctions and one cardiomyopathy) in the placebo groups and one subject with a cardiac event (acute myocardial infarction) in the natalizumab groups.

The adverse event profile does not suggest an increased incidence of cardiac events to warrant further studies by the applicant of the effect of natalizumab on ECG parameters.

7.1.9.4 Additional Analyses and Explorations

One 41 year-old woman who received natalizumab in a placebo-controlled MS study developed ST segment depression on an electrocardiogram, which was reported as a serious adverse event of moderate severity. The event occurred after the subject had received 16 infusions in Study 1801, and did not result in discontinuation of the study drug. The significance of this event, in isolation, is uncertain.

7.1.10 Immunogenicity

Treatment with therapeutic proteins such as natalizumab can lead to formation of antibodies directed against the product. The formation of antibodies may be either transient or persistent. In Studies 1801 and 1802, sera were obtained every 12 weeks for determination of anti-natalizumab antibodies. A screening ELISA assay was used, followed by a

assay in those who were screening antibody-positive and had no detectable natalizumab in the serum. Because of the high correlation between the screening ELISA results and the [redacted] assay, only the ELISA results are presented here. Antibody positivity was defined as a serum titer ≥ 0.5 µg/mL. For purposes of the 1-year analyses of Studies 1801 and 1802 presented in this review, antibody responses were characterized as persistently positive (positive on two or more occasions separated by at least 42 days or at the last time point tested), transiently positive (positive titer not fulfilling the criteria for persistently positive), or antibody negative (no detectable antibody at any timepoint). However, the assays used in these studies were unable to detect low to moderate levels of antibodies to natalizumab. One problem with the assay is that the presence of natalizumab was found to interfere with detection of antibodies to natalizumab. For a more detailed discussion of the limitations of the assay methods, please see the Chemistry, Manufacturing, and Controls (CMC) review by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang.

7.1.10.1 Immunogenicity Results

Of 1216 natalizumab-treated subjects evaluated in the combined Phase 3 MS studies, 10% (126) had a positive anti-natalizumab antibody titer at least once, and 6% (75) had persistently positive titers (Table 31). Of 863 natalizumab-treated subjects in the integrated CD studies (CD301, CD303, CD306, and CD351), 10% (87) had a positive anti-natalizumab antibody titer at least once, and 8% (70) had persistently positive titers.

Table 31: Studies 1801 and 1802: Antibody Status (Applicant's Analysis)

	Study 1801	Study 1802
	Natalizumab	Natalizumab + Avonex®
Subjects randomized	627	589
Subjects evaluated[1]	625 (99.7%)	585 (99.3%)
Antibody negative[2]	568 (91%)	516 (88%)
Any positive antibody	57 (9%)	69 (12%)
Transient antibody-positive[3]	20 (3%)	31 (5%)
Persistent antibody-positive[4]	37 (6%)	38 (6%)
Time to antibody-positive = 0-13 weeks[5]	47 (82%)	66 (96%)
Time to antibody-positive = 13 – 26 weeks[5]	7 (12%)	3 (4%)
Time to antibody-positive = > 26 weeks[5]	3 (5%)	0 (0%)
Anti-Avonex antibody at Week 24	-	18 (3%)[6]

[1] Subjects with one or more post-baseline screening antibody result.
[2] Defined as < 0.5 µg/mL at all post-baseline visits.
[3] Defined as ≥ 0.5 µg/mL at only one post-baseline visit prior to the last visit.
[4] Defined as ≥ 0.5 µg/mL at two or more post-baseline visits ≥ 42 days apart or ≥ 0.5 µg/mL at the last post-baseline visit.

[5] Percentage calculated as the number with the first positive result in the specified time period / number with one or more positive (≥ 0.5 µg/mL) post-baseline results.
[6] Compared to 10 (2%) in the Avonex® + placebo group

The time to antibody formation ranged from 6 to 60 weeks after the initial administration of natalizumab; however, 82 – 96% of subjects who developed detectable antibodies did so within the first 3 months.

The rate of antibody formation was similar in the two Phase 3 studies (Table 31), indicating that Avonex® did not have a substantial effect on the frequency of anti-natalizumab antibody positivity.

7.1.10.2 Antibody Status and Infusion Reactions

Table 32 enumerates the incidence of adverse events, including acute hypersensitivity reactions, according to antibody status, for subjects in Studies 1801 and 1802.

Table 32: Infusion Reactions[1] by Antibody Status, Studies 1801 and 1802 Combined

	Natalizumab Antibody Status		
	Negative	Transient positive	Persistent positive
N (%)	1084 (100)	51 (100)	75 (100)
Any infusion reaction	192 (18)	15 (29)	58 (77)
Rigors	1 (<1)	0 (0)	15 (20)
Urticaria	5 (<1)	1 (2)	11 (15)
Hypersensitivity	0 (0)	0 (0)	7 (9)
Pruritus	6 (1)	2 (4)	5 (7)
Anaphylactic / Anaphylactoid	0 (0)	1 (2)	4 (5)
Dyspnea	0 (0)	0 (0)	4 (5)
Tremor	0 (0)	0 (0)	4 (5)
Tachycardia	1 (<1)	0 (0)	4 (5)
Feeling cold	0 (0)	0 (0)	4 (5)
Nausea and/or vomiting	15 (1.4)	0 (0)	13 (17.3)
Headache	36 (3)	1 (2)	12 (16)
Flushing	6 (1)	0 (0)	7 (9)
Dizziness	29 (3)	0 (0)	5 (7)
Psychiatric disorders (including nervousness, anxiety, restlessness, disorientation, and depression)	2 (<1)	1 (2)	3 (4)
Hypotension	3 (<1)	0 (0)	3 (4)
Pyrexia	6 (1)	0 (0)	3 (4)

[1] By definition, "infusion reactions" were defined as any event that occurred within 2 hours of the initiation of study agent infusion. Includes all events that occurred in at least 3 subjects who were persistently antibody-positive. From sponsor's analysis of events.

Antibody formation is associated with an increase in the rate of infusion reactions. This is particularly true for infusion reactions that are generally considered to have an immune basis (e.g., urticaria, rigors, and anaphylaxis). Overall, 77% of subjects who were persistently antibody positive reported some type of infusion reaction. Conversely, subjects who have these typical immune-mediated infusion reactions are very likely to be persistently antibody-positive.

The protocols for Studies 1801 and 1802 specified that subjects who developed hypersensitivity reactions would discontinue study medication.

Table 33 summarizes the incidence of common adverse events in Studies 1801 and 1802 combined, grouped by natalizumab antibody status (as defined above). Events are listed in descending frequency for persistently positive subjects.