CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

SECONDARY REVIEW—CLINICAL STUDIES

BLA:	125104.0
Name of drug:	Natalizumab
Applicant:	Biogen, Inc.
Indication:	Reducing the frequency of clinical exacerbations for patients with relapsing forms of multiple sclerosis
Primary Statistical reviewer:	Kallappa M. Koti, Ph.D.
Project manager:	Cathleen Michaloski
Clinical reviewer:	Wilson Bryan, M.D.
Secondary Statistical reviewer:	Bo-guang Zhen, Ph.D., Statistical Team Leader
Concurring Reviewer:	Aloka Chakravarty, Ph.D., BTSS Director
Date:	November 22, 2004

This is a secondary review to the primary statistical review done by Dr. Kallappa Koti on BLA 125104 dated on October 25, 2004. While I commend Dr. Koti for his review of the data in this application and concur with his conclusions and some other views in principle, I have major reservations regarding his views on the study design and the labeling recommendation. My reservations and arguments are presented in the following sections.

I. The Labeling Issue

In Section 1.1 "Conclusions and Recommendations" on page 4, Dr. Koti wrote:
"This reviewer was able to reproduce the sponsor's results on the primary efficacy endpoint. The sponsor's results are not based on analyses stratified by site and it did not use the actual one-year data. The sponsor's efficacy results may support the efficacy claim subject to the condition: the sponsor may not describe the efficacy data as "one year data" and may not use the p-value for comparing the relapse rates in the labeling."

I agree with Dr. Koti's conclusion that the sponsor's efficacy results may support the efficacy claim subject to the condition that the sponsor may not describe the efficacy data as "*one year data*" in the labeling. In particular, I appreciate his thorough review on the efficacy data and his finding that the actual one-year data were not used. I suggest that a phrasing informatively describing the actual duration of patient study time be used. However, I believe that it is reasonable to present a p-value in the labeling and disagree with Dr. Koti's recommendation of "*may not use the p-value for comparing the relapse rates in the labeling*".

The next two sections provide the rationale to support the argument that a p-value should be used in the labeling since this is related to the study design and the sensitivity analyses.

II. The Study Design

Dr. Koti expressed his concerns about the study design and the primary efficacy analysis method in several places of his review (Section 1.3 on page 5, Section 3.1 on page 16, Section 5.1 on page 17, Section 5.2 on page 19). The following summarize his arguments: Since randomization was stratified by site, site should be a factor in the primary analysis. Since the sponsor was unable to incorporate site in the primary analysis due to sparse data in some sites, the study design was inadequate (bad). He further argues that it is possible that significant differences between sites exist and natalizumab may not be efficacious in some sites. The decision to keep sites out of the primary efficacy analyses is not justified. He states it is not possible to verify if substantial collective evidence for efficacy is provided by the entire application. Therefore, the p-value may not be used in the labeling.

While I agree with him that the primary analysis should, in general, take factors used to stratify the design into consideration, I do not think that this is mandatory in all circumstances.

When there are few subjects in some of the sites, including site as a covariate in the analysis could be problematic. Nine hundred and forty-two (942) subjects were enrolled in 99 sites in 19 countries in study C-1801 and 1171 subjects were enrolled in 123 sites in study C-1802 in 14 countries. Given the possible sparse data in some of the sites, it is very likely that incorporating site as a covariate in the Poisson regression model with the number of relapses as an outcome variable (primary efficacy endpoint) may be problematic. This led to the decision that site was not included in the primary analysis in the pre-specified statistical analysis plan. When Dr. Koti received the data sets, he failed to fit the Poisson model with site as a covariate ("*does not converge*" as he described on page 17 of his review). The algorithm of modeling failing to converge was expected since the number of subjects enrolled in each site ranged from 1 to 32 in Study C-1801 and ranged from in 1 to 31 in Study C-1802.

As I believe and Dr. Koti pointed out that there may be existing significant differences in terms of some baseline characteristics and the efficacy endpoint between sites, thus it is worthwhile to stratify site for the purpose of balancing subjects between the two arms within each site. In an ideal situation, important factors including those that are used to stratify the design should be treated as covariates in the primary analysis. However, since there are few subjects in some of the sites, site can not be incorporated in the Poisson model as a covariate. This is the dilemma we were facing. Simply not to stratify site at randomization may not be a good solution since it is important to increase the chance of equally distributing subjects between the two arms within site to the extent feasible.

Based on the above results and arguments, there is no doubt that the decision for stratifying site at randomization is appropriate. Although the primary analysis without site as a covariate is not an ideal (best) choice, it is one of the optimal choices given the dilemma we were facing. Therefore, the study design is adequate. The difference in some baseline characteristics and the efficacy endpoint estimate between sites should not prevent us from drawing conclusions based on the primary and sensitivity analyses. The following quotes from the ICH E9 Statistical Guidance (Section 5.7) also support this argument: "...If one or more factors are used to stratify the design, it is appropriate to account for those factors in the analysis. When the potential value of an adjustment is in doubt, it is often advisable to nominate the unadjusted analysis as the one for primary attention, the adjusted analysis being supportive....".

III. Sensitivity Analyses

Dr. Koti selected some of the sites with sufficient number of subjects that allow the algorithm to converge and re-analyzed the data as shown in Appendices 1.3, 2.3, and 2.4 of his review. After adjusting for sites, the p-values for testing the null hypothesis of no natalizumab-associated treatment effect in Appendices 1.3 and 2.3 are less than 0.0001.

On page 15, Dr. Koti pointed out '*no significant differences between the two treatment groups*" based on the p-value of 0.078 in Appendix 2.4. Given a small subgroup with only 8% of subjects (97/1171) in Study C-1802, it is very unlikely that there is enough power to obtain a statistically significant result in such a subgroup analysis. The fact that the point estimate for the treatment effect in Appendix 2.4 is consistent with that in the primary analysis also supports the underpowered scenario and the efficacy findings. Thus, Dr. Koti's sensitivity analyses show that the efficacy results with adjustment for sites in the selected patient populations are consistent with those from the primary analysis.

To further support the findings from the primary analysis, I conducted a number of sensitivity analyses for both studies: 1) repeating the analysis using the Poisson model by excluding all covariates; 2) pooling countries with subjects less than 20 together and repeating the analysis using the Poisson model by adding country as an additional covariate; 3) pooling countries with subjects less than 20 together and repeating the analysis using the Poisson model by treating country as the ONLY covariate. All the sensitivity analyses for both studies demonstrate that p-values from testing the null hypothesis of no treatment effect are less than 0.0001 (See Appendix A and B). Again, these results are consistent with those from the primary analysis.

IV. Conclusions and Recommendations

The study design with site as a stratification factor is adequate and the primary efficacy results from both studies are verified. The study results constitute sufficient evidence to support the claim. It is also recommended that a p-value be used in the labeling.

Appendix A – Additional Sensitivity Analyses for Study C-1801

1. Poisson model without any covariate

The GENMOD Procedure
Model Information

Data Set	WORK.NEW10	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	942	

Class Level Information

Class	Levels	Values
GROUPN	2	0 1

Parameter Information

Parameter	Effect	GROUPN
Prm1	Intercept	
Prm2	GROUPN	0
Prm3	GROUPN	1

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	940	992.6836	1.0560
Scaled Deviance	940	745.9410	0.7936
Pearson Chi-Square	940	1250.9334	1.3308
Scaled Pearson X2	940	940.0000	1.0000
Log Likelihood		-513.6053	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-1.3869	0.0898	-1.5629	-1.2109	238.50	<.0001
GROUPN	0	1	1.0544	0.1172	0.8247	1.2840	80.98	**<.0001**
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.1536	0.0000	1.1536	1.1536		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.3326	0.0753	1	19.53	<.0001	0.05	-0.4801	-0.1851
GROUPN	1	-1.3869	0.0898	1	238.50	<.0001	0.05	-1.5629	-1.2109

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha
GROUPN	0	1	1.0544	0.1172	1	80.98	**<.0001**	0.05

2. Poisson model with country as an additional covariate

The GENMOD Procedure
Model Information

Data Set	WORK.NEW0	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	942	

Class Level Information

Class	Levels	Values
_AGEGE40	2	AGE < 40 AGE >= 40
_EDSSG35	2	EDSS <= 3.5 EDSS > 3.5
_GDYES	2	gd > 0 gd = 0
GROUPN	2	0 1
COUNTRY	11	Canada United States 9 Countries UK Czech Rep Hungary Poland France NL Sweden Australia

Parameter Information

Parameter	Effect	_AGEGE40	_EDSSG35	_GDYES	GROUPN	COUNTRY
Prm1	Intercept					
Prm2	RLPS_1Y					
Prm3	_AGEGE40	AGE < 40				
Prm4	_AGEGE40	AGE >= 40				
Prm5	_EDSSG35		EDSS <= 3.5			
Prm6	_EDSSG35		EDSS > 3.5			
Prm7	_GDYES			gd > 0		
Prm8	_GDYES			gd = 0		
Prm9	COUNTRY					Canada
Prm10	COUNTRY					United States
Prm11	COUNTRY					9 Countries
Prm12	COUNTRY					UK
Prm13	COUNTRY					Czech Rep
Prm14	COUNTRY					Hungary
Prm15	COUNTRY					Poland
Prm16	COUNTRY					France
Prm17	COUNTRY					NL
Prm18	COUNTRY					Sweden
Prm19	COUNTRY					Australia
Prm20	GROUPN				0	
Prm21	GROUPN				1	

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	926	912.3509	0.9853
Scaled Deviance	926	735.9393	0.7948

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Pearson Chi-Square	926	1147.9710	1.2397
Scaled Pearson X2	926	926.0000	1.0000
Log Likelihood		-518.9356	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-2.0214	0.4976	-2.9967	-1.0462	16.50	<.0001
RLPS_1Y		1	0.1317	0.0561	0.0217	0.2417	5.51	0.0190
_AGEGE40	AGE < 40	1	0.3915	0.1227	0.1510	0.6320	10.18	0.0014
_AGEGE40	AGE >= 40	0	0.0000	0.0000	0.0000	0.0000	.	.
_EDSSG35	EDSS <= 3.5	1	-0.4026	0.1536	-0.7037	-0.1015	6.87	0.0088
_EDSSG35	EDSS > 3.5	0	0.0000	0.0000	0.0000	0.0000	.	.
_GDYES	gd > 0	1	0.2620	0.1134	0.0398	0.4843	5.34	0.0208
_GDYES	gd = 0	0	0.0000	0.0000	0.0000	0.0000	.	.
COUNTRY	Canada	1	0.5799	0.4782	-0.3574	1.5172	1.47	0.2253
COUNTRY	United States	1	0.2701	0.4872	-0.6848	1.2251	0.31	0.5793
COUNTRY	9 Countries	1	0.1446	0.4910	-0.8177	1.1068	0.09	0.7684
COUNTRY	UK	1	0.7821	0.4717	-0.1425	1.7066	2.75	0.0974
COUNTRY	Czech Rep	1	0.1605	0.4794	-0.7791	1.1002	0.11	0.7377
COUNTRY	Hungary	1	-0.0057	0.5292	-1.0429	1.0316	0.00	0.9915
COUNTRY	Poland	1	-0.1531	0.4919	-1.1173	0.8110	0.10	0.7556
COUNTRY	France	1	0.5848	0.5508	-0.4948	1.6643	1.13	0.2884
COUNTRY	NL	1	0.5863	0.5076	-0.4085	1.5811	1.33	0.2480
COUNTRY	Sweden	1	0.6917	0.5187	-0.3250	1.7084	1.78	0.1824
COUNTRY	Australia	0	0.0000	0.0000	0.0000	0.0000	.	.
GROUPN	0	1	1.1176	0.1140	0.8943	1.3410	96.19	**<.0001**
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.1134	0.0000	1.1134	1.1134		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.2469	0.1030	1	5.75	0.0165	0.05	-0.4487	-0.0451
GROUPN	1	-1.3645	0.1136	1	144.25	<.0001	0.05	-1.5871	-1.1418

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha
GROUPN	0	1	1.1176	0.1140	1	96.19	**<.0001**	0.05

3. Poisson model with country as the ONLY covariate

The GENMOD Procedure
Model Information

Data Set	WORK.NEW0	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	942	

Class Level Information

Class	Levels	Values
GROUPN	2	0 1
COUNTRY	11	Canada United States 9 Countries UK Czech Rep Hungary Poland France NL Sweden Australia

Parameter Information

Parameter	Effect	GROUPN	COUNTRY
Prm1	Intercept		
Prm2	COUNTRY		Canada
Prm3	COUNTRY		United States
Prm4	COUNTRY		9 Countries
Prm5	COUNTRY		UK
Prm6	COUNTRY		Czech Rep
Prm7	COUNTRY		Hungary
Prm8	COUNTRY		Poland
Prm9	COUNTRY		France
Prm10	COUNTRY		NL
Prm11	COUNTRY		Sweden
Prm12	COUNTRY		Australia
Prm13	GROUPN	0	
Prm14	GROUPN	1	

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	930	945.7004	1.0169
Scaled Deviance	930	748.5825	0.8049
Pearson Chi-Square	930	1174.8890	1.2633
Scaled Pearson X2	930	930.0000	1.0000
Log Likelihood		-522.4356	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-1.7355	0.4645	-2.6460	-0.8251	13.96	0.0002
COUNTRY	Canada	1	0.5270	0.4817	-0.4171	1.4710	1.20	0.2739
COUNTRY	United States	1	0.1577	0.4906	-0.8037	1.1192	0.10	0.7478
COUNTRY	9 Countries	1	0.2045	0.4938	-0.7633	1.1722	0.17	0.6788
COUNTRY	UK	1	0.8568	0.4743	-0.0728	1.7864	3.26	0.0708
COUNTRY	Czech Rep	1	0.1502	0.4828	-0.7961	1.0965	0.10	0.7557
COUNTRY	Hungary	1	-0.0116	0.5338	-1.0577	1.0346	0.00	0.9827
COUNTRY	Poland	1	-0.2020	0.4956	-1.1735	0.7694	0.17	0.6836
COUNTRY	France	1	0.5855	0.5549	-0.5020	1.6730	1.11	0.2914
COUNTRY	NL	1	0.6464	0.5110	-0.3551	1.6479	1.60	0.2059
COUNTRY	Sweden	1	0.6739	0.5232	-0.3516	1.6993	1.66	0.1978
COUNTRY	Australia	0	0.0000	0.0000	0.0000	0.0000	.	.
GROUPN	0	1	1.0708	0.1143	0.8468	1.2947	87.82	**<.0001**
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.1240	0.0000	1.1240	1.1240		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.3385	0.0871	1	15.10	0.0001	0.05	-0.5093	-0.1678
GROUPN	1	-1.4093	0.0997	1	199.94	<.0001	0.05	-1.6047	-1.2140

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha
GROUPN	0	1	1.0708	0.1143	1	87.82	**<.0001**	0.05

Appendix B – Additional Sensitivity Analyses for Study C-1802

1. Poisson model without any covariate

The GENMOD Procedure
Model Information

Data Set	WORK.NEW10	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	1171	

Class Level Information

Class	Levels	Values
GROUPN	2	0 1

Parameter Information

Parameter	Effect	GROUPN
Prm1	Intercept	
Prm2	GROUPN	0
Prm3	GROUPN	1

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	1169	1335.6043	1.1425
Scaled Deviance	1169	1103.8285	0.9443
Pearson Chi-Square	1169	1414.4603	1.2100
Scaled Pearson X2	1169	1169.0000	1.0000
Log Likelihood		-835.6229	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-1.0426	0.0733	-1.1863	-0.8989	202.14	<.0001
GROUPN	0	1	0.7688	0.0889	0.5945	0.9430	74.77	**<.0001**
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.1000	0.0000	1.1000	1.1000		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.2739	0.0503	1	29.69	<.0001	0.05	-0.3724	-0.1753
GROUPN	1	-1.0426	0.0733	1	202.14	<.0001	0.05	-1.1863	-0.8989

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha
GROUPN	0	1	0.7688	0.0889	1	74.77	**<.0001**	0.05

2. Poisson model with country as an additional covariate

The GENMOD Procedure

Model Information

Data Set	WORK.NEW0	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	1171	

Class Level Information

Class	Levels	Values
_AGEGE40	2	AGE < 40 AGE >= 40
_EDSSG35	2	EDSS <= 3.5 EDSS > 3.5
_GDYES	2	gd = 0 gd > 0
GROUPN	2	0 1
COUNTRY	9	USA 6 Countries Germany Italy Turkey France Netherlands Spain Israel

Parameter Information

Parameter	Effect	_AGEGE40	_EDSSG35	_GDYES	GROUPN	COUNTRY
Prm1	Intercept					
Prm2	RLPS_1Y					
Prm3	_AGEGE40	AGE < 40				
Prm4	_AGEGE40	AGE >= 40				
Prm5	_EDSSG35		EDSS <= 3.5			
Prm6	_EDSSG35		EDSS > 3.5			
Prm7	_GDYES			gd = 0		
Prm8	_GDYES			gd > 0		
Prm9	COUNTRY					USA
Prm10	COUNTRY					6 Countries
Prm11	COUNTRY					Germany
Prm12	COUNTRY					Italy
Prm13	COUNTRY					Turkey
Prm14	COUNTRY					France
Prm15	COUNTRY					Netherlands
Prm16	COUNTRY					Spain
Prm17	COUNTRY					Israel
Prm18	GROUPN				0	
Prm19	GROUPN				1	

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	1157	1283.0788	1.1090
Scaled Deviance	1157	1078.5226	0.9322
Pearson Chi-Square	1157	1376.4405	1.1897
Scaled Pearson X2	1157	1157.0000	1.0000

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Log Likelihood		-827.8138	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-0.8668	0.2468	-1.3505	-0.3830	12.33	0.0004
RLPS_1Y		1	0.1901	0.0495	0.0931	0.2872	14.74	0.0001
_AGEGE40	AGE < 40	1	0.2262	0.0875	0.0547	0.3978	6.68	0.0098
_AGEGE40	AGE >= 40	0	0.0000	0.0000	0.0000	0.0000	.	.

_EDSSG35	EDSS <= 3.5	1	-0.1715	0.1117	-0.3905	0.0475	2.36	0.1248
_EDSSG35	EDSS > 3.5	0	0.0000	0.0000	0.0000	0.0000	.	.
_GDYES	gd = 0	1	-0.2524	0.0852	-0.4193	-0.0855	8.78	0.0030
_GDYES	gd > 0	0	0.0000	0.0000	0.0000	0.0000	.	.
COUNTRY	USA	1	-0.3490	0.2202	-0.7805	0.0826	2.51	0.1130
COUNTRY	6 Countries	1	-0.3860	0.2940	-0.9623	0.1903	1.72	0.1892
COUNTRY	Germany	1	-0.1669	0.2468	-0.6505	0.3167	0.46	0.4988
COUNTRY	Italy	1	-0.2208	0.2917	-0.7926	0.3509	0.57	0.4491
COUNTRY	Turkey	1	-0.1736	0.3568	-0.8729	0.5257	0.24	0.6266
COUNTRY	France	1	-0.1922	0.2478	-0.6779	0.2934	0.60	0.4379
COUNTRY	Netherlands	1	-0.2314	0.3467	-0.9109	0.4482	0.45	0.5046
COUNTRY	Spain	1	-0.2891	0.3090	-0.8948	0.3165	0.88	0.3495
COUNTRY	Israel	0	0.0000	0.0000	0.0000	0.0000	.	.
GROUPN	0	1	0.7625	0.0883	0.5895	0.9355	74.64	**<.0001**
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.0907	0.0000	1.0907	1.0907		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.1475	0.0799	1	3.41	0.0650	0.05	-0.3042	0.0091
GROUPN	1	-0.9101	0.0958	1	90.24	<.0001	0.05	-1.0978	-0.7223

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha
GROUPN	0	1	0.7625	0.0883	1	74.64	**<.0001**	0.05

3. Poisson model with country as the ONLY covariate

The GENMOD Procedure

Model Information

Data Set	WORK.NEW0
Distribution	Poisson
Link Function	Log
Dependent Variable	TOTREL No. of relapses
Offset Variable	lyears
Observations Used	1171

Class Level Information

Class	Levels	Values
GROUPN	2	0 1
COUNTRY	9	USA 6 Countries Germany Italy Turkey France Netherlands Spain Israel

Parameter Information

Parameter	Effect	GROUPN	COUNTRY
Prm1	Intercept		
Prm2	COUNTRY		USA
Prm3	COUNTRY		6 Countries
Prm4	COUNTRY		Germany
Prm5	COUNTRY		Italy
Prm6	COUNTRY		Turkey
Prm7	COUNTRY		France
Prm8	COUNTRY		Netherlands
Prm9	COUNTRY		Spain
Prm10	COUNTRY		Israel
Prm11	GROUPN	0	

Prm12 GROUPN 1

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	1161	1326.3302	1.1424
Scaled Deviance	1161	1093.6028	0.9419
Pearson Chi-Square	1161	1408.0701	1.2128
Scaled Pearson X2	1161	1161.0000	1.0000
Log Likelihood		-829.8473	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-0.7784	0.2205	-1.2106	-0.3461	12.46	0.0004
COUNTRY	USA	1	-0.3412	0.2189	-0.7703	0.0879	2.43	0.1191
COUNTRY	6 Countries	1	-0.3917	0.2945	-0.9690	0.1855	1.77	0.1835
COUNTRY	Germany	1	-0.1097	0.2447	-0.5893	0.3700	0.20	0.6540
COUNTRY	Italy	1	-0.2219	0.2899	-0.7901	0.3463	0.59	0.4441
COUNTRY	Turkey	1	-0.1153	0.3547	-0.8104	0.5798	0.11	0.7451
COUNTRY	France	1	-0.0934	0.2463	-0.5762	0.3893	0.14	0.7045
COUNTRY	Netherlands	1	-0.1458	0.3475	-0.8268	0.5353	0.18	0.6749
COUNTRY	Spain	1	-0.2179	0.3057	-0.8171	0.3812	0.51	0.4759
COUNTRY	Israel	0	0.0000	0.0000	0.0000	0.0000	.	.
GROUPN	0	1	0.7686	0.0890	0.5941	0.9432	74.51	**<.0001**
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.1013	0.0000	1.1013	1.1013		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.1916	0.0730	1	6.89	0.0086	0.05	-0.3346	-0.0486
GROUPN	1	-0.9603	0.0903	1	113.16	<.0001	0.05	-1.1372	-0.7833

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha
GROUPN	0	1	0.7686	0.0890	1	74.51	**<.0001**	0.05

SIGNATURES/DISTRIBUTION LIST PAGE

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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:	125104 (0)
Drug Name:	Natulizumab
Indication(s):	Relapsing-remitting
Applicant:	Biogen Inc
Date(s):	24-MAY-2004
Review Priority:	Accelerated
Biometrics Division:	BTSS / OB / CDER
Statistical Reviewer:	Kallappa M. Koti, Ph.D.
Concurring Reviewers:	Dr. Boguang Zhen (Team Leader) Dr. Aloka Chakravarty (Staff Director)
Medical Division:	DTBIMP
Clinical Team:	Dr. Wilson Bryan (primary reviewer); Dr. Ellis Unger (team leader)
Project Manager:	Cathleen Michaloski

Keywords: Recombinant humanized anti-α4 integrin antibody, interferon beta-1a, parallel group design, EDSS score, relapse rate, Poisson regression, sustained progression of disability, Cox regression.

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APPENDICES

1. EXECUTIVE SUMMARY

The BLA STN 125104 (0) is the original submission on natalizumab for the treatment of multiple sclerosis and seeks for an accelerated approval of the product. This submission includes two studies and contains data for the use of natalizumab as a monotherapy as well as an adjunct therapy combined with AVONEX.

1.1 Conclusions and Recommendations

Based on the sponsor's efficacy results on the annualized relapse rate, natalizumab is effective in the treatment of multiple sclerosis. It established superiority to placebo as a monotherapy (see Table 3.1.1.8) and to AVONEX as an adjunct therapy to AVONEX (see Table 3.1.2.7).

This reviewer was able to reproduce the sponsor's results on the primary efficacy endpoint. The sponsor's results are not based on analyses stratified by site and it did not use the actual one-year data. The sponsor's efficacy results may support the efficacy claim subject to the condition: the sponsor may not describe the efficacy data as "one year data" and may not use the p-value for comparing the relapse rates in the labeling.

1.2 Brief Overview of Clinical Studies

Study C-1801 was a multi-center, double blind, placebo-controlled, parallel-group trial where subjects were randomized to one of two treatments, stratified by site:

Six hundred twenty seven (627) received 300 mg of natulizumab by IV infusion every 4 weeks for up to 116 weeks and three hundred fifteen (315) received placebo by IV infusion every 4 weeks for up to 116 weeks.

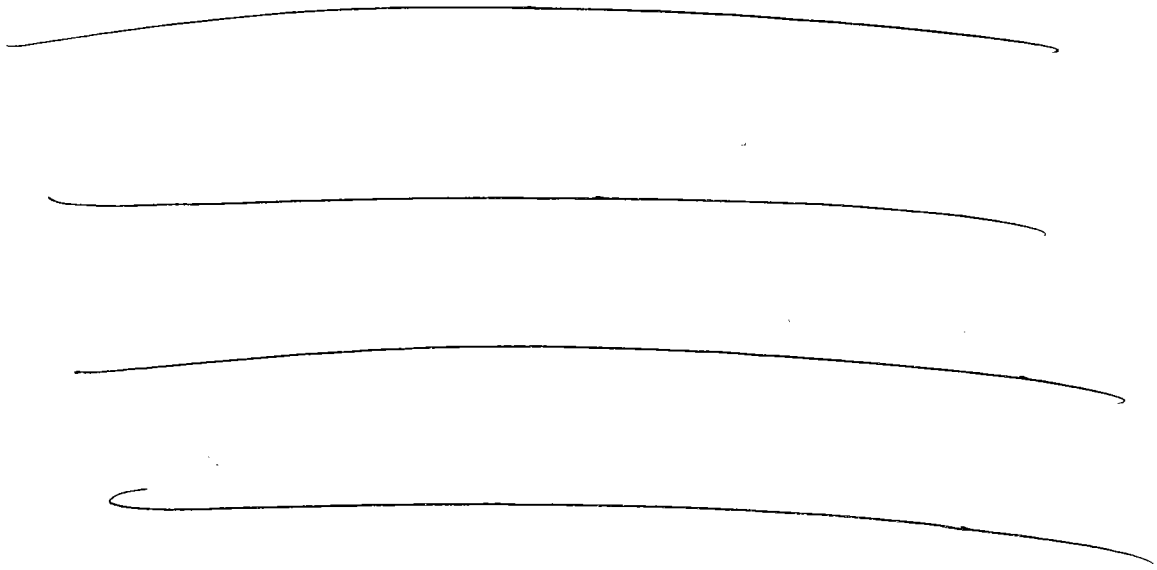
Study C-1802 was a multi-center, double blind, placebo-controlled, parallel-group trial where subjects were randomized to one of two treatments, stratified by site:

Five hundred and eighty nine (589) patients received 300 mg of natalizumab by IV infusion every 4 weeks in addition to 30 mcg of Avonex® by IM injection weekly for up to 116 weeks and five hundred and eighty two (582) patients received placebo by IV infusion every 4 weeks in addition to 30 mcg of Avonex® by IM injection weekly for up to 116 weeks.

The protocol proposed two primary efficacy endpoints:

Relapse rate: The sponsor defines a relapse as new or recurrent neurological symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. The relapse rate

will be calculated as the number of relapses divided by days in study, multiplied by 365 to get the annualized rate.



This reviewer was able to reproduce the sponsor's results on the primary efficacy endpoint. The sponsor's results are not based on analyses stratified by site and it did not use the actual one-year data. The sponsor's efficacy results may support the efficacy claim subject to the condition: the sponsor may not describe the efficacy data as "one year data" and may not use the p-value for comparing the relapse rates in the labeling.

1.3 Statistical Issues and Findings

Every patient's time of exposure to natualizumab is not the same. It varies from two months to two years. The sponsor's description of the submitted data as *one year data* is not appropriate.

Study C-1801 included 99 sites in 19 countries whereas C-1802 was conducted in 123 sites in 14 countries. In both studies, randomization is stratified by site. Exploratory analysis of variance of square-root transformed data on the baseline number of relapses indicates that disease severity was not uniform across study sites. The Poisson regression model for the number of relapses, when site is included as a class (stratification) variable, does not converge. Sensitivity analysis described in Section 3 below demonstrates that significant differences exist between sites- in both studies.

The sponsor analyzes the data on the number of relapses without including the only stratification factor site in the Poisson regression model. The sponsor's model included arbitrarily dichotomized EDSSG35, GDYES, and AGEGE40 as class variables and the baseline number of

relapses as a covariate. I was able to reproduce the sponsor's results on the primary efficacy endpoint.

2. INTRODUCTION

2.1 Overview

The submission contains two phase 3 clinical trial protocols: C-1801 and C-1802.

The study C-1801 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety and efficacy of natalizumab in subjects with relapsing-remitting multiple sclerosis. The trial included 315 subjects in the placebo group and 627 in the natalizumab group.

The study C-1802 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety and efficacy of natalizumab, when added to Avonex® (interferon beta-1a) in subjects with relapsing-remitting multiple sclerosis. Avonex® is considered as a placebo. The trial included 582 subjects in the Avonex® (placebo) group and 589 in the natalizumab+ Avonex® group.

Male and female subjects between 18 and 50 years of age who have a diagnosis of relapsing-remitting sclerosis (MS) per the criteria of McDonald et al. and an EDSS score between 0 and 5 with at least one medically documented clinical relapse within the 12 months prior to randomization are included. For study C-1802, subjects, to be included in the study, were supposed to be on Avonex® within 12 months prior to randomization.

Randomization was stratified by site.

A primary objective was to see if natalizumab is effective in:

- reducing the rate of clinical relapses at 1 year.
- [redacted]

[redacted] The relapse rate is calculated as the number of relapses divided by days in study, multiplied by 365. Relapse rate data are analyzed using Poisson regression.

This review is mainly focused on the first co-primary efficacy end-point- the relapse rate.

2.2 Data Sources

All datasets and study reports were stored in the EDR file bla125104. The data files for study C-1801 were obtained using the electronic path:

Bla125104 → m5 → 53-clin-stud-rep → 535-rep-effic-safety-stud → multiple sclerosis → 5351-stud-rep-contr → c-1801.

Data sets demog.xpt, d_mri.xpt, edss.xpt, d_mri.xpt, phys1.xpt, d_rlps.xpt, and d_surv.xpt located in the folder c-1801 were analyzed.

The data files for study C-1802 were obtained using the electronic path:

Bla125104 → m5 → 53-clin-stud-rep → 535-rep-effic-safety-stud → multiple sclerosis → 5351-stud-rep-contr → c-1802.

Data sets demog.xpt, d_mri.xpt, edss.xpt, d_mri.xpt, phys1.xpt, d_rlps.xpt, and d_surv.xpt located in the folder c-1801 were analyzed.

3. STATISTICAL EVALUATION

As mentioned earlier, this review is mainly focused on the first co-primary efficacy end-point-the relapse rate. Relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS accompanied by objective neurological worsening, consistent with an increase of at least half a step on the expanded disability status scale (EDSS). The relapse rate is defined in Section 3.1 below.

3.1 Evaluation of Efficacy

- **Study Design and Endpoints**

Both studies were multi-center, double blind, placebo-controlled, parallel-group trial where subjects were randomized to one of two treatments, stratified by site. Study C-1802 was balanced whereas Study C-1801 had a 2:1 allocation in favor of natulizumab. A common schedule of events was adopted:

Table 3.1.1.1: Schedule of events [Chart I of III]

	Phase: Pre-Treatment*		Treatment Phase									
			Week #									
	SCR[A]	Pre-test	0[B]	4	12	16/20	24	28/32	36	40/44	48	52[A]
Randomization			X									
VAS			X									
MSFC/VF Test		X	X		X		X		X		X	
EDSS	X		X		X		X		X		X	
Diary Review			X	X	X	X	X	X	X	X	X	X
Study Drug Infusion			X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X

[A] Medical history or physical exam [B] Baseline visit

Table 3.1.1.1: Schedule of events [Chart II of III]

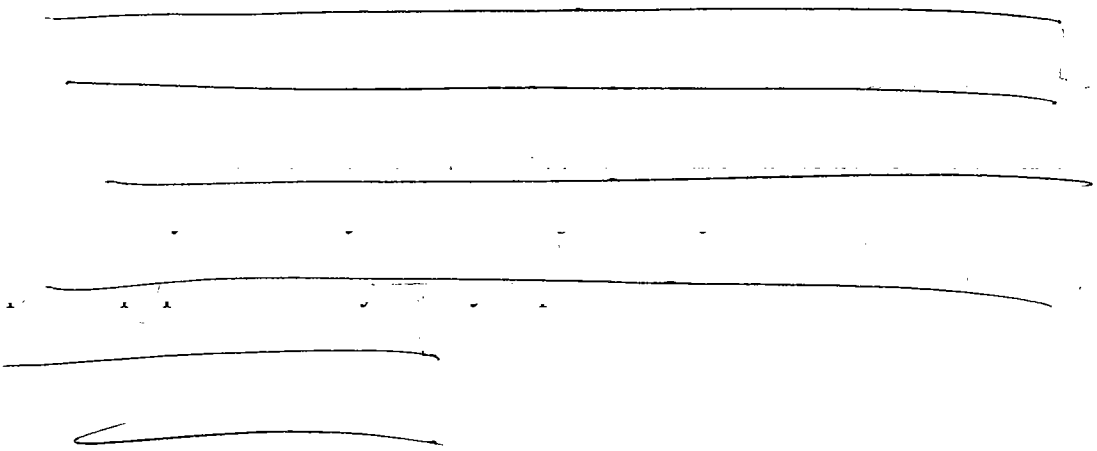
	Treatment Phase									
	Week #									
	56	60	64/68	72	76/80	84	88/92	96	100	104
Randomization										
VAS					X					X
MSFC/VF Test		X		X		X		X		
EDSS		X		X		X		X		
Diary Review	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X

Table 3.1.1.1: Schedule of events [Chart III of III]

	Treatment Phase			Post-treatment	Withdrawal Evaluation	Relapse Evaluation
	Week #			Week #		Unscheduled visit
	108	112	120	128		
Randomization						
VAS			X	X		
MSFC/VF Test	X		X	X		
EDSS	X		X	X		X
Diary Review	X	X	X	X		
Study Drug Infusion	X	X				
Adverse Events	X	X	X	X		X
Relapse Evaluation						X

The protocol proposed two primary efficacy endpoints:

1. *Relapse rate*: The sponsor defines a relapse as new or recurrent neurological symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. The relapse rate will be calculated as the number of relapses divided by days in study, multiplied by 365.



3.1.1. Statistical Methodologies: Study C-1801

Sponsor analyzes the data on the primary efficacy endpoint using Poisson regression with _EDSSG35, _GDYES, and _AGEGE40 as class variables and the number of relapses as a covariate. The stratification variables _EDSSG35, _GDYES, and _AGEGE40 are dichotomized versions of baseline EDSS score, presence or absence of Gd lesions, and age at screening, respectively. The observed frequency distributions of baseline relapse numbers and EDSS scores are given in Tables 3.1.1.2 and 3.1.1.3, respectively.

A subject having at least one relapse during the past year was eligible to be included in the study. However, twelve subjects with 0 relapses during the baseline year were included in the study. The baseline numbers of relapses are:

Table 3.1.1.2: Observed frequency distribution of the baseline number of relapses

Number of relapses	**0**	1	2	3	4	5	8	12
Frequency	12	548	299	63	14	3	2	1

The baseline EDSS score are:

Table 3.1.1.3: Observed frequency distribution of baseline EDSS scores

EDSS score	0	1	1.5	2	2.5	3	3.5	4	4.5	5	**5.5**	**6**
Frequency	38	103	164	199	118	117	88	43	43	25	1	2

The sponsor dichotomizes these baseline EDSS scores and classifies the subjects if EDSS score < = 3.5 or >3.5 for primary analysis. See Table 3.1.1.4 below.

Table 3.1.1.4: Baseline EDSS

	EDSS <=3.5	EDSS > 3.5	Total
Natalizumab	548	79	627
Placebo	278	37	315
Total	**826**	**116**	942

The sponsor classifies the subjects if they have the baseline gd lesions = 0 or > 0 for primary analysis. See Table 3.1.1.5 below.

Table 3.1.1.5: Table of Treatment by GD lesions

	GD = 0	GD > 0	Total
Natalizumab	311	316	627
Placebo	172	143	315
Total	483	459	942

The following is a summary of demographics.

Table 3.1.1.6 : Treatment-wise demographics

	Placebo	Natalizumab	Total
GENDER			
F	211	449	660
M	104	178	282
Total	315	627	942
RACE			
White	296	602	898
Others	18	22	40
	1 missing	3 missing	4 missing
Total	315	627	942
AGE in years			
Mean (SD)	36.7 (7.8)	35.6 (8.5)	

Table 3.1.1.7 shows the number of subjects who were randomized, the number of who continued study drug and the number of who withdrew from the study.

Table 3.1.1.7: Patient disposition in Study C-1801

	Placebo		Natalizumab		Total	
Number of subjects randomized	315	(100)	627	(100)	942	(100)
Number of subjects who withdrew prior to dosing	3	(<1)	0	(0)	3	(<1)
Number of subjects dosed	312	(99)	627	(100)	939	(>99)
Number of subjects who completed 24 weeks in the study (a)	307	(97)	617	(98)	924	(98)
Number of subjects who completed 1 year in the study (b)	280	(89)	568	(91)	848	(90)
Number of subjects who discontinued study drug	25	(8)	44	(7)	69	(7)
Lost to Follow-up	2	(<1)	0		2	(<1)
Adverse Event	8	(3)	31	(5)	39	(4)
Voluntary Withdrawal Due to Reasons Other than Adverse Event	11	(3)	7	(1)	18	(2)
Non-compliance	0		1	(<1)	1	(<1)
Death	0		0		0	
Other	4	(1)	5	(<1)	9	(<1)
Number of subjects who withdrew from study	18	(6)	21	(3)	39	(4)
Lost to Follow-up	2	(<1)	0		2	(<1)
Adverse Event	6	(2)	12	(2)	18	(2)
Voluntary Withdrawal Due to Reasons Other than Adverse Event	8	(3)	4	(<1)	12	(1)
Non-compliance	0		1	(<1)	1	(<1)
Death	0		0		0	
Other	2	(<1)	4	(<1)	6	(<1)

Note: Numbers in parentheses are percentages.

(a) Defined as having completed the Week 24 visit, and/or have been in the study for 24 weeks or more

(b) Defined as having completed the Week 24 visit, and/or have been in the study for 24 weeks or more

The efficacy results as reported by the sponsor are summarized in Table 3.1.1.8 below.

Table 3.1.1.8: Sponsor's efficacy summary for C-1801

Efficacy endpoint	Placebo	Natalizumab	Decrease / Reduction	p-value
Primary:				
Annualized relapse rate	0.805	0.261	68%	<0.001

The sponsor's analysis of primary efficacy data from C-1801 is reproduced in the SAS OUTPUT in Appendix 1.1.

The SAS OUTPUT of Appendix 1.2 shows an exploratory analysis of the baseline number of relapses. As seen from Appendix 1.2, one-way analysis of variance is used on the square root of the number of relapses is the dependent variable. The results indicate that the disease severity differs among sites.

The sponsor's analysis of the first primary efficacy endpoint does not include the only stratification factor site. The SAS OUTPUT in Appendix 1.3 shows an exploratory analysis to see if differences exist among sites. The analysis includes a few arbitrarily chosen sites in the Poisson regression the number of relapses. The results indicate that differences exist among sites.

3.1.2. Statistical Methodologies: Study C-1802

Sponsor analyzes the data on the primary efficacy endpoint using Poisson regression with _EDSSG35, _GDYES, and _AGEGE40 as class variables and the number of relapses as a covariate. The stratification variables _EDSSG35, _GDYES, and _AGEGE40 are dichotomized versions of baseline EDSS score, presence or absence of Gd lesions, and age at screening, respectively. The observed frequency distributions of baseline relapse numbers and EDSS scores are given in Tables 3.1.2.1 and 3.1.2.2, respectively.

A subject having at least one relapse during the past year was eligible to be included in the study. The baseline numbers of relapses are:

Table 3.1.2.1: Observed frequency distribution of the baseline number of relapses

Number of relapses	0	1	2	3	4	5	6	7
Frequency	**1**	747	327	71	18	3	1	1

The baseline GDSS score are:

Table 3.1.2.2: Observed frequency distribution of baseline EDSS scores

EDSS score	0	1	1.5	2	2.5	3	3.5	4	4.5	5	**5.5**	**6**
Frequency	38	103	164	199	118	117	88	43	43	25	1	2

The sponsor dichotomizes these baseline EDSS scores and classifies the subjects if EDSS score < = 3.5 or >3.5 for primary analysis. See Table 3.1.2.3 below.

Table 3.1.2.3: Baseline EDSS score

	EDSS <=3.5	EDSS > 3.5	Total
Natalizumab	548	79	627
Placebo	278	37	315
Total	**826**	**116**	942

The sponsor classifies the subjects if they have the baseline gd lesions = 0 or > 0 for primary analysis. See Table 3.1.2.4 below.

Table 3.1.2.4: Table of Treatment by GD lesions

	GD = 0	GD > 0	Total
Natalizumab	311	316	627
Placebo	172	143	315
Total	483	459	942

The following is a summary of demographics.

Table 3.1.2.5 : Treatment-wise demographics

	Placebo	Natalizumab	Total
GENDER			
F	420	442	862
M	162	147	309
Total	582	589	1171
RACE			
White	542	551	1093
Others	40	38	78
Total	582	589	1171
AGE in years			
Mean (SD)	39 (7.6)	38.8 (7.7)	

Table 3.1.2.6 shows the number of subjects who were randomized, the number of who continued study drug and the number of who withdrew from the study.

Table 3.1.2.6 : Patients' disposition in Study C-1802

	Placebo + Avonex		Natalizumab + Avonex		Total	
Number of subjects randomized	582	(100)	589	(100)	1171	(100)
Number of subjects who withdrew prior to dosing	0		0		0	
Number of subjects dosed	582	(100)	589	(100)	1171	(100)
Number of subjects who completed 24 weeks in the study (a)	573	(98)	580	(98)	1153	(98)
Number of subjects who completed 1 year in the study (b)	387	(66)	393	(67)	780	(67)
Number of subjects who discontinued study drug	70	(12)	61	(10)	131	(11)
Lost to Follow-up	2	(<1)	3	(<1)	5	(<1)
Adverse Event	24	(4)	33	(6)	57	(5)
Voluntary Withdrawal Due to Reasons Other than Adverse Event	30	(5)	16	(3)	46	(4)
Non-compliance	1	(<1)	3	(<1)	4	(<1)
Death	0		0		0	
Other	13	(2)	6	(1)	19	(2)
Number of subjects who withdrew from study	41	(7)	29	(5)	70	(6)
Lost to Follow-up	2	(<1)	3	(<1)	5	(<1)
Adverse Event	4	(<1)	7	(1)	11	(<1)
Voluntary Withdrawal Due to Reasons Other than Adverse Event	24	(4)	11	(2)	35	(3)
Non-compliance	1	(<1)	1	(<1)	2	(<1)
Death	1	(<1)	0		1	(<1)
Other	9	(2)	7	(1)	16	(1)

Note: Numbers in parentheses are percentages.

(c) Defined as having completed the Week 24 visit, and/or have been in the study for 24 weeks or more

(d) Defined as having completed the Week 24 visit, and/or have been in the study for 24 weeks or more

The efficacy results as reported by the sponsor are summarized in Table 3.1.1.7 below.

Table 3.1.2.7: Sponsor's efficacy summary for C-1802

Efficacy endpoint	Placebo (avonex)	Natalizumab + avonex	Decrease / Reduction	p-value
Primary:				
Annualized relapse rate	0.816	0.383	53%	<0.001

The sponsor's analysis of primary efficacy data from C-1802 is reproduced in the SAS OUTPUT in Appendix 2.1.

The SAS OUTPUT of Appendix 2.2 shows an exploratory analysis of the baseline number of relapses. As seen from Appendix 2.2, one-way analysis of variance is used on the square root of the number of relapses is the dependent variable. The results indicate that the disease severity differs among sites.

The sponsor's analysis of the first primary efficacy endpoint does not include the only stratification factor site. The SAS OUTPUT in Appendix 2.3 shows an exploratory analysis to see if differences exist among sites. The analysis includes a few arbitrarily chosen sites in the Poisson regression the number of relapses. The results indicate that differences exist among sites.

The SAS OUTPUT in Appendix 2.4 shows an exploratory analysis to see if natalizumab is not effective in some sites. The analysis includes a few arbitrarily chosen sites. The results indicate that no significant differences between the two treatment groups.

Results and Conclusions

As mentioned earlier, the sponsor analyzes the data on the primary efficacy endpoint using Poisson regression with _EDSSG35, _GDYES, and _AGEGE40 as class variables and the number of relapses as a covariate. The stratification variables _EDSSG35, _GDYES, and _AGEGE40 are dichotomized versions of baseline EDSS score, presence or absence of Gd lesions, and age at screening, respectively.

The sponsor concludes the results for Study C-1801: "Treatment with 300 mg natalizumab resulted in a 68% decrease in the annualized relapse rate versus placebo, the primary endpoint ($p < 0.001$). The annualized relapse rate in the placebo group was 0.805 (95% CI: 0.669, 0.969) and 0.261 (95% CI: 0.211, 0.323) in the natalizumab group.

The sponsor concludes the results for Study C-1802: "Treatment with 300 mg natalizumab when added to AVONEX resulted in a 53% decrease in the annualized relapse rate versus treatment with AVONEX in patients inadequately responding to AVONEX ($p < 0.001$). The annualized relapse rate in the AVONEX only group was 0.815 (95% CI: 0.721, 0.923) compared to 0.383 (95% CI: 0.325, 0.45) for the group that received AVONEX plus natalizumab.

This reviewer was able to reproduce the sponsor's results on the primary efficacy endpoint.

The sponsor's analysis is not the optimal one for confirmatory trials. The sponsor's analyses are not consistent with study designs. The results are based on an invalidated assumption of no center effect or center×treatment interaction. This raises a concern about bias of the study.

3.2 Safety Evaluation

See Dr. Wilson Bryan's report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The study C-1801 recruited 660 females and 282 males. Subjects were between 18 and 50 years of age. The average age was 36 years with a standard deviation of 8.3 years. Tables 4.1.1 to 4.1.4 provide descriptive statistics on annualized relapse rates in various demographics. As most of them (95.7%) were whites, race-wise descriptive statistics on annualized relapse rates are not provided.

Table 4.1.1: Treatment by Age-group Annualized relapse rate in C-1801

	Placebo		Natalizumab	
AGE GROUP	Mean	Std. Dev.	Mean	Std. Dev.
AGE < 40	0.98	1.44	0.27	0.63
AGE >= 40	0.53	0.83	0.26	0.62

Table 4.1.2: Treatment by Gender Annualized relapse rate in C-1801

	Placebo		Natalizumab	
GENDER	Mean	Std. Dev.	Mean	Std. Dev.
F	0.83	1.24	0.28	0.65
M	0.74	1.28	0.28	0.58

The study C-1802 recruited 862 females and 309 males. Most of them (93.4%) were whites. Subjects were between 18 and 50 years of age. The average age was 39 years with a standard deviation of 7.65 years.

Table 4.1.3: Treatment by Age-group Annualized relapse rate in C-1802

	Placebo		Natalizumab	
AGE GROUP	Mean	Std. Dev.	Mean	Std. Dev.
AGE < 40	1.08	1.29	0.43	0.76
AGE >= 40	0.735	1.106	0.43	0.75

Table 4.1.4: Treatment by Gender Annualized relapse rate in C-1802

	Placebo		Natalizumab	
GENDER	Mean	Std. Dev.	Mean	Std. Dev.
F	0.9	1.18	0.44	0.76
M	0.94	1.3	0.41	0.74

4.2 Other Special/Subgroup Populations

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Randomization is stratified by site. The sponsor implemented bad design in each study. Each study has several sites with fewer than four subjects. As indicated by the SAS OUTPUT in Appendix 1.1 and SAS OUTPUT in Appendix 2.1, sites appear to be different with respect to disease severity- prior to randomization. The Poisson regression model for the number of relapses (primary efficacy endpoint), when site is included as a stratification variable, does not converge. The sponsor is unable to include sites or adequately pooled sites in the primary efficacy analysis. The design, in each case, is preventing a correct analysis from being done. The SAS OUTPUTS in Appendices 1.3 and 2.3 indicate that the sponsor's analysis is not the optimal for confirmatory trials. The results are based on an invalidated assumption that no center effect or treatment×center interaction. This raises a concern about bias of the study.

In the labeling, the sponsor may not use the p-value for comparing the relapse rates.

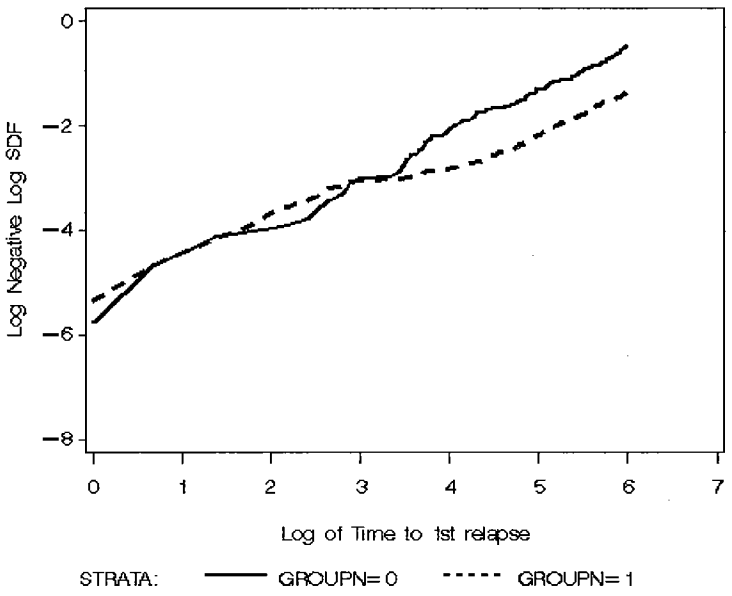
The sponsor's statement of the first objective " .. to see if natulizumab is effective in reducing the rate of clinical relapses at 1 year" and the sponsor's characterization of submitted data as "one year data" are misleading. Technically, as indicated in the Appendix, the response rate for the last subject is expressed in terms of the exposure time of the remaining subjects. The sponsor's data analytic method does not incorporate this *dependence* making interpretation of the results hard.

In the labeling, the sponsor may not describe the data as "one year data".

The sponsor has analyzed data on time to first relapse using the standard log-rank test and Kaplan-Meier estimation. In Study C-1801, due to disproportionate number of censors, 180/315

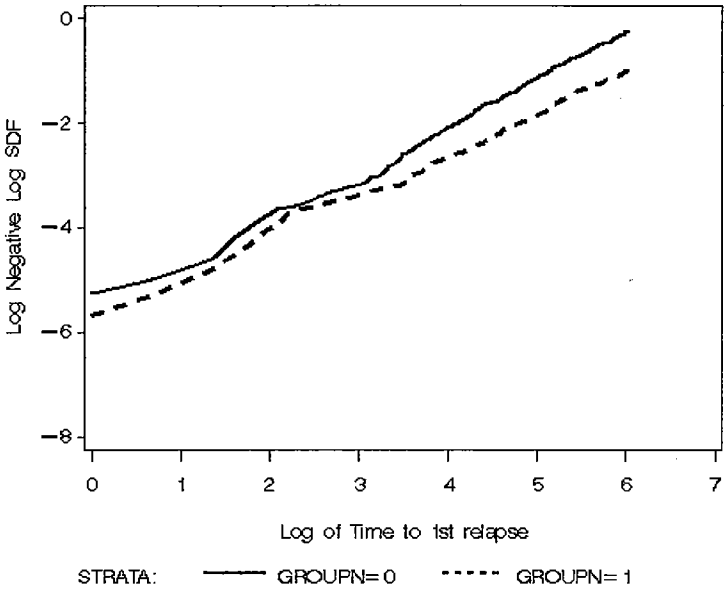
in placebo and 493/627 in the natalizumab arm, the Kaplan-Meier estimates may be biased. Median estimates are not available. Furthermore, the SAS "LLS" plot indicates that the proportional hazard assumption is in question (see Figure 5.1.1 below) leading to concern about appropriateness of the log-rank test.

Figure 5.1.1: C—1801 log—log survival plot



Similarly, in Study C-1802, 289 out of the 582 in the placebo group are censored. The number of censored observations in the natalizumab group is 419 (out of 589). Therefore, the Kaplan-Meier estimates are biased. Median estimates are not available. However, in this case the SAS "LLS" looks better (see Figure 5.1.2 below).

Figure 5.1.2: C–1802 log–log survival plot



5.2 Conclusions and Recommendations

It appears that different centers were not reasonably uniform at the design stage. It is possible that significant differences between sites exist. Decision to keep sites out of the primary efficacy analyses is not justified. As seen from the SAS OUTPUT of Appendix 2.4, natalizumab may not be efficacious in some sites. It is not possible to verify if substantial collective evidence for efficacy is provided by the entire application.

The sponsor's efficacy claim for the accelerated approval may be accepted subject to the condition: The sponsor may not describe the data as "one year data" and may not use the p-value for comparing the relapse rates in the labeling.

APPENDICES

Appendix 1.1: SAS OUTPUT- Sponsor's Analysis (C-1801)

The GENMOD Procedure

Model Information

Data Set	WORK.NEW10	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	942	

Class Level Information

Class	Levels	Values
_AGEGE40	2	AGE < 40 AGE >= 40
_EDSSG35	2	EDSS <= 3.5 EDSS > 3.5
_GDYES	2	gd > 0 gd = 0
GROUPN	2	0 1

Parameter Information

Parameter	Effect	_AGEGE40	_EDSSG35	_GDYES	GROUPN
Prm1	Intercept				
Prm2	RLPS_1Y				
Prm3	_AGEGE40	AGE < 40			
Prm4	_AGEGE40	AGE >= 40			
Prm5	_EDSSG35		EDSS <= 3.5		
Prm6	_EDSSG35		EDSS > 3.5		
Prm7	_GDYES			gd > 0	
Prm8	_GDYES			gd = 0	
Prm9	GROUPN				0
Prm10	GROUPN				1

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	936	950.6916	1.0157
Scaled Deviance	936	747.7808	0.7989
Pearson Chi-Square	936	1189.9841	1.2714
Scaled Pearson X2	936	936.0000	1.0000
Log Likelihood		-521.0992	

Algorithm converged.

The GENMOD Procedure

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-1.6190	0.1968	-2.0047	-1.2333	67.67	<.0001
RLPS_1Y		1	0.1607	0.0518	0.0591	0.2623	9.61	0.0019
_AGEGE40	AGE < 40	1	0.3622	0.1227	0.1217	0.6027	8.72	0.0032
_AGEGE40	AGE >= 40	0	0.0000	0.0000	0.0000	0.0000	.	.
_EDSSG35	EDSS <= 3.5	1	-0.5059	0.1505	-0.8009	-0.2110	11.30	0.0008
_EDSSG35	EDSS > 3.5	0	0.0000	0.0000	0.0000	0.0000	.	.
_GDYES	gd > 0	1	0.2789	0.1143	0.0549	0.5028	5.96	0.0147
_GDYES	gd = 0	0	0.0000	0.0000	0.0000	0.0000	.	.

GROUPN	0	1	1.1103	0.1153	0.8843	1.3364	92.67	<.0001
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.1275	0.0000	1.1275	1.1275		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.1964	0.0900	1	4.76	0.0292	0.05	-0.3729	-0.0199
GROUPN	1	-1.3067	0.1028	1	161.51	<.0001	0.05	-1.5083	-1.1052

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	1	1.1103	0.1153	1	92.67	<.0001	0.05	0.8843	1.3364

Appears This Way
On Original

Appendix 1.2: SAS OUTPUT - Baseline number of relapses (comparison among sites) (C-1801)

The SAS System: The ANOVA Procedure
Dependent Variable: square-root of baseline number of relapses in C-1801

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	98	15.31039699	0.15622854	1.69	<.0001
Error	843	78.00761800	0.09253573		
Corrected Total	941	93.31801498			

R-Square	Coeff Var	Root MSE	y1801 Mean
0.164067	25.49866	0.304197	1.192992

Source	DF	Anova SS	Mean Square	F Value	Pr > F
SITE	98	15.31039699	0.15622854	1.69	<.0001

Appendix 1.3: SAS OUTPUT- Analysis of efficacy data from some selected sites (C-1801)

The GENMOD Procedure: C-1801

Model Information

Data Set	WORK.NEW81	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	183	

Class Level Information

Class	Levels	Values
SITE	10	116 125 126 313 322 323 402 407 440 449
_EDSSG35	2	EDSS <= 3.5 EDSS > 3.5
GROUPN	2	0 1

Parameter Information

Parameter	Effect	SITE	_EDSSG35	GROUPN
Prm1	Intercept			
Prm2	SITE	116 (usa)		
Prm3	SITE	125 (usa)		
Prm4	SITE	126 (usa)		
Prm5	SITE	313 (uk)		
Prm6	SITE	322 (uk)		
Prm7	SITE	323 (uk)		
Prm8	SITE	402 (czech)		
Prm9	SITE	407 (Czech)		
Prm10	SITE	440 (Poland)		
Prm11	SITE	449 (Poland)		
Prm12	_EDSSG35		EDSS <= 3.5	
Prm13	_EDSSG35		EDSS > 3.5	
Prm14	GROUPN			0
Prm15	GROUPN			1

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	171	163.7342	0.9575
Scaled Deviance	171	138.8495	0.8120
Pearson Chi-Square	171	201.6468	1.1792
Scaled Pearson X2	171	171.0000	1.0000
Log Likelihood		-90.6021	

The GENMOD Procedure

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-2.8803	1.1176	-5.0708	-0.6897	6.64	0.0100
SITE	116	1	0.6219	1.5367	-2.3901	3.6338	0.16	0.6857
SITE	125	1	2.0327	1.1731	-0.2664	4.3319	3.00	0.0831
SITE	126	1	2.0871	1.1518	-0.1703	4.3446	3.28	0.0700
SITE	313	1	2.8956	1.1178	0.7048	5.0864	6.71	0.0096*
SITE	322	1	2.4074	1.1272	0.1982	4.6166	4.56	0.0327*
SITE	323	1	3.3955	1.1103	1.2194	5.5717	9.35	0.0022*
SITE	402	1	2.7786	1.1215	0.5804	4.9767	6.14	0.0132*
SITE	407	1	0.0510	1.5358	-2.9591	3.0612	0.00	0.9735
SITE	440	1	1.9107	1.1731	-0.3885	4.2099	2.65	0.1034
SITE	449	0	0.0000	0.0000	0.0000	0.0000	.	.

_EDSSG35	EDSS <= 3.5	1	-0.8100	0.2767	-1.3522	-0.2677	8.57	0.0034
_EDSSG35	EDSS > 3.5	0	0.0000	0.0000	0.0000	0.0000	.	.
GROUPN	0	1	1.1036	0.2285	0.6557	1.5515	23.32	<.0001
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.0859	0.0000	1.0859	1.0859		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.3636	0.2544	1	2.04	0.1530	0.05	-0.8623	0.1351
GROUPN	1	-1.4672	0.2539	1	33.39	<.0001	0.05	-1.9649	-0.9695

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	1	1.1036	0.2285	1	23.32	<.0001	0.05	0.6557	1.5515

Appears This Way
On Original

Appendix 2.1: SAS OUTPUT – Sponsor's analysis (C-1802)

The GENMOD Procedure

Model Information

Data Set	WORK.NEW51	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	1171	

Class Level Information

Class	Levels	Values
_AGEGE40	2	AGE < 40 AGE >= 40
_EDSSG35	2	EDSS <= 3.5 EDSS > 3.5
_GDYES	2	gd = 0 gd > 0
GROUPN	2	0 1

Parameter Information

Parameter	Effect	_AGEGE40	_EDSSG35	_GDYES	GROUPN
Prm1	Intercept				
Prm2	RLPS_1Y				
Prm3	_AGEGE40	AGE < 40			
Prm4	_AGEGE40	AGE >= 40			
Prm5	_EDSSG35		EDSS <= 3.5		
Prm6	_EDSSG35		EDSS > 3.5		

Prm7	_GDYES	gd = 0	
Prm8	_GDYES	gd > 0	
Prm9	GROUPN		0
Prm10	GROUPN		1

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	1165	1289.0282	1.1065
Scaled Deviance	1165	1289.0282	1.1065
Pearson Chi-Square	1165	1382.9049	1.1870
Scaled Pearson X2	1165	1382.9049	1.1870
Log Likelihood		-987.7944	

Algorithm converged.

The GENMOD Procedure

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-1.1249	0.1457	-1.4105	-0.8394	59.62	<.0001
RLPS_1Y		1	0.1868	0.0446	0.0993	0.2743	17.50	<.0001
_AGEGE40	AGE < 40	1	0.2352	0.0777	0.0829	0.3876	9.16	0.0025
_AGEGE40	AGE >= 40	0	0.0000	0.0000	0.0000	0.0000	.	.
_EDSSG35	EDSS <= 3.5	1	-0.1956	0.1017	-0.3949	0.0036	3.70	0.0543
_EDSSG35	EDSS > 3.5	0	0.0000	0.0000	0.0000	0.0000	.	.
_GDYES	gd = 0	1	-0.2666	0.0775	-0.4186	-0.1146	11.82	0.0006
_GDYES	gd > 0	0	0.0000	0.0000	0.0000	0.0000	.	.
GROUPN	0	1	0.7587	0.0808	0.6003	0.9172	88.08	<.0001
GROUPN	1	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	-0.2059	0.0572	1	12.96	0.0003	0.05	-0.3180	-0.0938
GROUPN	1	-0.9646	0.0756	1	162.97	<.0001	0.05	-1.1127	-0.8165

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	0	1	0.7587	0.0808	1	88.08	<.0001	0.05	0.6003	0.9172

Appendix 2.2: SAS OUTPUT- Baseline number of relapses (comparison among sites) (C-1802)

The SAS System: The ANOVA Procedure
Dependent Variable: square-root of baseline number of relapses in C-1802

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	122	13.93681536	0.11423619	1.70	<.0001
Error	1048	70.44459257	0.06721812		
Corrected Total	1170	84.38140793			

R-Square	Coeff Var	Root MSE	y1802 Mean
0.165165	21.95777	0.259265	1.180742

Source	DF	Anova SS	Mean Square	F Value	Pr > F
SITE	122	13.93681536	0.11423619	1.70	<.0001

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On Original

Appendix 2.3: SAS OUTPUT- Analysis of efficacy data from some selected sites (C -1802)

The GENMOD Procedure: C-1802 (All US sites)

Model Information

Data Set	WORK.SUBSITES	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	348	

Class Level Information

Class	Levels	Values
SITE	18	121 125 136 137 142 143 144 151 155 156 157 160 167 168 170 176 179 197 - all US sites
_AGEGE40	2	AGE >= 40 AGE < 40
_EDSSG35	2	EDSS <= 3.5 EDSS > 3.5
_GDYES	2	gd > 0 gd = 0
GROUPN	2	1 0

Parameter Information

Parameter	Effect	SITE	_GDYES	GROUPN
Prm1	Intercept			
Prm2	RLPS_1Y			
Prm3	SITE	121		
Prm4	SITE	125		
Prm5	SITE	136		
Prm6	SITE	137		
Prm7	SITE	142		
Prm8	SITE	143		
Prm9	SITE	144		
Prm10	SITE	151		
Prm11	SITE	155		
Prm12	SITE	156		
Prm13	SITE	157		
Prm14	SITE	160		
Prm15	SITE	167		
Prm16	SITE	168		
Prm17	SITE	170		
Prm18	SITE	176		
Prm19	SITE	179		
Prm20	SITE	197		
Prm21	_GDYES		gd > 0	
Prm22	_GDYES		gd = 0	
Prm23	GROUPN			1
Prm24	GROUPN			0

The GENMOD Procedure

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	327	359.1311	1.0983
Scaled Deviance	327	298.6439	0.9133
Pearson Chi-Square	327	393.2304	1.2025
Scaled Pearson X2	327	327.0000	1.0000
Log Likelihood		-222.8359	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-0.5786	0.3006	-1.1677	0.0106	3.70	0.0543
RLPS_1Y		1	0.2282	0.0780	0.0754	0.3810	8.57	0.0034
SITE	121	1	-1.4984	0.8163	-3.0984	0.1016	3.37	0.0664
SITE	125	1	-0.8665	0.4452	-1.7391	0.0062	3.79	0.0517
SITE	136	1	-2.2189	1.1252	-4.4243	-0.0135	3.89	0.0486*
SITE	137	1	0.1105	0.3789	-0.6321	0.8530	0.09	0.7706
SITE	142	1	-1.2611	0.5513	-2.3417	-0.1805	5.23	0.0222*
SITE	143	1	-0.1706	0.4177	-0.9892	0.6481	0.17	0.6830
SITE	144	1	0.0560	0.3878	-0.7040	0.8161	0.02	0.8851
SITE	151	1	0.0692	0.3346	-0.5866	0.7250	0.04	0.8362
SITE	155	1	0.0368	0.3764	-0.7008	0.7745	0.01	0.9221
SITE	156	1	-0.9117	0.4850	-1.8624	0.0389	3.53	0.0601
SITE	157	1	0.4201	0.4092	-0.3818	1.2220	1.05	0.3045
SITE	160	1	0.2870	0.4343	-0.5643	1.1383	0.44	0.5088
SITE	167	1	-0.5463	0.4438	-1.4162	0.3236	1.51	0.2184
SITE	168	1	-0.5569	0.3635	-1.2694	0.1556	2.35	0.1255
SITE	170	1	-0.5580	0.3800	-1.3028	0.1867	2.16	0.1419
SITE	176	1	-0.1208	0.3845	-0.8744	0.6328	0.10	0.7534
SITE	179	1	-0.4844	0.4438	-1.3542	0.3855	1.19	0.2751
SITE	197	0	0.0000	0.0000	0.0000	0.0000	.	.
_GDYES	gd > 0	1	0.5298	0.1577	0.2206	0.8389	11.28	0.0008
_GDYES	gd = 0	0	0.0000	0.0000	0.0000	0.0000	.	.
GROUPN	1	1	-0.8028	0.1642	-1.1246	-0.4810	23.91	<.0001
GROUPN	0	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.0966	0.0000	1.0966	1.0966		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

The GENMOD Procedure

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	1	-1.2161	0.1563	1	60.51	<.0001	0.05	-1.5225	-0.9097
GROUPN	0	-0.4133	0.1158	1	12.73	0.0004	0.05	-0.6403	-0.1863

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	1	0	-0.8028	0.1642	1	23.91	<.0001	0.05	-1.1246	-0.4810

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On Original

Appears This Way
On Original

Appendix 2.4: SAS OUTPUT - Sites where results are non-significant (C-1802)

The GENMOD Procedure

Model Information

Data Set	WORK.CTR198	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	TOTREL	No. of relapses
Offset Variable	lyears	
Observations Used	97	

Class Level Information

Class	Levels	Values
US SITE	5	121 125 142 170 198
GROUPN	2	1 0

Parameter Information

Parameter	Effect	GROUPN
Prm1	Intercept	
Prm2	RLPS_1Y	
Prm3	GROUPN	1
Prm4	GROUPN	0

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	94	78.8977	0.8393
Scaled Deviance	94	65.6194	0.6981
Pearson Chi-Square	94	113.0211	1.2024
Scaled Pearson X2	94	94.0000	1.0000
Log Likelihood		-48.4983	

Algorithm converged.

The GENMOD Procedure

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-1.8968	0.4079	-2.6963	-1.0972	21.62	<.0001
RLPS_1Y		1	0.5742	0.1667	0.2476	0.9009	11.87	0.0006
GROUPN	1	1	-0.7719	0.4379	-1.6301	0.0863	3.11	0.078 NS
GROUPN	0	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.0965	0.0000	1.0965	1.0965		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

Least Squares Means

Effect	GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	1	-1.8636	0.3679	1	25.66	<.0001	0.05	-2.5846	-1.1426
GROUPN	0	-1.0917	0.2545	1	18.40	<.0001	0.05	-1.5905	-0.5928

Differences of Least Squares Means

Effect	GROUPN	_GROUPN	Estimate	Standard Error	DF	Chi-Square	Pr > ChiSq	Alpha	Confidence Limits	
GROUPN	1	0	-0.7719	0.4379	1	3.11	0.0779	0.05	-1.6301	0.0863

Appears This Way
On Original

Appendix 3: A technical note on Possion regression

Let $\mu(\mathbf{x})$ denote the expected value of the number of events $n(\mathbf{x})$, $\mathbf{x}$ is the vector of explanatory variables, $\mathbf{x} = (x_1, x_2, .., x_t)'$. Let $N(\mathbf{x})$ denote the known total exposure (in years) to risk in the unit in which the events occur. The rate of incidence is written

$$\lambda(\mathbf{x}) = \mu(\mathbf{x})/N(\mathbf{x})$$

The most common model for Poisson regression is the log-linear model:

$$\mu(\mathbf{x}) = \{N(\mathbf{x})\}\{\exp(\mathbf{x}'\boldsymbol{\beta})\}$$

The SAS GENMOD is used to obtain the maximum likelihood estimate of $\boldsymbol{\beta}$. If there are s "independent" groups referenced by $i = 1, 2, \ldots s$, each with a vector $\mathbf{x}_i = (x_{i1}, x_{i2}, .. x_{it})$ of t explanatory variables, a likelihood function for a Poisson regression model is

$$\ell(\mathbf{n} \mid \boldsymbol{\mu}) = \prod_{i=1}^{s} \mu_i^{n_i} \{\exp(-\mu_i)\}/n_i!,$$

where $\mathbf{n} = (n_1, n_2, \ldots n_s)$ and $\boldsymbol{\mu} = (\mu_1, \mu_2, .., \mu_s)$. The parameter vector $\boldsymbol{\beta}$ is estimated by maximizing $\log \ell$. See Stokes, Davis and Koch (1997, SAS Institute Inc.: 471-472).

If the clinical trial, in case of Study C-1801, is designed to have the total exposure time (in years) $\sum_{i=1}^{s} N(\mathbf{x}_i) = 942$, for example, the time to exposure for the last group (subject)

$$N(\mathbf{x}_s) = 942 - N(\mathbf{x}_1) - N(\mathbf{x}_2) - \cdots - N(\mathbf{x}_{s-1}),$$

the independence assumption is lost. That is, the incidence rate for one of the subjects depends upon the remaining subjects. I do not know how to incorporate the condition $\sum N(\mathbf{x}_i) = 942$ and find $\hat{\beta}$s.

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