Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA:	**204063**
Drug Name:	**BG00012 (Dimethyl Fumarate) delayed action capsule**
Indications:	**Multiple Sclerosis**
Applicants:	**Sponsor: Biogen Idec, Inc.** **14 Cambridge Center, Cambridge, MA 02142** (b) (4) [redacted]
Date(s):	**Submitted: 27 February 2012** **To Reviewer: 30 July 2012**
Review Priority:	**Standard**
Biometrics Division:	**Division 6**
Statistical Reviewer:	**Steve Thomson**
Concurring Reviewers:	**Karl Lin, Ph.D.**
Medical Division:	**Neurology Products**
Toxicologist Team:	**Melissa Banks-Muckenfuss, Ph.D.**
Project Manager:	**Nicole Bradley, Pharm.D.**

Keywords: Bayesian analysis, Carcinogenicity, Cox regresson, Kaplan-Meier product limit, Survival analysis, Trend test

Table of Contents

1. EXECUTIVE SUMMARY 3

1.1. CONCLUSIONS AND RECOMMENDATIONS 3
1.2. BRIEF OVERVIEW OF THE STUDIES 11
1.3. STATISTICAL ISSUES AND FINDINGS 11
1.3.1. Statistical Issues 11
1.3.2. Statistical Findings 17

2. INTRODUCTION 17

2.1. OVERVIEW 17
2.2. DATA SOURCES 17

3. STATISTICAL EVALUATION 17

3.1. EVALUATION OF EFFICACY 17
3.2. EVALUATION OF SAFETY 17

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 36

5. SUMMARY AND CONCLUSIONS 36

5.1. STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 36
5.2. CONCLUSIONS AND RECOMMENDATIONS 36

APPENDICES 37

APPENDIX 1. FDA SURVIVAL ANALYSIS 37
APPENDIX 2. FDA POLY-K TUMORIGENICITY ANALYSIS 42
APPENDIX 3. BAYESIAN TUMORIGENICITY ANALYSIS IN RATS 66
APPENDIX 4. REFERENCES 70

1. EXECUTIVE SUMMARY

Reports and data from two studies, in rats and mice, were provided. (b) (4) The study report and data for the rat study were originally submitted with IND 73061 from the same Sponsor. The results of the FDA analysis of the rat study are summarized in the statistical carcinogenicity review dated 22 April 2008. Although the current analysis of the rat study is slightly different, only the new mouse study contains completely new results.

According to the mouse report provided by the Sponsors: "The purpose of this study was to evaluate the potential carcinogenicity of BG00012 following once daily oral gavage to CD-1 mice for at least 104 weeks and toxicokinetics following once daily oral gavage for 180 days." (page 18 of report) The objective of the rat report is expressed similarly. Each study included five treatment groups, as described below.

1.1. Conclusions and Recommendations

The Sponsor describes the drug vehicle as hydroxypropylmethylcellulose (HPMC) or hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water. For each study, in each gender, there are five treatment groups. Animals were dosed once daily by oral gavage. Gross aspects of the study designs for the main study animals are summarized in Tables 1 and 2 below:

Table 1. Design of Rat Study (75 animals per main study group/gender)

Treatment Group	Vehicle or Test Article	BG00012 Dosage (mg/kg/day)	Dose Volume (mL/kg)	Dosing Concentration[a]
1. Vehicle	HPMC[a]	0	10	0
2. Low	BG00012	25	10	2.5
3. Medium	BG00012	50	10	5
4. Med-High[b]	BG00012	100	10	10
5. High[b]	BG00012	150	10	15

[a] Hydroxypropylmethylcellulose or Hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water.
[b] Due to mortality, the High dose group (150 mg/kg/day, Group 5) males were terminated during Week 86 and the Medium-High (100 mg/kg/day,Group 4) males were terminated during Week 88.

Table 2. Design of Mouse Study (75 animals per main study group/gender)

Treatment Group	Vehicle or Test Article	BG00012 Dosage (mg/kg/day)	Dose Volume (mL/kg)	Dosing Concentration[a]
1. Vehicle[a]	HPMC	0	10	0
2. Low	BG00012	25	10	2.5
3. Medium	BG00012	75	10	7.5
4. Med-High	BG00012	200	10	20
5. High	BG00012	600/400[b]	10	60/40[b]

[a] Hydroxypropylmethylcellulose or Hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water.
[b] Due to mortality observed in the high-dose group, beginning on Day 9,.the dose level for Group 5 was decreased from 600 mg/kg/day to 400 mg/kg/day (40 mg/mL) . For tests it is treated as dosage at 400 mg/kg/day.

More detailed descriptions of the studies are provided in Section 3.2.1 and 3.2.2 below. In this report the vehicle group is sometimes referred to as the "HPMC" or "control group" while the other dose groups are referred to as "actual dose groups", and, purposes of assessing trend, the Vehicle, Low, Medium, Medium-High, and High dose groups (i.e., Groups 1-5) as "treated groups." Simple summary life tables in mortality are presented in the report in these sections of this report. Also, because early very high mortality in the mice study, on day 9 dosage was reduced from 600 mg/kg/day to 400 mg/kg/day. On all tests used in the FDA analysis it is treated as the 400 mg/kg/day.

In Appendix 1, Figures A.1.1 and A.1.2 for rats display Kaplan-Meier estimated survival curves for each study group for each gender. Two sets of plots are displayed for mice. Figures A.1.3 and A.1.4 for mice display the Kaplan-Meier estimated survival curves for gender using the original data while Figures A.1.5 and A.1.6 display the corresponding plots deleting those animals that died before day 9, because of initial high mortality. Results of tests on survival in rats and mice are summarized below:

Table 3. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study

Hypothesis Tested	Males [a]		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Rat Homogeneity over Groups 1-5	< 0.0001	< 0.0001	0.4421	0.2737
Homogeneity over Groups 1-4	< 0.0001	< 0.0001	0.2904	0.1602
Homogeneity over Groups 1-3	0.0292	0.0153	0.2090	0.1594
No trend over Groups 1-5	< 0.0001	< 0.0001	0.3427	0.2033
No trend over Groups 1-4	< 0.0001	< 0.0001	0.1345	0.0389
No trend over Groups 1-3	0.0169	0.0119	0.1386	0.0734
No Difference Between Groups 1 vs 5	< 0.0001	< 0.0001	0.4943	0.3229
No Difference Between Groups 1 vs 4	< 0.0001	< 0.0001	0.2503	0.0931
No Difference Between Groups 1 vs 3	0.0180	0.0142	0.1205	0.0613

[a] Due to mortality, the High dose group (150 mg/kg/day, Group 5) males were terminated during Week 86 and the Medium-High (100 mg/kg/day,Group 4) males were terminated during Week 88.

From Figure A.1.1, in male rats, the HPMC vehicle and Low dose group are largely intertwined, with the highest survival, while the Medium dose group has the next highest survival, and the Medium-High and High dose groups having the lowest but quite close survival over the study period. Note these groups were sacrificed early due to low survival, but in the analysis such deaths are considered as censored times, not deaths. This is sufficient to cause significant tests of lack of homogeneity, no trend, and no difference between the highest doses and vehicle in groups 1-4 and groups 1-5 (all 12 $p < 0.0001$, usually much less than the 0.0001 level). Even the seperation of the Medium dose group from the Vehicle and Low dose is sufficient to result in consistently statistically significant results (all six $p \leq 0.0292$). The situation in female rats is quite different. From Figure A.1.2, in female rats, although the HPMC vehicle seems to have slightly highest survival, the survival curves of the other four dose groups are generally quite close and are largely intertwined. While this is not strong evidence of no

differences, it is evidence of no strong differences when comparing all five groups plus the High dose to HPMC (all six $p \geq 0.2033$). Results of the tests using treatment subgroups 1-4 and 1-3 are primarily included to match those for male rats. Note that the Wilcoxon test is more sensitive to early differences in survival and the corresponding test of lack of trend is barely statistically significant at the usual level (i.e., Wilcoxon $p = 0.0389$), but this conclusion is not supported by the Logrank test ($p = 0.1386$).

Table 4. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Mouse Homogeneity over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Homogeneity over Groups 1-4	0.1115	0.3129	0.4603	0.5208
No trend over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No trend over Groups 1-4	0.1119	0.3181	0.1847	0.2348
No Difference Between Groups 1 vs 5[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No Difference Between Groups 1 vs 4	0.4876	0.7711	0.1099	0.1322

[a] Printed P-value bounds are identical whether one conditions on survival to day 9 or not.

Figures A.1.3 and A.1.4, in Appendix 1, display the gender specific survival curves over the five dose groups in mice. Note that in both genders the High dose group is clearly separated from the remaining dose groups. This is sufficient to result in the highly statistically significant tests of homogeneity, lack of trend, and no difference between the High dose and the vehicle dose group (for each gender all six $p < 0.0001$). One might speculate that the separation of the High dose from the other dose groups may be due solely to the early deaths in the High dose group, reflected in the initial drop in the Kaplan-meier curve apparent in the figures. Figures A.1.5 and A.1.6 in the appendix display the survival curves over the five dose groups conditional upon animals surviving to at least until day 9. Even with this criterion, the High dose remains seperated from the remaining dose groups. While the actual values of the significance levels for the tests of homogeneity and trend over groups 1-5, and the pairwise comparison between the High dose and vehicle are larger (and thus less statistically significant), the printed values remain the same (i.e., all tests still have all six $p < 0.0001$).

In both sets of plots, for both genders, the survival curves for the dose groups 1-4 are more or less closely intertwined, but with much higher survival than that in the High dose group. This is consistent with the tests of survival completely deleting the High dose group, i.e., none of the tests of homogeneity, lack of trend, and no difference between the next highest dose and the Vehicle dose group were particularly statistically significant, at least at the usual 0.05 level (Males: all six $p \geq 0.1115$, Females all six $p \geq 0.1009$). This suggests that differences in survival are largely due to differences in the High dose from the remaining dose groups.

Of course in a carcinogenicity study, primary interest is on the occurrence of cancers. The statistical analysis of tumors compares tumor incidence over dose groups. Complete tumor

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.