CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204063Orig1s000

STATISTICAL REVIEW(S)

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- ADDENDUM

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:	**To Reviewer: 16 January 2013**
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: Carcinogenicity, Cochran-Armitage test, Poly-k test, Trend test

The original submissions for this carcinogenicity study involved two standard two year studies, in rats and mice. (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. The data for the mice were submitted later, and the data for both species were reanalyzed in a review dated 28 September 2012.

After completion and posting of these reviews the Sponsor submitted new data for the renal data in both rats and mice. The table below indicates the changes in reported tumor incidence:

Table Add 1. Kidney Tumor Incidence (Adenomas and Carcinomas Only)

	Original Incidence					Revised Incidence				
Animal-Tumor	Veh-icle	Low	Med-ium	High-Med	High	Veh-icle	Low	Med-ium	High-Med	High
Male Rats – Adenomas	0	0	1	1	4	0	0	1	1	**0**
Female Rats– Adenomas	1	0	0	0	2	1	0	**1**	0	2
Carcinomas	0	0	0	2	4	0	0	0	**0**	**1**
Male Mice – Adenomas	1	2	0	5	3	**2**	2	0	5	3
Carcinomas	0	0	2	4	3	0	0	2	4	3
Female Mice–Adenomas	0	0	0	2	4	0	0	0	2	4
Carcinomas	0	0	0	0	1	0	0	0	0	1

All these changes in incidence tend to reduce any apparent dose related indication of carcinogenicity in kidneys. This caused some concern to this reviewer, but the toxicology reviewer noted that: “An expert in rat renal histopathology conducted a re-evaluation of the original renal findings in the carcinogenicity assays. His re-evaluation was conducted to identify the nature of the reported lesions, taking into account histopathological events that would yield information about the mode of renal tumor formation. In his analysis of the rat renal data, he discovered that three of the identified renal tumors were of non-renal origin and that a number of others were of a particular morphology now known to be of spontaneous origin in rats. These alterations in the interpretation of the findings produced a substantially different renal tumor incidence in rats.” (personal communication)

For incidence only data, the typical analysis is based on a so-called Cochran-Armitage test of trend, which basically does a regression type analysis of the incidence of the event under study, in this case the development of a specific organ tumor combination, regressed on dose. Each animal at each dose level is treated as being equally likely to develop the tumor. But in practice some animals die early and it may not be appropriate to consider those animals as having the same chance of developing the tumor as those animals in the same dose group that survive to the end of the study. The usual FDA analysis for carcinogenicity uses the so-called poly-k modification of the Cochran-Armitage test of trend where the risk set for the specific organ tumor combination is reduced by animals that die early in the study without the tumor..

Inspecting a large number of studies, Bailer and Portier (1988) noted that survival time seemed to fit a Weibull distribution, generally with a shape parameter of between 1 and 5, with 3 a typical value. With t_{max} denoting the maximal time to terminal sacrifice and t_{obs} the time to death of the animal, they proposed weighting the animal by $(t_{obs}/t_{max})^k$, so that an animal that survives for say 52 weeks in 104 week study without the tumor being analyzed is counted as $(1/2)^k$ of an animal when computing the size of the risk set for that tumor. For k = 3, that means that particular animal would count as 1/8 of an animal in the Cochran-Armitage analysis of that tumor. Further, the k = 3 specification seems to represent tumor incidence where some animals are perhaps more sensitive and respond earlier to the insult than the remaining animals. Under this structure, time to incidence would tend to follow a cubic expression. Thus an animal with the specific tumor being studied or who survives to terminal sacrifice without the tumor will be given a weight of 1 when counting the number of animals at risk. However, animals that die early without the tumor are down weighted when counting the number of animals in the risk set for that specific tumor. With differential mortality, this can mean a substantial reduction in the size of that risk set. This seems to be an appropriate adjustment whenever there is differential mortality across dose groups. The report of the Society of Toxicological Pathology "town hall" meeting in June 2001 recommended the use of this poly-k modification of the so-called Cochran-Armitage tests of trend.

As transmitted to this reviewer the data consisted only of revised tumor incidence without the attendant mortality data. Under some circumstances, this could present a problem, and requesting original data was considered. However, it seems clear that in this case imputing a few new values will have no particular effect upon conclusions. In particular, data values were recoded as discussed below:

1. In the original data, the high dose group in male rats included four rats identified with adenomas in the kidneys. The Sponsor's reanalysis deleted all four of these adenomas. Note that this change is unique in the sense that we know exactly which animals should have the tumor incidence changed, and hence the computed p-values would be remain the same if the Sponsor had provided the corrected data.

2. In female rats, one adenoma was added to control group totals, the tumors assigned to the original two identified carcinomas in the high medium dose group were deleted (animals E660 and E663) as in 1. above. Further, three of the four carcinomas in the high dose group were deleted. Since animals that die early are downweighted, and thus reduce the size of the risk set, choosing a control group animal that survived to the end of the study will have the smallest effect. This was done for the single imputed adenoma in the control. Among the four animals originally identified with carcinomas in the high dose group, retention of the highest surviving animal will be least favorable for the Sponsor and thus is used here. Any other choice would increase the size of the risk set, thus decreasing statistical significance.

3. In male mice, one adenoma was added to the control group. An animal with the least effect on the overall risk set was selected (animal 43 with survival to day 735). Again, this choice would be least favorable to the Sponsor.

4. In female mice, the tumor reanalysis had no effect on tumor incidence and hence results are unchanged.

Using these imputed values allows one to use the poly-k methodology and adjust for differences in mortality. Note that in cases 2. and 3. above, these imputations will increase uncertainty and thus actual variance in results. But it was felt that this increase in "noise" would be difficult to assess, should be conservative, and did not warrant actual adjustment of results.

In the following tables, for each species by gender the number of animals analyzed and used in the statistical tests is presented first. The entry for each tumor is preceded by the adjusted number of animals at risk for that tumor. It seems clear that an animal that dies early without a tumor reduces the size of the risk set for that getting that particular umor. The poly-k test down weights such animals, and the sum of these poly-k weights seems to be a better estimate of the number of animals at risk of getting that tumor. This sum is given in the row labeled "Adjusted # at risk". Tumor incidence is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high, high-medium, low-medium, and low dose groups versus vehicle. For this analysis, incidence in the vehicle group is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence <1%) or common. Finally, the significance level of the original Cochran-Armitage test of trend over all five dose groups, with no poly-k adjustment for mortality, is presented under the heading for trend, below the corresponding poly-k trend result. Please note that the poly-k results are strongly recommended, but the Cochran-Armitage test does not depend upon the imputed incidence cited in 2. and 3. above.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman (HLR) rules are often applied. That is, when testing for trend over dose groups and the difference between the highest dose group with a control group, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. Using these adjustments for other tests, like testing the comparisons between the low, medium, and medium-high dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Table Add. 2. Kidney Tumors in Rats

Gender/Tumor	Incidence					Significance Levels				
	Veh	Low	Med-ium	MedHi	High	Trend	Hi vs Veh	MedHi vsVeh	Medvs Veh	Low vsVeh
Male Rats										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.7	25.9	22.2					
RENAL TUBULE- ADENOMA	0	0	1	1	0	.3026	.	.3378	.4494	.
Cochran-Armitage test						.4802				

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