CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-838

STATISTICAL REVIEW(S)

FEB 1 2 1998

STATISTICAL REVIEW AND EVALUATION

NDA: NDA #20-838

Applicant: Astra Merck

Name of Drug: Atacand (candesartan cilexetil or TCV-116)

Documents Reviewed: Volumes ~~1-13~~, ~~1-60~~, A21.1, A36.1

1. Introduction

This statistical review focuses on the carcinogenicity studies submitted by Astra Merck for NDA #20-838. The purpose of the studies was to assess the carcinogenic potential of TCV-116 to male and female mice and rats. The review was based on the datasets for mouse study submitted on November, 25, 1997 and for rat study submitted on December 23, 1997 in which the wrong coding, as pointed by this reviewer, for the variable "Tissue Examination Code" in the sponsor's earlier data submission was corrected.

2. Mouse Study

2.1 Overview

This 104 week carcinogenicity study had a parallel-group design with two control groups and four dosage groups. The study animals were Charles River B6C3F1/CrlBR mice. In the study, a total of 360 male and the same number of female mice were randomized separately to receive TCV-116 by gavage at dosage levels of 0 (120 animals in two controls), 3 (60 animals), 10 (60 animals), 30 (60 animals) or 100 (60 animals) mg/kg/day once daily.

All mice were observed at least twice a day for mortality and morbidity. A detailed clinical examination of each mouse was done once a week. The examination included the occurrence, size, location and description of palpable masses. All mice in the study received a complete postmortem examination. Protocol-desinated organs and tissues were examined for all animals microscopically in the control groups and in 100 mg/kg (high dosage) group. For animals in the moderate dosage groups, the examination was done only for those which were dead or sacrificed in extremis during the course of study.

2.2 Sponsor's Results

The sponsor's data analyses were carried out for each sex separately. The survival distributions among the

experimental groups were compared using log-rank test. If the result was significant, survival curves between each control and each dosage group were compared using log-rank test. The sponsor's survival analysis showed no statistical evidence of a survival difference among the experimental groups for male and female mice.

Table 1. Animal allocation and scheduled or unscheduled death (mice)

sex	type of death	dose (mg/kg/day)				
		0	3	10	30	100
male	total number of animals	120	60	60	60	60
	killed in extremis	3	3	1	8	3
	natural death	14	7	10	5	8
	other	0	1	0	0	0
	terminal kill	103	49	49	47	49
female	total number of animals	120	60	60	60	60
	killed in extremis	12	5	4	9	5
	natural death	20	8	13	7	8
	other	2	0	0	1	2
	terminal kill	86	47	43	43	45

The sponsor's methods to analyze tumor incidence data were Cochran-Armitage tread test, Fisher's exact test (pair-wise comparison between a dose group and a control), survival-adjusted linear trend test. All tests were performed twice using different controls and done only when, for a given tumor type, at least one experimental group had more than 2 occurrences of the same kind of tumor.

No statistically significant difference in tumor incidence between a control group and the high dosage group was found by the sponsor at α=0.05 for male and female mice. Since only animals which did not survive to the time of terminal sacrifice were examined microscopically in the moderate dosage groups, the tumor incidences in these groups often were higher as compared to either the control or high dosage group. In this case, it is hard to interpret the results from the sponsor's overall trend tests and the results of pair-wise comparisons between a moderate dosage group and a control.

2.3 The Reviewer's Evaluation and Comments

This reviewer analyzed the survival and tumor data for male and female mice separately. In all analyses, the combined control group was used and all moribund-killed animals were considered as same as the found-dead. Since there was no scheduled interim sacrifice, the censoring of survival time occurred at the time of a terminal sacrifice.

Mortality/survival analyses

In the reviewer's analyses, homogeneity of survival distributions across the experimental groups was assessed using Cox test and Gehan-Breslow test ([1]). No evidence of a difference in survival distributions among the groups was found for male or female mice. The K-M estimates of the survival functions across the groups were obtained and graphically presented in the appendix (pp.9-10). The homogeneity in death rate across the groups and a positive mortality-dose trend were also tested. No statistically significant difference was found.

Table 2. Homogeneity in survival distribution/mortality rate

test for homogeneity in survival or mortality	p-values	
	male mice	female mice
Cox (homogeneity in survival)	0.7714	0.7685
Gehan-Breslow (homogeneity in survival)	0.7533	0.7583
chi-square (homogeneity in mortality rate)	0.7858	0.7704

Tumor analyses

In the submitted datasets for the mouse study, causes of animals' death were not indicated. Therefore, the tumor-dose trend was tested in two ways: (i) treating all tumors as incidental and using only Peto's prevalence method and (ii) treating all tumors as fatal and using Peto's death rate method ([2]). The exact permutation method and asymptotic method were used to calculated the p-values for all trend tests. However, p-values based on the exact method were used to draw conclusions. In the analyses with prevalence method, a set of fixed time intervals (with the cut-offs at Week 51, 78, 92, and 104) were used to adjust for survival. In all analyses, the magnitude of each dose was used and a significant tumor-dose trend was claimed if the p-value of corresponding test was less than 0.025 for a rare tumor (defined as a tumor with the incidence less than or equal to 1% in the control group) or 0.005 for a common tumor (defined as the negation of the rare type of tumor). All analyses were done using only the combined control group and high dosage group because, as mentioned earlier, the tissues were microscopically examined for very limited number of animals in the

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moderate dosage groups. The computation for the analyses was carried out using StatXact software.

The reviewer's analyses showed no evidence of a tumor-dose relationship between the high dosage group and control for male and female mice by either prevalence or death rate method. The results based on the prevalence method are presented in the appendix (pp. 13-15). Numerically higher incidence of malignant lymphoblastic lymphoma in male mice could be seen in several tissues, for instance, hemolymphoreticular system (2/13 for the control and 4/6 for the high dosage group, p=0.0510, mesenteric lymph node (1/118 for the control and 4/59 for the high dosage, p=0.0659), and spleen (1/120 for the control and 3/60 for the high dosage, p=0.1581). The comparison of the numbers of animals with lymphoma (center cell or lyphomblastic) between the control and the high dosage group showed no statistically significant difference (3/120 for the control, 4/60 for the high dosage group, p=0.2212).

3. Rat Study

3.1 Overview

This 104 week carcinogenicity study had a parallel-group design with two control groups and three dosage groups. The study animals were F344/Jcl rats. In the study, a total of 250 male and the same number of female rats were randomized separately to receive TCV-116 administrated orally at dosage levels of 0 (combined vehicle-control, 100 animals), 100 (50 animals), 300 (50 animals), or 1000 (50 animals) mg/kg/day once daily.

All rats were observed twice daily for mortality. Examination of each animal for masses was done at least twice daily. In addition to the cage-side observations, further detailed observations and palpation for masses were done weekly. According to the sponsor, gross pathological examinations were performed on all animals that were dead spontaneously, killed in a moribund state, or sacrificed at the end of the study. Organs or tissues like liver, kidney, adrenal gland, stomach, spleen, testes and uterus were examined by light microscopy for all animals, and for the other desinated organs or tissues, this was done for all animals in the control and high dosage group.

3.2 Sponsor's Results

The sponsor's data analyses were carried out for each sex separately. The dose trend in survival among the experimental groups was analyzed using Tarone's test. A paired comparison between the control and each

dosage group was done with a log-rank type method. All statistical tests were conducted as two-sided at significance level α=0.05. The sponsor used Peto's method for a tumor-dose trend and Fisher's exact method to compare tumor rates between the control and a dosage group. The analyses were done only for the tumors occurred in more than 5% of animals in either control or the 1000 mg/kg group. For tumors found in kidney, liver, stomach, adrenal glands, spleen, testes, and uterus, Peto's method was used to analyze the data from all experimental groups. The tests were conducted as one-sided at the significance level α=0.05.

Table 3. Animal allocation and scheduled or unscheduled death (rats)

sex	type of death	dose (mg/kg/day)			
		0	100	300	1000
male	total number of animals	100	50	50	50
	killed in extremis	6	2	5	3
	natural death	12	6	6	6
	terminal kill / other	82	42	39	41
female	total number of animals	100	50	50	50
	killed in extremis	2	2	4	1
	natural death	12	10	5	8
	terminal kill / other	86	38	41	41

The sponsor's survival analysis showed no statistical evidence of a difference in survival among experimental groups in male and female rats. Unscheduled deaths were mainly due to pituitary adenoma and mononuclear cell leukemia in males (7 and 17 animals, respectively) and pituitary adenoma/adenocarcinoma and uterine adenocarcinoma in females (10 and 12 animals, respectively).

A positive dose trend in tumor incidence of adrenal gland pheochromocytomas (benign) was reported by the sponsor for female rats (p=0.044). Combining benign and malignant adrenal gland pheochromocytomas, the trend was still statistically significant at α=0.05 (p=0.045). For male rats, a positive tumor-dose trend in fatal spleen mononuclear cell leukemia (3/100 for control, 3/50 for 100mg/kg, 3/50 for 300mg/kg, and 8/50 for 1000mg/kg) was found (p=0.006). When it was combined with the incidental spleen mononuclear cell leukemia, the result was not statistically significant (p>0.05). For male rats, a tumor-dose trend in bilateral testis interstitial cell tumors (84/100 for the control, 46/50 for 100mg/kg, 46/50 for 300mg/kg, and 49/50 for 1000mg/kg) was reported by the sponsor (p=0.004). However, when they were combined with unilateral testis

interstitial cell tumors, no statisticall evidence of such a trend was found.

3.3 The Reviewer's Evaluation and Comments

This reviewer analyzed the survival and tumor data for male and female rats separately. In all analyses, a combined control group was used, and all moribund-killed animals were considered as same as found-dead.

Mortality/survival analyses

In the reviewer's analyses, homogeneity of the survival time distributions across the experimental groups was assessed using Cox test and Gehan-Breslow test ([1]), a test more sensitive to an earlier departure from the homogeneity. No evidence of a difference in survival distributions was found for male or female rats. The K-M estimates of the survival functions across the experimental groups were obtained and graphically presented in the appendix (pp.11-12). The homogeneity in death rate across groups and a positive mortality-dose trend were also tested. Again, no statistically significant result was found. The following table summarizes the results of survival analyses.

Table 4. Homogeneity in survival distribution/mortality rate

test for homogeneity in survival or mortality	p-values	
	male rats	female rats
Cox (homogeneity in survival)	0.8288	0.2954
Gehan-Breslow (homogeneity in survival)	0.8569	0.3667
chi-square (homogeneity in mortality rate)	0.7795	0.2254

Tumor analyses

In the reviewer's analyses, a positive linear tumor-dose trend for an incidental or a fatal tumor was tested using Peto's prevalence method or death rate method ([2]) respectively. For a tumor occurring in both categories, a combined test was performed. The exact permutation method and asymptotic method were used to calculated the p-values for all trend tests. In the reviewer's analysis, the p-value based on the exact method was used if a tumor was fatal or non-fatal for all animals (single type). Otherwise (mixed type), the asymptotic p-value was used. In all trend analyses, the magnitude of each dose was used, and for incidental tumors, a set of fixed time intervals (with the cut-off at Week 51, 53, 78, 92, and 104) was used to adjust time effect,. The reviewer analyzed the data using both all experimental groups and only the control and high dosage group. A significant tumor-dose trend was claimed if the p-value of testing was less than 0.025 for a rare

tumor (defined as a tumor with the incidence less than or equal to 1% in the control group), or 0.005 for a common tumor (defined as the negation of the rare type of tumor). The computation for the tumor-dose trend test was carried out using StatXact software.

There were seven female rats with lung adenocarcinoma among which five cases were in the high dosage group, one in 100mg/kg group, and one in the control. In the submitted dataset, tumors were only indicated as metastatic tumors with no information about their fatality. Treating the tumors as fatal, the trend test gave p=0.0149, indicating a statistically significant positive tumor-dose relationship between the control and high dosage group (rare tumor, α=0.025). The trend tests for benign, or, malignant, or the combination of benign and malignant adrenal-gland pheochromocytomas for female rats were done and the results were not statistically significant at α=0.025 (p=0.0586, 0.395, and 0.0448 respectively).

For male rats, the reviewer only analyzed testis interstitial-cell-tumors pooling the bilateral and unilateral ones since the two types of tumors could not be differentiated based on the submitted datasets. The pooled analysis showed no tumor-dose trend (p=0.0869). Often, data for a tumor which is fatal for some animals and incidental for the others, are analyzed in a combined fashion by FDA's statisticians due to the facts that it is often difficult to determine the fatality of a tumor and the fatality status of a tumor may change during the course of a study. For spleen mononuclear cell leukemia, the reviewer's trend test, pooling incidences of fatal and non-fatal spleen mononuclear cell leukemia, gave p= 0.1471, thus, not statistically significant at α=0.005 (common tumor). The results of trend analyses are presented in the appendix (pp. 16-23).

4. Adequacy of Number of Animals

In male and female mice or rats, more than 50% of animals in each experimental group survived to the end of the two year study period, indicating that the study had a sufficient number of animals and an adequate exposure.

Summary

In the sponsor's study of the carcinogenic potential of TCV-116 in male and female mice and rats, a positive tumor-dose trend was found for bilateral interstitial cell tumors in male rats (p=0.004, the sponsor's analysis). When they were combined with unilateral interstitial cell tumors, however, the trend was not statistically significant. An increase tumor-dose trend for lung adenocarcinoma was found in female rats (p=0.0149). Most of such tumors were metastatic (secondary) tumors originated at uterus. The answer to the question of how important these findings are depends on their clinical implications and may not be addressed statistically.

No statistically significant survival difference among the experimental groups was found in both mice and rats. The studies appeared to have a sufficient number of animals and an adequate length of exposure.

References

[1] D. Thomas, N. Breslow, and J. Gart, 1977, *Trend and homogeneity analyses of proportions and life table data*, Computers and Biomedical Research 10, 373-381.

[2] R. Peto, and et al, 1980, *Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-term Animal Experiments*, WHO.

This review has been discussed with Dr. Proakis, the pharmacological reviewer.

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2/10/98

Concur: Dr. Kooros Mahjoob _____

Dr. George Chi _____

cc:

NDA #20-838, Atacand

HFD-110

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APPEARS THIS WAY
ON ORIGINAL

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