CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20575 AND 20758

STATISTICAL REVIEW(S)

JUL 9 1997

Statistical Review and Evaluation

Review of Carcinogenicity Data

DATE:

NDA#: 20-757

APPLICANT: Bristol-Myers Squibb/Sanofi

NAME OF DRUG: IRBESARTAN

DOCUMENTS REVIEWED: Volumes 1.49-1.56, 1.59-1.67 Containing Data, Results, and Study Reports of the Mouse and Rat Studies, and One Volume Dated 10/08/96 Containing the Data Layout and Diskettes for these Studies.

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I. Background

Dr. Gowra Jagadeesh (HFD-150) requested from the Division of Biometrics I a statistical review of the rat and mouse studies data as well as an evaluation of the sponsor's findings.

II. The Rat Study

II.a. Design

The drug was studied via gavage for 104 weeks in HanIbm Wistar rats. There were six groups of males and eight groups of females. Groups 1, 2, and 8 served as control animals receiving the vehicle only. Control group 1 was somewhat contaminated by the compound prior to being moved to a separate room. Group 8 was started at week 21 of the study and was housed with Group 1. Group 2 was the only control group which remained housed with the actively treated animals. The three treated groups of male rats received doses of 5, 50, and 500 mg/kg/day via gavage. The females had additional 1000 and 2000 mg/kg/day dose groups. The later group (group 7) had to be terminated after 14 weeks due to high mortality and is not part of the evaluation of the carcinogenic potential of the drug.

There were 55 animals per group, but not all organs were microscopically examined for all animals. Tissues from the kidney and pituitary were microscopically examined for all male and female rats. The heart was additionally examined for the males only and the adrenals, the uterus and mammary gland for the females only. The remaining organs were microscopically examined for all control animals and all high dose animals and those animals of the intermediary doses which died or were sacrificed in extremis during the study.

II.b. Sponsor's Analyses of the Rat Study

Survival Analysis

The sponsor tested for potential differences in survival of the three control groups first, assigning weights of 0, 1, and 2 to groups 8, 1 and 2, respectively, according to findings of the toxicokinetic analyses . As Tarone linear trend test did not reach statistical significance the control groups were pooled into one group. When comparing the combined controls versus the treated male rats the Tarone linear trend test again did not reach statistical significance ($p>0.300$). For the female rats there was a significant trend test ($p\leq 0.001$) whether or not the humane kills were treated as censored or uncensored in the analyses.

Tumor Data Analysis

The sponsor performed a life-table analysis for fatal tumors, a prevalence analysis for incidental tumors, and a combined analysis when a tumor manifested itself as both fatal and incidental. A

significant positive trend was observed for incidental and for incidental and fatal combined **malignant uterus adenocarcinomas** and for the combined **malignant and benign uterus tumors** (See table below). Pairwise comparisons between treated and control groups reached statistical significance at α=0.01 for the tumors observed in the incidental context only. No other tumor findings showed statistically significant increases in incidence rates.

Tumor of Uterus	Type	Context	P(Trend)	P(H vs. Cls)
Adenocarcinoma	Malignant	Incidental	.002	.014
		Incidental and Fatal	.002	.030
Tumors	Malignant and Benign	Incidental	.005	.014
		Incidental and Fatal	.003	.030

II.c. Reviewer's Analyses

Survival Analysis

The sponsor's survival analyses using Tarone's test is acceptable. This reviewer's summary findings of the rats are given inTables 1-2 and Figures 1-2. These findings are consistent with the sponsor's.

Tumor Data Analysis

The sponsor seemed to treat fatal and incidental tumors appropriately, however, reviewers of OEB use pre-set time intervals rather than ad hoc estimated ones which result in slightly different p-values. The use of pre-set intervals ensures consistency across reviews. The tumor data were analyzed by this reviewer using the methods described in the paper of Peto et al. (Guidelines for simple sensitive significance test for carcinogenic effects in long-term animal experiments, In: Long term and short term screening assays for carcinogens: A critical appraisal, International Agency for Research against Cancer Monographs, Annex to Supplement, WHO, Geneva, 311-426, 1980) and the method of the exact permutation trend test developed by the Division of Biometrics. The following criteria for the levels of significance ensure a false positive rate of about 10 % for the trend tests of the usual two-species two-sexes studies: Tumors with $\leq$ 1.00% occurrence in the control group are considered rare and a positive trend test is statistically significant when it reaches a p-value of $\leq$ 0.025 (one-sided). Higher tumor occurrences in the control group are considered common for these animals and a positive trend is statistically significant when its p-value is less than 0.005 (one-sided). An approximate permutation trend test is used when fatal and incidental tumors of the same kind are combined and have overlapping time intervals. All tests are survival adjusted and treatment groups are weighted by the actual dose levels. For tissues where not all dose groups were fully necropsied only pairwise

comparisons between the high and control groups were performed. The significance criteria for pairwise comparisons are α=0.05 for rare and α=0.01 for common tumors.

This reviewer constructed tumor incidence tables for all recorded tissues and tumors, treating fatal, incidental, and undetermined separately. Positive tumor trends with dose were statistically analyzed adjusting for mortality. This reviewer did not analyze any negative trends observed in tumor occurrences. For male rats no trends in tumor incidence rates reached statistical significance at the levels explained above. Incidental adenocarcinoma of the uterus and the combined incidental and fatal adenocarcinoma of the uterus had trend tests with associated p-values of 0.0068 and 0.0087, respectively. As these tumors occurred at a rate greater than 1 % among the controls the critical significance level of α=0.005 was not reached in either case. When combining adenocarcinomas and adenomas of the uterus the trend tests were not close to statistical significance. The findings are summarized below:

Tumor of the Uterus	Context	P(Trend)	P(H vs Cls)
Adenocarcinoma	Incidental	.0068	.0688
	Incidental and Fatal	.0087	.1249
Adenocarcinoma and Adenoma	Incidental	.0516	.0688
	Incidental and Fatal	.0621	.1249

The sponsor's analyses of these tumors have much higher levels of statistical significance, the difference likely being due to the sponsor using all three control groups whereas the data of only two were available to us on diskette and using a normal approximation when the number of tumor occurrences was small.

It also needs to be kept in mind that the lack of full necropsies of the intermediary dosed animals may have concealed trends in some incidental tumors.

II.d. Validity of the Rat Study

As there are no statistically significant tumor trends among the male rats and at best one borderline significant trend among the females, this reviewer evaluated the validity of the study. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

(i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls."

(ii) "The administered dose is also considered a MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD."

Survival at terminal sacrifice ranged from 75% - 84% for the male rats and from 53% - 85% for the female rats, clearly satisfying the requirement of a sufficient number of animals being exposed for a sufficient length of time to manifest late developing tumors. The bodyweight gain data showed that the high dose animals usually gained significantly less than their controls. For the female rats, this differential was well over ten percent indicating that the high dose (1000 mg/kg/day) may have exceeded the MTD. For the male rats, this differential gives less clear information, as it is about 15 percent during the first year and then falls to six percent for the whole treatment course. The following table gives the weight gain differential for the first 52 weeks and for the whole study. The figures are taken from the sponsor's Table 4B.

Mean Body Weight Gains - Rats

MALES				FEMALES			
Weeks 0-52*	Control 418.5 g	High 357.0 g	Diff (%) -61.5 g (14.7 %)	Weeks 0- 52*	Control 189.5 g	High 166.0 g	Diff (%) -23.5 g (12.4 %)
Weeks 0-104	Control 491.0 g	High 461.0 g	Diff (%) -30.0 g (6.1 %)	Weeks 0-104	Control 267.5 g	High 198.0 g	Diff (%) -69.5 g (26.0 %)

*The results for 0-52 weeks are approximate as they are the sum of the weight gain recorded for 0-13, 13-26, and 26-52 weeks. Little error should be introduced by this approach as the mortality rate was less than 4 percent at the end of one year except for the high dose females for which the mortality rate was 16.4 %.

Mean Body Weights - Rats

MALES				FEMALES			
Week	Control	High	% Control	Week	Control	High	% Control
0	126	137	108.7	0	114	116	101.8
52	561	494	88.0	52	305	282	92.5
104	645	598	92.8	104	381	315	82.7

From a statistical point of view, the findings for the male animals are equivocal, as the mortality experience suggested that the MTD was not reached, whereas the bodyweight gain data suggested that the MTD may have been exceeded. For the female rats, the high dose was 1000 mg/kg/day and this dose exceeded the MTD based on the statistical criteria listed above. The pharmacologist may confirm this finding by evaluating the clinical signs and severe histopathological effects among these animals.

II.e. Group 7 Study

This refers to the group of 55 female rats which were part of the original study and received 2000 mg/kg/day via gavage. Due to extreme mortality these animals could not be treated for 104 weeks and were sacrificed after 14 weeks. By that time thirty animals had already died or had been killed. These data do not lend themselves to statistical evaluation nor do they provide information regarding the carcinogenic potential of the compound. The sponsor concluded that this dose was associated with deaths and clear toxic changes and exceeded the MTD.

III. The Mouse Study

III.a. Design

This study was conducted in CD-1 mice for 104 weeks. For each sex there were 56 animals per group. The two vehicle control groups were combined in the analyses. The dosed animals received 100, 300, and 1000 mg/kg/day via gavage. Histology was performed on all listed tissues for all animals except on Harderian glands, mammary glands (a. cran. and other), muscolo-skeletal tissue, skin (other), and tail.

III.b. Sponsor's Analyses of the Mouse Study

Survival Analysis

Using Cox's proportional hazards model and Tarone's test the sponsor observed a significant positive trend and significant pairwise comparisons between the combined control groups and the intermediate and high dose groups in the male mice. For the female mice, there was also a significant positive trend and a significant pairwise comparison between the combined controls and the high dose animals.

Tumor Data Analysis

The sponsor observed significant age-adjusted trends for incidental and for incidental and fatal benign adrenal cortex adenomas in male mice. The pairwise comparisons between high dose and control animals were also significant. In addition there were statistically significant positive trends and pairwise comparisons between high dose and controls for various hepatic tumors as presented below. None of these findings were judged to be treatment-related by the sponsor. No tumor findings among the female mice were statistically significant.

Male Mice	Type	Context	P(Trend)	P(H vs. Cls)
Adrenal Cortex Adenoma	Benign	Incidental	.0140	.0014
		Incidental and Fatal	.0140	.0014
Adrenal Cortex Tumors	Malignant and Benign	Incidental	.0480	.0148
		Incidental and Fatal	.0480	.0148
Hepatocellular Adenoma	Benign	Incidental	.0209	.0891
		Fatal	.5151	.2135
		Incidental and Fatal	.0305	.1109

Hepatocellular Carcinoma	Malignant	Incidental	.5727	.6061
		Fatal	.0123	.0090
		Incidental and Fatal	.0913	.0939
Hepatocellular Tumors	Benign and Malignant	Incidental	.0212	.1304
		Fatal	.0240	.0189
		Incidental and Fatal	.0024	.0183

III.c. Reviewer's Analyses

The same statistical methods and approaches discussed for the rat study were applied to the mouse data.

Survival Analysis

Again, the sponsor's survival analyses seemed apropriate and this reviewer accepted their findings. The mortality experience is shown in Tables 3-4 and Figures 3-4.

Tumor Data Analysis

This reviewer's analyses obtained the following levels of significance for trend and pairwise comparison tests:

Male Mice	Type	Context	P(Trend)	P(H vs. Cls)
Adrenal Cortex Adenoma	Benign	Incidental	.0113*	.0122*
Adrenal Cortex Tumors	Malignant and Benign	Incidental	.0293	.0418
Hepatocellular Adenoma	Benign	Incidental	.0970	.1377
Hepatocellular Carcinoma	Malignant	Incidental	.3865	.6354
		Fatal	.0420	.0960
		Incidental and Fatal	.1430	.1464

Hepatocellular Tumors	Benign and Malignant	Incidental	.1361	.0726
		Fatal	.0420	.0960
		Incidental and Fatal	.0178	.0102*

* Statistically significant after accounting for multiplicity of testing.

When the p-values were adjusted for multiplicity of testing, the trend and pairwise comparison tests of the incidental adrenal cortex adenomas were statistically significant as was the pairwise comparison of high dose versus controls for all hepatocellular tumorsin male mice. No other trends or pairwise comparison reached the statistical criteria of significance for rare or common tumors. This was also true when tumors were grouped according to McConnell, et al., Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies, JNCI, Vol 76, No.2.

It is pointed out that the grouping of 'fatal and incidental' combined adrenal cortex tumors reported by the sponsor is somewhat misleading, as there occurred no fatal tumors of these kinds and the combined tumors were just the incidental ones. As these tumors are no longer statistically significant when the p-values are adjusted for multiplicity, it is an academic point.

III.d. Validity of the Mouse Study

As two of the statistically significant tumor findings among the male mice were numerically slightly above the cut-off this reviewer evaluated the validity of the study in both sexes applying the same criteria outlined for the rat study above.

The male mice experienced survival of at least 62 percent through week 78 (Table 3) indicating that for at least 1 ½ years there remained a sufficient number of animals to manifest any late developing tumors. The female mice experienced survival of at least 55 percent through week 78, again indicating that for at least 1 ½ years there was a sufficient number of animals exposed to the compound.

The body weight gain data (see Table below) showed a slightly higher gain for the high dose males during the first year than for the controls indicating that the high dose may not have been close enough to the MTD. The body weight gain of the high dose female mice were over 17 percent lower than their controls and would indicate that the high dose may have exceed the MTD in this sex.

As noted before for either sex the drug affected the survival not just numerically but to a statistically significant degree indicating that the high dose, which was the same for both sexes, had exceeded the MTD.

Therefore, from a statistical point of view the findings are inconsitent for assessing the validity of the study in either sex. For the male mice the body weight data did not support the notion that the high dose was close to the MTD and for the female mice these data suggested that the high dose had exceeded the MTD. The other statistical criteria used in establishing the validity of a tumorogenicity study were met. The toxic and severe histopathological findings discussed by the sponsor are left to the expertise of the pharmacologist to evaluate.

Mean Body Weight Gains - Mice

MALES				FEMALES			
Weeks 0-52*	Control 17.8 g	High 18.1 g	Diff (%) +0.3 g (1.7 %)	Weeks 0- 52*	Control 14.9 g	High 12.1 g	Diff (%) -2.8 g (18.8 %)
Weeks 0-104	Control 14.0 g	High 13.4 g	Diff (%) -0.6 g (4.3 %)	Weeks 0-104	Control 15.9 g	High 13.2 g	Diff (%) -2.7 g (17.0 %)

Mean Body Weights - Mice

MALES				FEMALES			
Week	Control	High	% Control	Week	Control	High	% Control
0	29.9	28.9	96.8	0	22.9	22.6	98.7
52	47.6	46.9	98.5	52	37.8	34.9	92.4
104	43.7	42.4	97.0	104	38.8	36.1	93.0

IV. Summary and Conclusion

The rat study was unusual inasmuch as there were three vehicle control groups which did not distinguish themselves in design but were started at slightly different times and two of them were housed separately to minimize/avoid cross contamination of the compound. The sponsor pooled all three of them in their analyses. The data of only two of these control groups were provided on diskette and this reviewer's results may therefore differ slightly from the sponsor's. This reviewer found the sponsor's approach to survival analysis acceptable. In the analysis of tumor incidence rates this reviewer used an exact permutation trend test. After adjusting for multiplicity of testing none of the trends in tumor incidence rates reached statistical significance. The significant findings reported by the sponsor were for malignant adenocarcinoma of the uterus and for all uterus tumors. In evaluating the validity of this study this reviewer observed that there were a sufficient number of animals exposed to the compound for a sufficient length of time to show late developing tumors. In assessing whether the high dose (500 mg/kg/day for the males

and 1000 mg/kg/day for the females) was close to the MTD the statistical criteria were not clearly met for the male rats and this reviewer interpreted the findings as equivocal, whereas for the female rats the high dose seemed to have exceeded the MTD.

The seventh dose group of 2000 mg/kg/day for the female rats was not considered in the analyses of the study because of the unexpected high mortality which necessitated the early (week 14) termination of this arm. As there remained three dose groups any potential dose responses could still be evaluated.

The mouse study showed statistically significant trends in mortality for both sexes. One trend in tumor incidences reached borderline statistical significance and two pairwise comparisons of high dose versus controls reached statistical significance among the male mice. No tumor findings reached statistical significance among the female mice. In evaluating the validity of the study in either sex this reviewer came to the conclusion that there were sufficient numbers of animals surviving long enough for late developing tumors. Similarly to the rat study, the data of the male mice did not give a clear indication as to whether the high dose was close to the MTD whereas those of the female mice suggested that the high dose (which was identical for both sexes) may have exceeded the MTD.

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Mathematical Statistician

Concur:

Kooros Mahjoob 07/09/97

Kooros Mahjoob, Ph. D.
Team Leader

Antonis Kountsoukos 7/9/97 (for Dr. Chi)

George Chi, Ph.D.
Director, DB I

cc:Archival NDA 20-757, Irbesartan Tablets, Bristol-Myers Squibb/Sanofi.
HFD-110/Division File
HFD-110/Dr. Jagadeesh
HFD-110/Dr. Resnick
HFD-110/Ms. Bongiovanni, CSO
HFD-344/Dr. Barton
HFD-710/Chron.
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Ms. Kelly

This review consists of 11 pages of text, 4 tables and 4 figures.
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Table 1
INTERCURRENT MORTALITY RATES

FEMALE RATS

Weeks	mg/kg/day 0	5	50	500	1000
0- 52	1/110 (1%)	1/55 (2%)	1/55 (2%)	0/55 (0%)	9/55 (16%)
53- 78	5/109 (5%)	2/54 (5%)	1/54 (4%)	5/55 (9%)	2/46 (20%)
79- 92	4/104 (10%)	2/53 (9%)	4/53 (11%)	4/50 (16%)	8/44 (35%)
93-104	12/100 (20%)	8/51 (24%)	2/49 (15%)	6/46 (27%)	7/36 (47%)
Term. Sac.	88/110 (80%)	42/55 (76%)	47/55 (85%)	40/55 (73%)	29/55 (53%)

MALE RATS

Weeks	mg/kg/day 0	5	50	500
0- 52	3/110 (3%)	1/55 (2%)	3/55 (5%)	0/55 (0%)
53- 78	6/107 (8%)	4/54 (9%)	1/52 (7%)	4/55 (7%)
79- 92	4/101 (12%)	3/50 (15%)	3/51 (13%)	3/51 (13%)
93-104	9/97 (20%)	6/47 (25%)	2/48 (16%)	7/48 (25%)
Term. Sac.	88/110 (80%)	41/55 (75%)	46/55 (84%)	41/55 (75%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 2

Results of Survival Analyses

Female Rats

Groups Compared	Direction	Two-tailed p-value of Test Cox	Kruskal/Wallis
C,L,M1,M2,H	pos	.0000 ***	.0000 ***
C,L	pos	.750	.641
C,M1	neg	.540	.444
C,M2	pos	.353	.256
C,H	pos	.0002 ***	.0001 ***
L,M1	neg	.363	.291
L,M2	pos	.744	.565
L,H	pos	.010 *	.004 **
M1,M2	pos	.159	.112
M1,H	pos	.0003 ***	.0001 ***
M2,H	pos	.032 *	.016 *

Male Rats

Groups Compared	Direction	Two-tailed p-value of Test Cox	Kruskal/Wallis
C,L,M,H	pos	.538	.684
C,L	pos	.552	.457
C,M	neg	.739	.628
C,H	pos	.605	.553
L,M	neg	.369	.296
L,H	pos	.927	.865
M,H	pos	.393	.337

* p<.05
** p<.005
*** p<.0005

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Table 3
INTERCURRENT MORTALITY RATES

	FEMALE MICE mg/kg/day			
Weeks	0	100	300	1000
0- 52	6/112 (5%)	5/56 (9%)	6/56 (11%)	16/56 (29%)
53- 78	16/106 (20%)	6/51 (20%)	5/50 (20%)	9/40 (45%)
79- 92	17/90 (35%)	7/45 (32%)	10/45 (38%)	9/31 (61%)
93-104	23/73 (55%)	12/38 (54%)	12/35 (59%)	11/22 (80%)
Term. Sac.	50/112 (45%)	26/56 (46%)	23/56 (41%)	11/56 (20%)

	MALE MICE mg/kg/day			
Weeks	0	100	300	1000
0- 52	5/112 (4%)	2/56 (4%)	2/56 (4%)	8/56 (14%)
53- 78	13/107 (16%)	7/54 (16%)	9/54 (20%)	13/48 (38%)
79- 92	15/94 (29%)	11/47 (36%)	16/45 (48%)	11/35 (57%)
93-104	31/79 (57%)	15/36 (63%)	14/29 (73%)	8/24 (71%)
Term. Sac.	48/112 (43%)	21/56 (37%)	15/56 (27%)	16/56 (29%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 4

Results of Survival Analyses

Female Mice

Groups Compared	Direction	Two-tailed P-Value of Test Cox	Kruskal/Wallis
C,L,M,H	pos	.0000 ***	.0000 ***
C,L	neg	.892	.821
C,M	pos	.760	.720
C,H	pos	.0001 ***	.0000 ***
L,M	pos	.646	.584
L,H	pos	.0009 **	.0003 ***
M,H	pos	.006 **	.002 **

Male Mice

Groups Compared	Direction	Two-tailed P-Value of Test Cox	Kruskal/Wallis
C,L,M,H	pos	.0027 **	.0003 ***
C,L	pos	.477	.403
C,M	pos	.029 *	.029 *
C,H	pos	.005 **	.0006 **
L,M	pos	.267	.244
L,H	pos	.101	.026 *
M,H	neg	.547	.171

* p<.05
** p<.005
*** p<.0005

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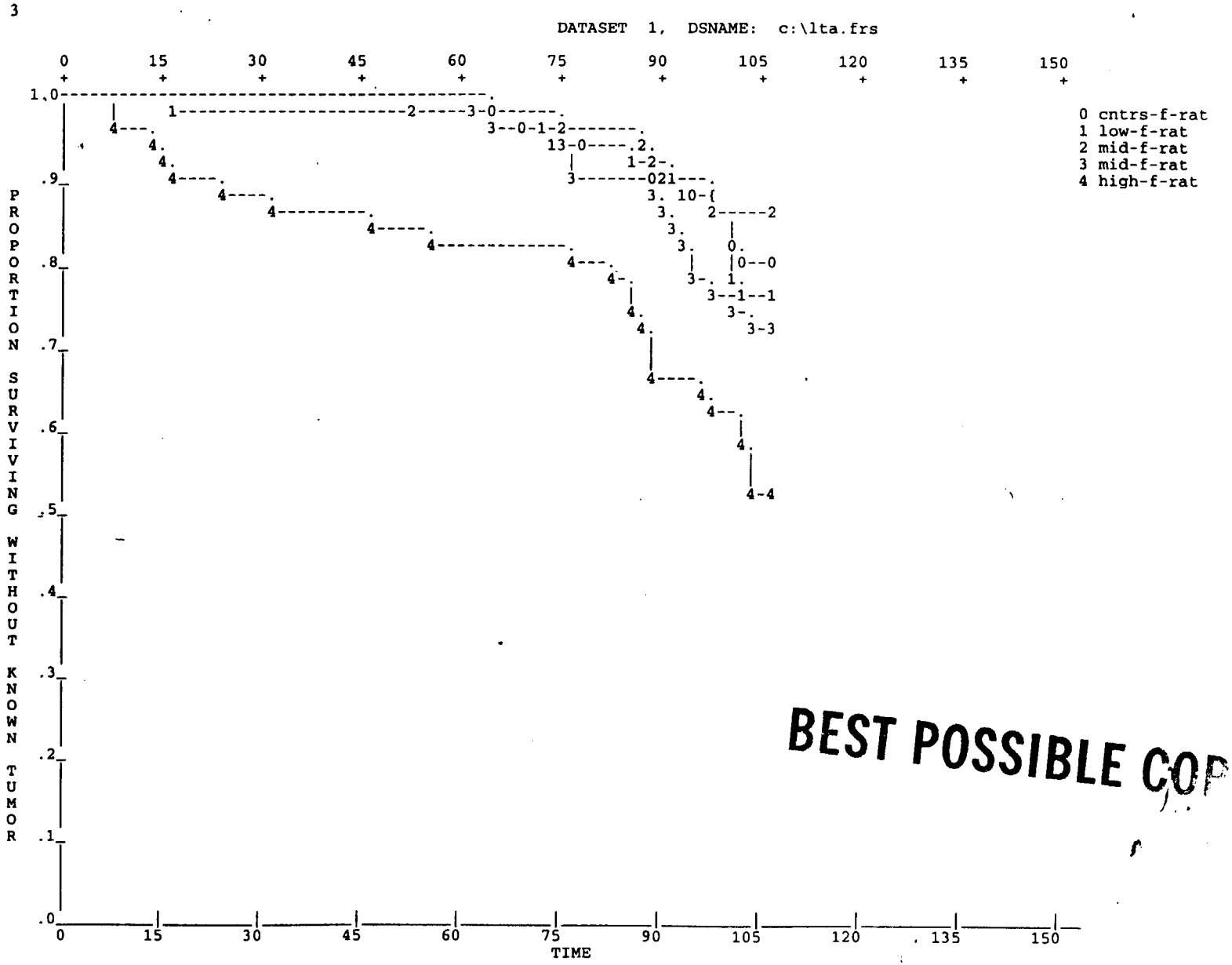

Figure 1 : Survival - Female Rats

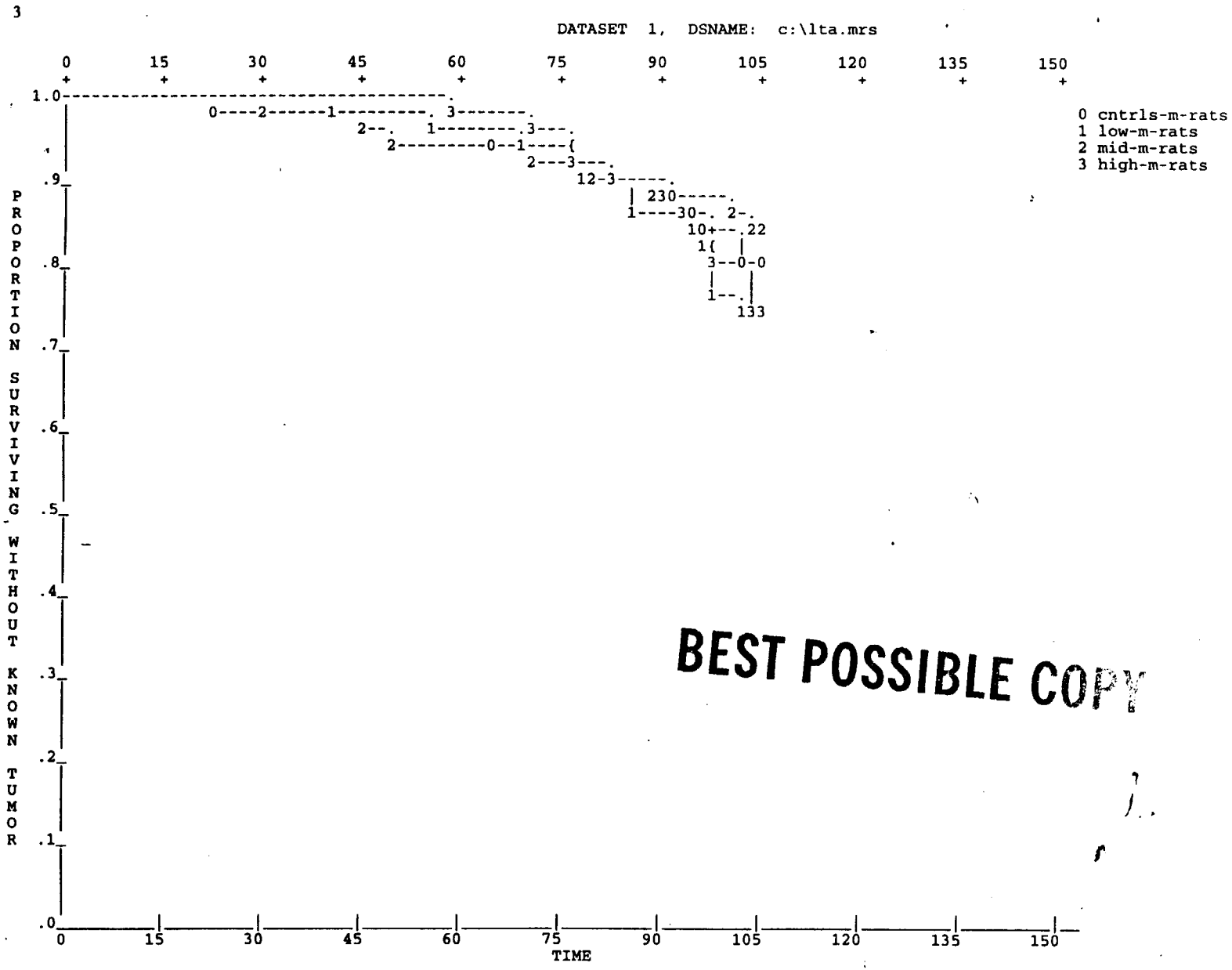

Figure 2: Survival - Male Rats

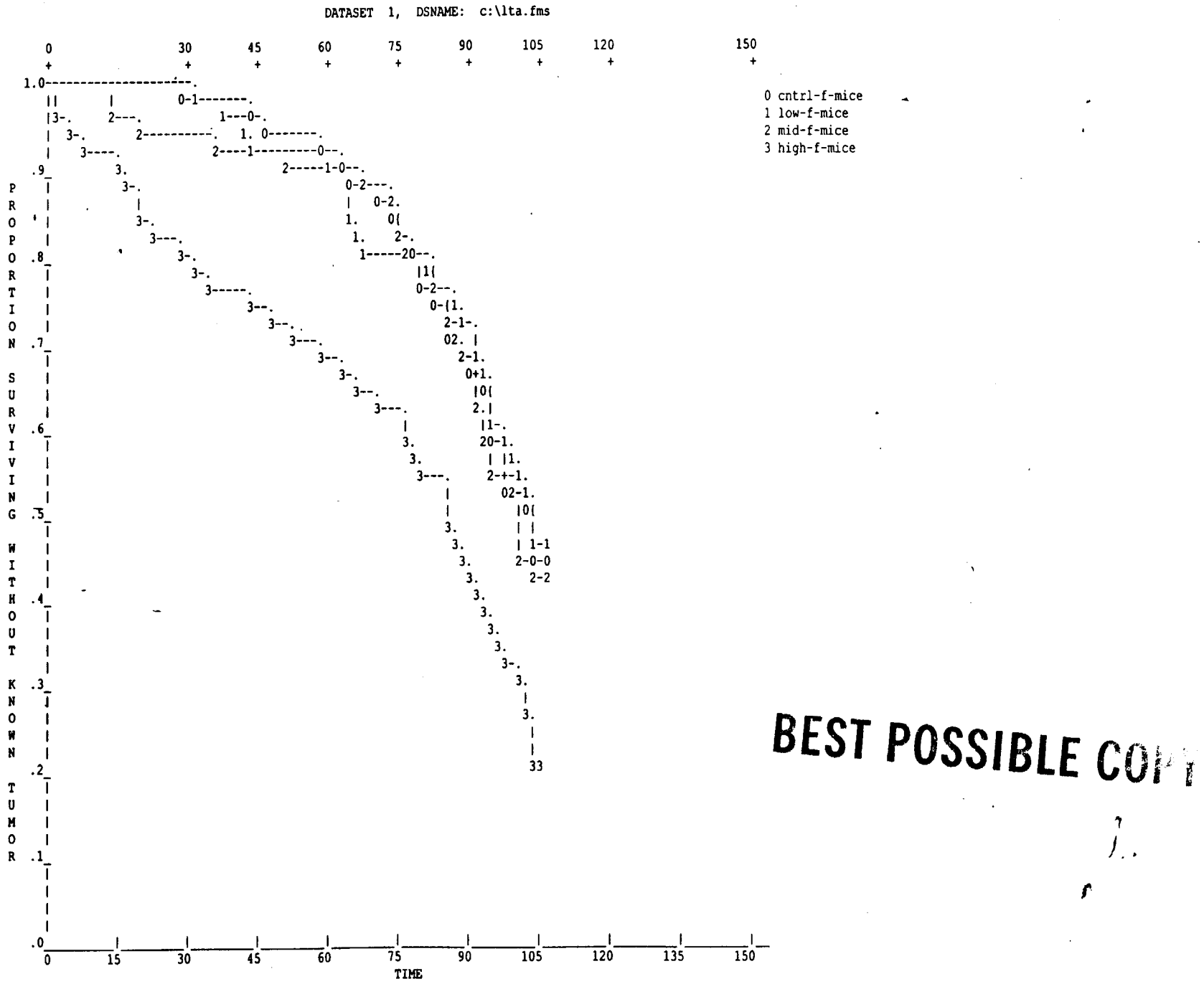

Figure 3: Survival - Female Mice

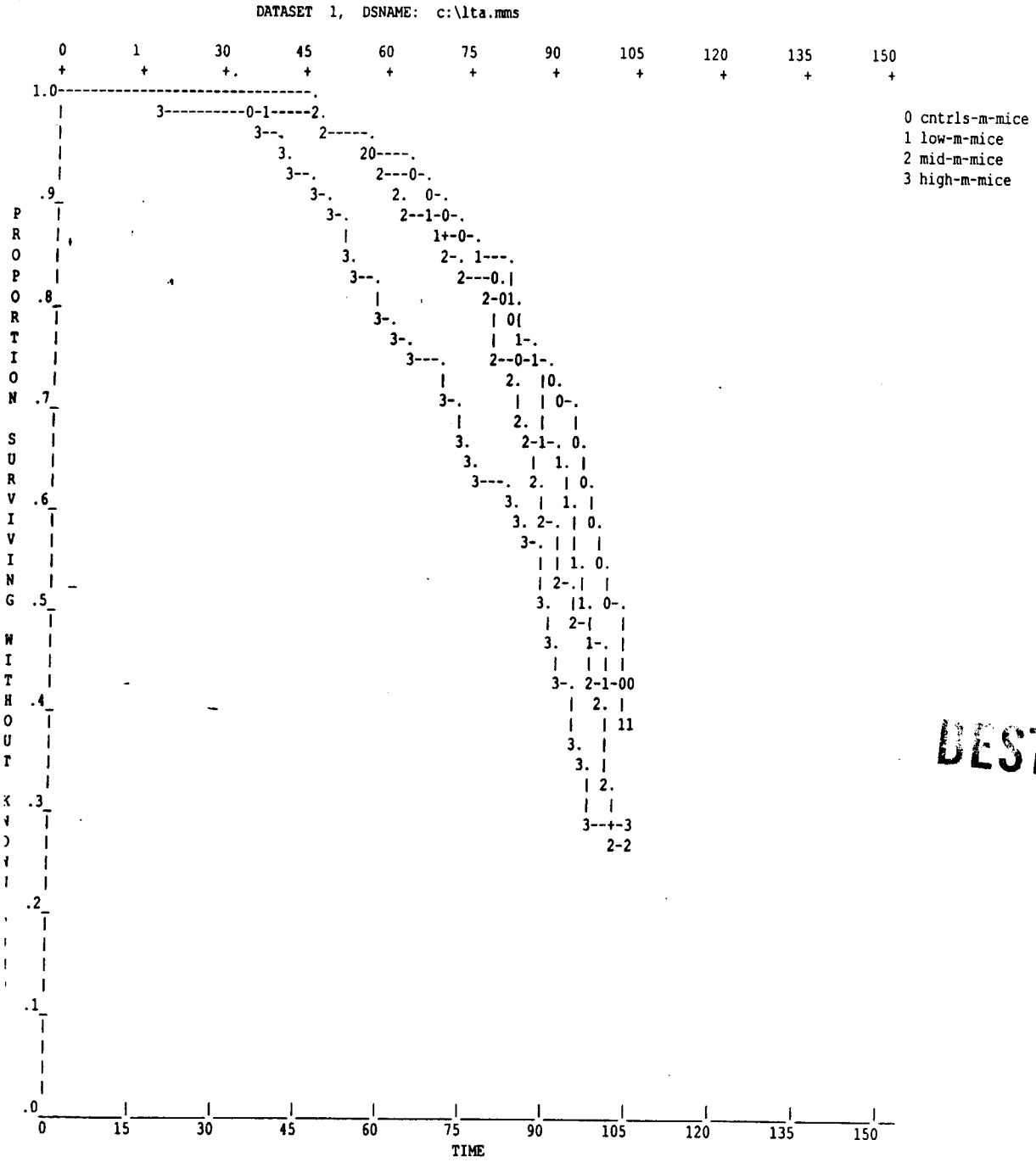

Figure 4: Survival - Male Mice.

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APPLICATION NUMBER: NDA 20757 AND 20758

ADMINISTRATIVE DOCUMENTS

CERTIFICATION OF PATENT INFORMATION

The following declaration is made under 21 CFR §§314.53(c) and (d) for Irbesartan described in Sanofi Pharmaceutical's pending NDA No. 20-757.

The undersigned declares that Patent No. 5,270,317 (having a normal expiration date of March 20, 2011) covers the drug substance Irbesartan and compositions of Irbesartan the subject of this application for which approval is being sought.

Declaration by:

Date 8 July 1997

William J. Davis
Assistant Secretary
SANOFI PHARMACEUTICALS, INC.

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EXCLUSIVITY SUMMARY for NDA # 20 757 **SUPPL #** _____

Trade Name _____ **Generic Name** Irbesartan

Applicant Name Sanofi Pharmaceuticals **HFD-** 110

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO <u>ALL</u> OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Kathleen F. Longmann — February 10, 1997

Signature — Date

Title: Regulatory Health Project Manager

Robert Temple — 9/21/97

Signature of Division Director — Date

Ada

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95