Statistical Review and Evaluation

Review of Carcinogenicity Data

NDA#:	21-344, #000
Applicant:	AstraZeneca Pharmaceuticals LP
Drug Name:	Faslodex® (fulvestrant, ICI 182,780)
Indication:	[redacted]
Document Reviewed:	Electronic submissions dated October 29 and December 11, 2001.
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TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1 BACKGROUND

Reference is made to the statistical consult request dated November 28, 2001, by Dr. Rosario, the reviewing pharmacologist, for a statistical review of the carcinogenicity study in the NDA submission.

The carcinogenicity data were first submitted on October 29, 2001. Since certain variables were not coded properly, a request was made by the Division on December 6 to ask the sponsor to re-examine and to re-submit the data. The updated data were submitted on December 11, 2001.

This review is focused on dose-mortality and dose-tumor trends. Several comparisons are made for each sex: (1) the two vehicle controls and the saline group, (2) the two vehicle controls and the three ICI 182,780 groups, and (3) a pooled comparison of combined vehicles and combined treated. In addition, in male rats, the comparison among the two vehicle controls and the low and middle dose levels of ICI 182,780 groups are also made.

2 INTRODUCTION

A carcinogenicity study was conducted in rats to assess the carcinogenic potential of ICI 182,780 given intramuscularly at 15 or 30 day intervals. The study was designed as a 2-year study. Rats were randomly divided into 6 groups stratifying by sex. There were three controls and three separate dose level groups. The study design is listed in Table 1. It is noted, that the dosing schedule does not readily translate into an intuitive dose response, such as 1, 2, 3. The low dose is given per kg of the animal but the medium and high doses are not adjusted by weight. As the animals grow, the low dose becomes much closer to the mid-dose when the 'per kg' dose is calculated. Therefore, this reviewer performed two analyses: one using 0, 1, 2, 3 as weights in the dose-tumor trend tests and a pair-wise comparison of all controls with all treated, since final doses do not differ greatly from each other. No p-values are reported when the tumor findings depended on observing a gross lesion first in an area where tissues were not routinely collected (e.g. tail).

In the study, all analyses were performed separately by sex. After the treatment period, all surviving animals were sacrificed. All animals were fully necropsied and histopathologically examined.

Table 1: Study Design

Group No. Identification	Dose Levels	Dose Volume	Number of animals	
			Males	Females
1. vehicle control	0 mg/kg/15 days	0.2 mL/rat	50	50
2. vehicle control	0 mg/kg/30 days	0.2 mL/rat	50	50
3. Saline control	0 mg/kg/15 days	0.2 mL/rat	50	50
4. ICI 182,780 (low)	15 mg/kg/30 days †	0.3 mL/kg †	50	50
5. ICI 182,780 (med)	10 mg/rat/30 days	0.2 mL/rat	50	50
6. ICI 182,780 (high)	10 mg/rat/15 days	0.2 mL/rat	50	50

† Dose limited to maximum injection volume of 0.2mL/rat.

3 SUMMARY OF SPONSOR'S ANALYSIS

An apparent reduction was seen in the mortality rate for animals receiving ICI 182,780. This reduction was observed in both sexes and attained statistical significance ($p<0.05$) for all treated groups compared to their respective controls.

An increase in the incidence of ovarian benign granulosa cell tumors was only recorded in the high dose female animals. There was also evidence of an increase in the incidence of testicular interstitial Leydig cell tumors in male animals given ICI 182,780. Interstitial cell adenomas were absent in the vehicle control groups and present at a low incidence in the saline control group. The sponsor noted, that the incidence in the high dose group was similar to controls whilst in the two low dose groups the incidence was slightly increased although within the expected range for this age and strain of rat.

It was concluded by the sponsor that ICI 182,780 showed no evidence for direct carcinogenic activity. Induction of benign ovarian granulosa cell tumors and benign testicular Leydig cell tumors was consistent with the pharmacological activity of an anti-estrogen.

4 REVIEWER'S ANALYSIS AND CONCLUSIONS

P-values for dose-mortality pair-wise or trend analyses are two-sided and are compared with a significance level of 0.05. P-values from analyses of dose-tumor positive linear trend are one-sided and are compared with a significance level of 0.05 for rare tumors, defined as tumors in the control group with a spontaneous tumor rate of 1% or less, and with a significance level of 0.01 for common tumors. Exact permutation trend tests are used unless both incidental and fatal tumor types are found in the same time interval, in which case a normal approximation is used, which gives the 'asymptotic' p-value. For pair-wise comparisons, the levels of significance are 0.05 and 0.01 for rare and common tumors, respectively.

4.1 REVIEWER'S ANALYSIS

4.1.1 Comparisons among the Three Controls

The number of rats in each group who died in different time intervals appears in Table 2. The Kaplan-Meier estimates of the survival curves appear in Figure 1 and Figure 2. The table and figures did not suggest a difference in survival curves in male rats. However, in female rats there is a suggestion of decreased survival in saline control.

As there is no inherent order among the two vehicle and the saline groups, the tests for homogeneity are appropriate. Table 3 shows that there was no statistically significant heterogeneity ($p>0.245$) among the survival patterns of the three groups for either sex. The apparent decreased survival in the female saline group seen in the Kaplan Meier curves was not borne out numerically. Results of pair-wise comparisons also show no statistically significant difference in survival in either sex.

Results of the pair-wise comparisons among the three controls in male rats show no significant difference in tumor incidences at any tumor site.

Results of the pair-wise comparisons among the three controls in female rats show no significant difference in tumor incidences at any tumor site, except for adenoma (pars distalis) of the pituitary. There were 37 incidences in the vehicle control 1 and 46 incidences in the saline group. Both exact and asymptotic p-values of the corresponding pair-wise comparison are identical and equal to 0.0124. This finding is nearly statistically significant at the significance level of 0.01 when the tumor is considered common and when no further multiplicity adjustment for p-values is required.

Table 2: Number of Deaths Per Control Group in Different Time Intervals.

Sex	Week	Group		
		Vehicle Control 1	Vehicle Control 2	Saline Control
Male	0 – 52	6	5	4
	53 – 78	19	15	13
	79 – 91	4	11	10
	92 – 103	12	10	12
	104 – 104	9	9	11
	Total	50	50	50
Female	0 – 52	1	3	2
	53 – 78	11	12	16
	79 – 91	10	5	11
	92 – 103	9	14	7
	104 – 104	19	16	14
	Total	50	50	50

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