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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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.

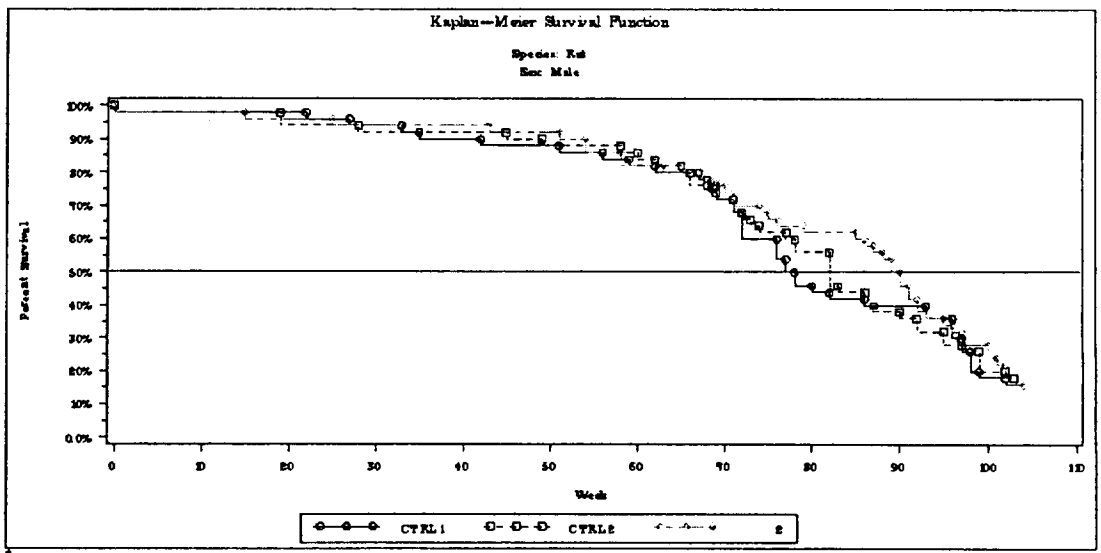
Sex	Week	Group		
		Vehicle Control 1	Vehicle Control 2	Saline Control
Male	0 – 52	6	5	4
	53 – 78	19	15	13
	79 – 91	4	11	10
	92 – 103	12	10	12
	104 – 104	9	9	11
	Total	50	50	50
Female	0 – 52	1	3	2
	53 – 78	11	12	16
	79 – 91	10	5	11
	92 – 103	9	14	7
	104 – 104	19	16	14
	Total	50	50	50

Table 3: Dose-Mortality Trend Tests† for Control Groups

Sex	Method	Time-Adjusted Trend Test	Statistic	P-value
Male	Cox	Dose-Mortality Trend	0.52	0.4724
		Depart from Trend	0.08	0.7817
		Homogeneity	0.59	0.7434
	Kruskal-Wallis	Dose-Mortality Trend	0.71	0.3992
		Depart from Trend	0.09	0.7667
		Homogeneity	0.80	0.6707
Female	Cox	Dose-Mortality Trend	2.06	0.1514
		Depart from Trend	0.02	0.8778
		Homogeneity	2.08	0.3532
	Kruskal-Wallis	Dose-Mortality Trend	2.76	0.0965
		Depart from Trend	0.05	0.8236
		Homogeneity	2.81	0.2451

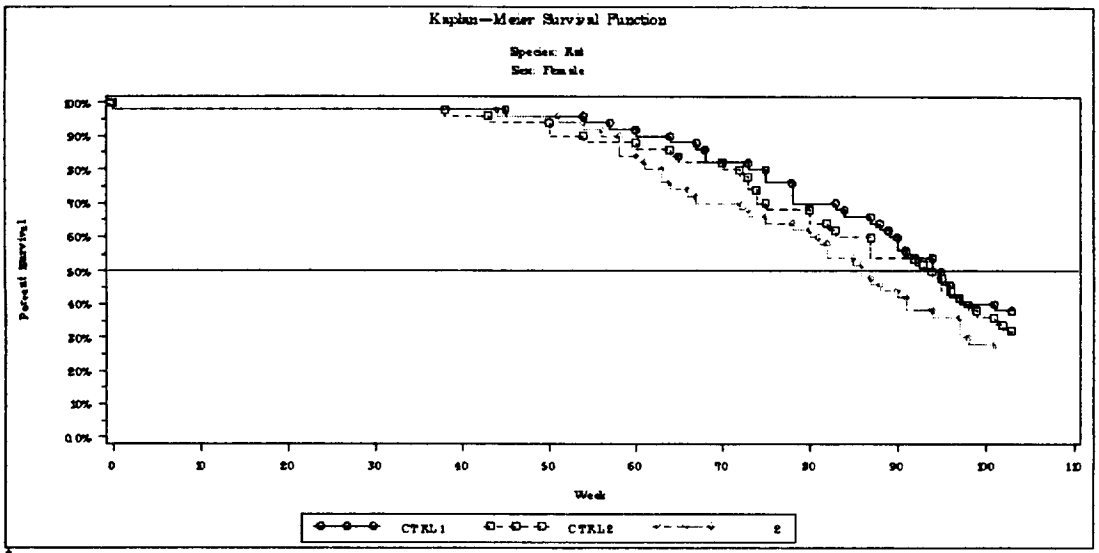
† This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1 by Donald G. Thomas, National Cancer Institute.

Figure 1: Kaplan-Meier Estimates of Survival Curves in Male Rats†, Controls Only



† Due to limitation of the labeling, the saline control group is labeled as '2' in the plot.

Figure 2: Kaplan-Meier Estimates of Survival Curves in Female Rats†, Controls Only



† Due to limitation of the labeling, the saline control group is labeled as '2' in the plot.

4.1.2 Comparisons among Vehicle Controls and Treated, Excluding Saline Control

In this section the saline control group is excluded from the analysis because saline only served as a comparator to potential vehicle effects. In addition, results are reported from the analyses with both vehicle control groups combined.

The number of rats in each group who died in different time intervals appears in Table 4. The Kaplan-Meier estimates of the survival curves appear in Figure 3 and Figure 4. The table and figures suggest an increased trend with treatment in survival in either sex. However, in male rats the increased survival trend seems to be greatly influenced by the high-dose group, whereas in female rats the control groups overlap and the treated groups overlap separately.

The p-values from the dose-mortality trend tests appear in Table 5. The results of these tests confirm what is visually apparent form the Kaplan-Meier curves and the number of deaths per time interval. The p-value for the dose-mortality trend test is significant (p-value < 0.001) in either sex.

The entire table of comparisons of organ specific tumors appears in Appendix 5.1. In male rats, there are no sites with a significant dose-tumor positive linear trend. All eleven testicular interstitial Leydig cell tumors appear in the treated groups, but in a non-linear pattern. Therefore, the p-value for the linear trend is not significant (exact p-value = 0.3148). However, results of the pooled comparison between the combined vehicle controls and the combined treated groups show a significant difference (exact p-value = 0.0068). In addition, the trend for lipoma of the subcutaneous tissue in male rats approaches statistical significance (exact p-value = 0.0514, non-overlapping time intervals for fatal and incidental tumors) at a significance level of 0.05.

In female rats, a positive linear trend for ovarian granulosa cell tumors is found statistically significant (exact p-value = 0.0001) at a significance level of 0.05. Results of the pooled comparison between the combined vehicle controls and the combined treated groups also show a significant difference (exact p-value = 0.0126). In addition, the trend for fibrosarcoma of the subcutaneous tissue in female rats is statistically significant (exact p-value = 0.0366, non-overlapping time intervals for fatal and incidental tumors) at a significance level of 0.05.

Table 4: Number of Deaths Per Treatment Group in Different Time Intervals, Excluding Saline

Sex	Week	Group				
		Vehicle Control 1	Vehicle Control 2	Low	Medium	High
Male	0 – 52	6	5	3	3	0
	53 – 78	19	15	11	12	5
	79 – 91	4	11	12	11	7
	92 – 103	12	10	7	10	13
	104 – 104	9	9	17	14	25
	Total	50	50	50	50	50
Female	0 – 52	1	3	1	1	2
	53 – 78	11	12	3	5	6
	79 – 91	10	5	8	4	2
	92 – 103	9	14	6	7	9
	104 – 104	19	16	32	33	31
	Total	50	50	50	50	50

Table 5: Dose-Mortality Trend Tests[†], Excluding Saline

Sex	Method	Time-Adjusted Trend Test	Statistic	P Value
Male	Cox	Dose-Mortality Trend	18.12	0.0000
		Depart from Trend	3.25	0.3542
		Homogeneity	21.37	0.0003
	Kruskal-Wallis	Dose-Mortality Trend	20.52	0.0000
		Depart from Trend	3.20	0.3625
		Homogeneity	23.71	0.0001
Female	Cox	Dose-Mortality Trend	14.54	0.0001
		Depart from Trend	9.25	0.0262
		Homogeneity	23.79	0.0001
	Kruskal-Wallis	Dose-Mortality Trend	13.89	0.0002
		Depart from Trend	9.08	0.0282
		Homogeneity	22.97	0.0001

[†] This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1 by Donald G. Thomas, National Cancer Institute.

Figure 3: Kaplan-Meier Estimates of Survival Curves in Male Rats, Excluding Saline

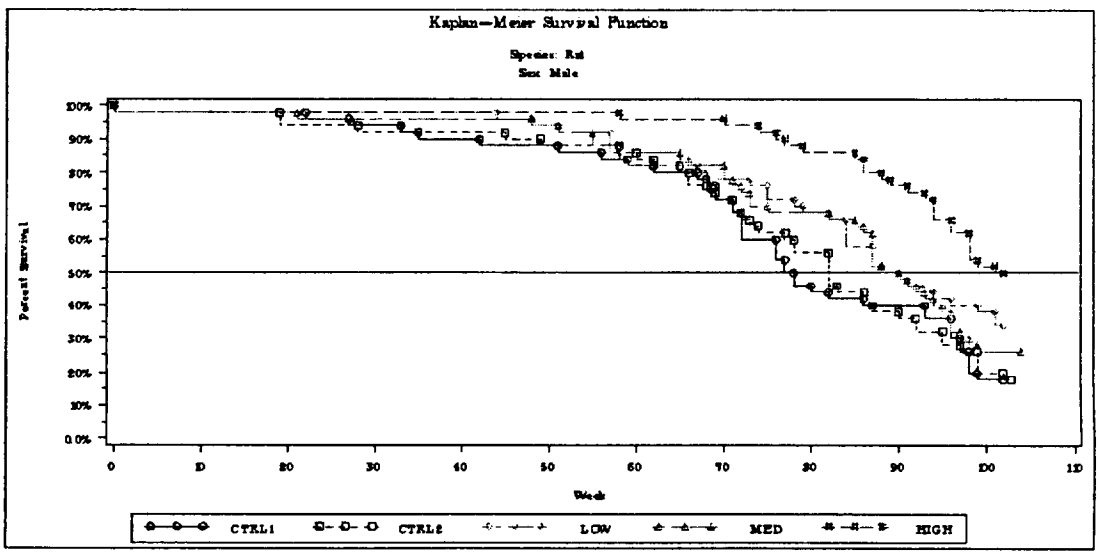
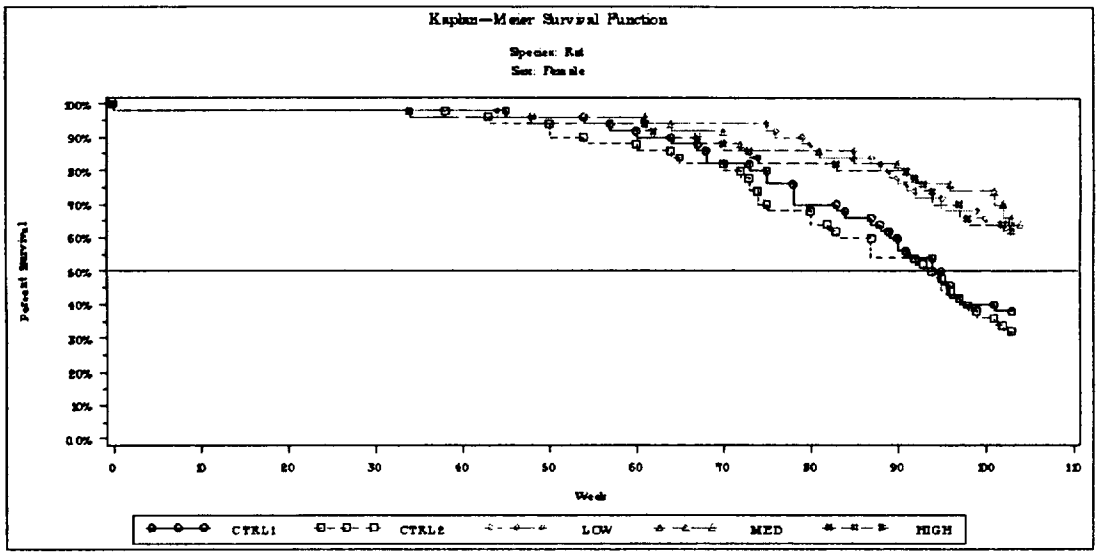


Figure 4: Kaplan-Meier Estimates of Survival Curves in Female Rats, Excluding Saline



4.1.3 Comparisons among Vehicle Controls and Treated, Excluding Saline Control and High Dose Level, Male Rats Only

In the previous section, though there were eleven testicular interstitial Leydig cell tumors and all among the treated, the linear trend test did not reach statistical significance. In order to explore this finding, the dose-tumor trend analysis in male rats is repeated in this section but with the high dose level removed.

The entire table of comparisons of organ specific tumors appears in Appendix 5.2. The p-value for the testicular interstitial Leydig cell tumors now reaches statistical significance when the high dose level is removed from the analysis (p-value = 0.0206 as compared to 0.3148 when included). This reviewer is aware that the decision to exclude the high dose from the analysis was post-hoc and is therefore, biased. However, as mentioned above, attributing a right order to the doses of ICI 182,780 administered to the rats is not straightforward in this study and the non-linear trend observed among the testicular interstitial Leydig cell tumors may reflect this problem. Also, the trend in lipoma in the subcutaneous tissue is no longer statistically significant at a significance level of 0.05 (p-value = 0.0682).

4.2 REVIEWER'S CONCLUSIONS

4.2.1 Conclusions for Comparisons among the Three Controls

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

In female rats, 37 incidences of adenoma (pars distali) of the pituitary appear in the vehicle control 1 and 46 in the saline control. The pair-wise comparison approaches statistical significance (p-value = 0.0124) when the tumor is considered common and when no further multiplicity adjustment for p-values is required.

4.2.2 Conclusions for Comparisons among the Two Vehicle Controls and the Treated

In male rats, there is a statistically significant relationship between dose and increased length of survival (p-value < 0.001). There is also a statistically significant dose-tumor positive linear trend for the testicular interstitial Leydig cell tumors (p-value = 0.0206) when the high dose level is excluded from the comparison. The finding is not significant (p-value = 0.3148) when the high dose level is included into the analysis. However, results of the pooled comparison of this tumor between the combined vehicle controls and the combined treated groups show a significant difference (exact p-value = 0.0068). In addition, the trend for lipoma of the subcutaneous tissue approaches statistical significance (exact p-value = 0.0514) at a significance level of 0.05.

In female rats, there is a statistically significant relationship between dose and increased length of survival (p-value < 0.001). There is also a statistically significant dose-tumor positive linear trend for the ovarian granulosa cell tumors (p-value = 0.0001) where 7 of the 10 incidences occurred in the high-dose group. Results of the pooled comparison in this tumor site between the combined vehicle controls and the combined treated groups also show a significant difference (exact p-value = 0.0126). In addition, the trend for fibrosarcoma of the subcutaneous tissue is statistically significant (exact p-value = 0.0366) at a significance level of 0.05.

4.2.3 Overall Conclusions

A nearly significant difference in tumor incidences is found in adenoma (pars distalis) of the pituitary in female rats between the vehicle control 1 and the saline control when the tumor is considered common and when no further multiplicity adjustment for p-values is required.

The statistical findings in this review are similar to the sponsor's report with respect to analyses of dose-mortality trend, of dose-tumor positive linear trend for the testicular interstitial Leydig cell tumors and for ovarian granulosa cell tumors. However, due to the difficulty in assigning proper dose levels reflecting the changing relationship of the doses administered, this reviewer considers the comparison of the combined vehicle controls and the combined treated as the most appropriate. In these analyses, the differences in testicular interstitial Leydig cell tumors and in ovarian granulosa cell tumors reach statistical significance. Other factors associated with these

findings (such as attributing the findings to the pharmacological activity of an anti-estrogen) are beyond this review.

5 APPENDIX

5.1 TUMOR FINDINGS FOR VEHICLE AND TREATED GROUPS, EXCLUDING SALINE CONTROL

Table 6: Test for Dose-Tumor Positive Linear Trend in Tumors for Male Rats, Excluding Saline

Organ Name	Tumor Name	CTRL 1	CTRL 2	LOW	MED	HIGH	pValue (Exact)	pValue (Asymp)	Tumor type
BRAIN	Malignant granular cell t	1	0	0	0	0	1.0000	0.9466	FA
BRAIN	Malignant astrocytoma	0	0	0	0	1	0.3378	0.2287	IN
BRAIN	Malignant schwannoma	0	0	1	0	0	0.7568	0.8286	IN
BRAIN	Malignant ependymoma	0	1	0	0	0	1.0000	0.9287	FA
HEART	Chemodectoma	1	0	0	0	0	1.0000	0.9228	IN
HEART	Malignant schwannoma: end	1	0	0	0	0	1.0000	0.9478	FA
LIVER	Carcinoma: hepatocellular	0	2	3	1	1	0.7871	0.7916	MX
LIVER	Adenoma: hepatocellular	0	3	0	3	3	0.3350	0.3334	IN
LIVER	Cholangioma	0	0	0	1	0	0.5270	0.5410	IN
PANCREAS	Adenoma: islet cell	2	2	4	0	3	0.7579	0.7613	IN
PANCREAS	Adenoma: acinar cell	0	0	0	0	1	0.3378	0.2287	IN
PANCREAS	Carcinoma: islet cell	0	1	2	3	0	0.7264	0.7305	MX
KIDNEY	Lipoma	0	0	0	1	0	0.4000	0.3978	IN
KIDNEY	Adenoma: tubular cell	0	0	0	1	0	0.5270	0.5410	IN
URINARY BLADDER	Lipoma	1	0	0	0	0	1.0000	0.9637	IN
URINARY BLADDER	Papilloma: transitional c	0	1	0	0	0	1.0000	0.9228	IN
TESTIS	Adenoma: interstitial cel	0	0	6	4	1	0.3148	0.3150	IN
SEMINAL VESICLE	Leiomyoma	0	1	0	0	0	1.0000	0.9228	IN
SUBCUTANEOUS TISSUE	Fibroma	3	6	2	2	2	0.5589	0.5681	MX
SUBCUTANEOUS TISSUE	Lipoma	0	0	1	1	1	0.0514	0.0360	MX
SUBCUTANEOUS TISSUE	Osteosarcoma	0	0	1	0	0	0.4615	0.5837	FA
SUBCUTANEOUS TISSUE	Rhabdomyosarcoma	0	0	0	1	0	0.1667	0.1884	FA
SUBCUTANEOUS TISSUE	Leiomyoma	0	0	0	1	0	0.2963	0.2832	FA
SUBCUTANEOUS TISSUE	Squamous cell carcinoma:	0	1	0	0	0	1.0000	0.8906	FA
SUBCUTANEOUS TISSUE	Hemangioma	0	1	0	0	0	1.0000	0.9160	IN
PITUITARY	Adenoma: pars distalis	26	27	26	22	27	0.9967	0.9965	MX
PITUITARY	Adenoma: pars intermedia	0	0	0	1	1	0.1228	0.1039	IN
THYROID	Adenoma: C-cell	1	2	2	2	2	0.7508	0.7536	IN
THYROID	Carcinoma: C-cell	1	3	3	3	4	0.5603	0.5613	IN

THYROID	Adenoma: follicular cell	0	0	0	1	1	0.1967	0.1740	IN
PARATHYROID GLAND	Adenoma	0	2	0	1	0	0.8945	0.9039	IN
ADRENAL	Malignant pheochromocytom	4	0	1	2	1	0.8948	0.8963	MX
ADRENAL	Adenoma: cortical	1	0	0	1	0	0.6975	0.7244	IN
ADRENAL	Benign pheochromocytoma	0	5	8	7	5	0.4476	0.4482	MX
HEMOLYM. TISSUE	Malignant lymphoma	1	2	1	0	1	1.0000	0.9789	MX
HEMOLYM. TISSUE	Histiocytic sarcoma	2	0	0	0	2	0.6917	0.6850	FA
MAMMARY GLAND	Adenocarcinoma	2	0	0	0	0	1.0000	0.9711	MX
MAMMARY GLAND	Adenoma	0	0	1	0	2	0.1692	0.1689	IN
MAMMARY GLAND	Fibroma	0	1	0	0	0	1.0000	0.9483	FA
SKIN MISCELLANEOUS	Keratoacanthoma	3	2	0	3	3	0.6823	0.6850	MX
SKIN MISCELLANEOUS	Fibroma: dermal	1	0	0	0	0	1.0000	0.9257	IN
SKIN MISCELLANEOUS	Polyp	1	0	0	0	0	1.0000	0.8957	IN
SKIN MISCELLANEOUS	Fibroma	1	1	0	1	0	0.9163	0.9225	IN
SKIN MISCELLANEOUS	Fibrosarcoma	0	0	1	0	0	0.5870	0.7402	IN
SKIN MISCELLANEOUS	Adenoma: sebaceous	0	0	1	0	0	0.7429	0.8185	IN
SKIN MISCELLANEOUS	Papilloma: squamous cell	0	1	1	0	0	0.9366	0.9450	IN
SKIN MISCELLANEOUS	Carcinoma: squamous cell	0	0	0	1	1	0.2232	0.2059	IN
THORAX	Hibernoma: benign	0	1	0	0	0	1.0000	0.9088	FA
THORAX	Hibernoma: malignant	0	1	0	0	0	1.0000	0.8556	FA
ABDOMEN	Leiomyosarcoma	0	0	1	0	0	N/A	N/A	FA
JEJUNUM	Adenoma	0	0	1	0	0	0.7133	0.8042	FA
JEJUNUM	Leiomyosarcoma	0	1	0	0	0	1.0000	0.9494	FA

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Table 7: Test for Dose-Tumor Positive Linear Trend in Tumors for Female Rats, Excluding Saline

Organ Name	Tumor Name	CTRL 1	CTRL 2	LOW	MED	HIGH	pValue (Exact)	pValue (Asymp)	Tumor type
BRAIN	Glioma (not otherwise spe	1	0	0	0	0	1.0000	0.9285	FA
MENINGES	Meningeosarcoma	0	0	0	0	1	N/A	N/A	FA
CAVITY ORAL	Amelanotic melanoma	0	0	0	0	1	N/A	N/A	IN
CECUM	Leiomyoma	1	0	0	0	0	1.0000	0.8990	IN
LIVER	Adenoma: hepatocellular	2	3	2	5	1	0.7151	0.7197	IN
LIVER	Cholangioma	0	1	0	0	0	1.0000	0.9110	IN
PANCREAS	Adenoma: islet cell	3	0	3	0	2	0.6921	0.6993	IN
PANCREAS	Carcinoma: islet cell	2	1	2	2	0	0.9043	0.9045	MX
KIDNEY	Lipoma	0	0	0	1	0	0.4885	0.4851	IN
KIDNEY	Adenoma: tubular cell	0	1	0	0	0	1.0000	0.9597	IN
KIDNEY	Carcinoma: tubular cell	0	0	1	0	0	0.6033	0.7272	FA
SUBCUTANEOUS TISSUE	Fibroma	3	2	2	1	0	0.9848	0.9739	IN
SUBCUTANEOUS TISSUE	Lipoma	0	0	0	1	0	0.2500	0.2658	FA
SUBCUTANEOUS TISSUE	Fibrosarcoma	0	0	1	1	1	0.0366	0.0298	MX
SUBCUTANEOUS TISSUE	Hemangiosarcoma	1	0	0	0	1	0.2795	0.2858	MX
OVARY	Carcinoma: sertoliform	0	1	0	0	0	1.0000	0.9019	IN
OVARY	Adenoma: sertoliform tubu	2	2	0	0	0	1.0000	0.9864	IN
OVARY	Granulosa cell tumor	0	0	1	2	7	0.0001	0.0002	IN
UTERUS	Polyp: endometrial stroma	4	4	0	0	0	1.0000	0.9996	IN
UTERUS	Leiomyoma	1	0	0	0	0	1.0000	0.9597	IN
UTERUS	Leiomyosarcoma	0	1	0	0	0	1.0000	0.9340	FA
UTERUS	Adenocarcinoma: endometri	0	1	0	0	0	1.0000	0.9597	IN
PITUITARY	Adenoma: pars distalis	37	45	32	36	29	1.0000	1.0000	MX
PITUITARY	Carcinoma: pars distalis	1	1	2	0	0	0.9669	0.9634	MX
PITUITARY	Adenoma: pars intermedia	0	0	0	1	0	0.3556	0.3533	IN
THYROID	Adenoma: C-cell	0	1	3	3	1	0.2240	0.2241	IN
THYROID	Carcinoma: C-cell	1	1	2	2	1	0.5840	0.5924	IN
THYROID	Carcinoma: follicular cel	1	1	0	0	0	1.0000	0.9856	IN
THYROID	Adenoma: follicular cell	0	2	0	3	0	0.6131	0.6253	IN
PARATHYROID GLAND	Adenoma	2	0	0	0	0	1.0000	0.9507	IN
PARATHYROID GLAND	Fibroma	0	0	0	1	0	0.4839	0.4612	IN
ADRENAL	Adenoma: cortical	3	1	1	0	0	0.9888	0.9785	IN
ADRENAL	Benign pheochromocytoma	2	2	1	0	1	0.9133	0.9111	IN
ADRENAL	Carcinoma: cortical	2	0	0	1	1	0.6677	0.6766	MX
HEMOLYM. TISSUE	Malignant lymphoma	1	3	0	0	1	0.8951	0.8927	MX
HEMOLYM. TISSUE	Histiocytic sarcoma	0	3	3	1	0	0.8312	0.8367	MX
HEMOLYM. TISSUE	Leukemia (not otherwise s	0	0	0	0	1	0.2000	0.1325	IN
THYMUS	Sarcoma: thymic	0	0	1	0	0	0.7364	0.8072	IN
MAMMARY GLAND	Adenocarcinoma	11	11	1	1	0	1.0000	1.0000	IN
MAMMARY GLAND	Adenoma	10	7	0	0	0	1.0000	1.0000	MX
MAMMARY GLAND	Fibroadenoma	18	20	0	0	1	1.0000	1.0000	MX
MAMMARY GLAND	Fibroma	3	2	0	0	0	1.0000	0.9962	IN
SKIN MISCELLANEOUS	Keratoacanthoma	1	1	0	0	0	1.0000	0.9490	IN
SKIN MISCELLANEOUS	Fibroma	0	0	0	1	0	0.4639	0.4688	IN

SKIN MISCELLANEOUS	Papilloma: squamous cell	0	0	1	0	0	0.7216	0.7925	IN
SKIN MISCELLANEOUS	Carcinoma: squamous cell	0	0	0	1	0	0.4639	0.4688	IN
SKIN MISCELLANEOUS	Carcinoma: basal cell	0	0	0	1	0	0.4639	0.4688	IN
DIAPHRAGM	Osteosarcoma (metastasis)	0	0	0	0	1	N/A	N/A	FA
MUSCLE SKELETAL MISC	Hemangioma	0	1	0	0	0	N/A	N/A	IN
TAIL	Leiomyoma	0	0	1	0	0	N/A	N/A	IN
INJECTION SITE	Fibrosarcoma	0	0	0	0	1	0.2366	0.1762	IN
THORAX	Hibernoma: benign	1	0	0	0	0	1.0000	0.8556	FA
ABDOMEN	Fibrosarcoma	0	1	0	0	0	1.0000	0.8556	FA
ABDOMEN	Hemangioma	1	0	0	0	1	N/A	N/A	IN

5.2 TUMOR FINDINGS FOR VEHICLE AND TREATED GROUPS, EXCLUDING SALINE CONTROL AND HIGH DOSE LEVEL, MALE RATS ONLY

Table 8: Test for Dose-Tumor Positive Linear Trend in Tumors for Male Rats, Excluding Saline and High Dose

Organ Name	Tumor Name	CTRL 1	CTRL 2	LOW	MED	pValue (Exact)	PValue (Asymp)	Tumor type
BRAIN	Malignant granular cell t	1	0	0	0	1.0000	0.9428	FA
BRAIN	Malignant schwannoma	0	0	1	0	0.6327	0.6986	IN
BRAIN	Malignant ependymoma	0	1	0	0	1.0000	0.9353	FA
HEART	Chemodectoma	1	0	0	0	1.0000	0.9192	IN
HEART	Malignant schwannoma: end	1	0	0	0	1.0000	0.9436	FA
LIVER	Carcinoma: hepatocellular	0	2	3	1	0.5795	0.5906	MX
LIVER	Adenoma: hepatocellular	0	3	0	3	0.4365	0.4423	IN
LIVER	Cholangioma	0	0	0	1	0.2857	0.2347	IN
PANCREAS	Adenoma: islet cell	2	2	4	0	0.8987	0.8967	IN
PANCREAS	Carcinoma: islet cell	0	1	2	3	0.1418	0.1394	MX
KIDNEY	Lipoma	0	0	0	1	0.2895	0.2303	IN
KIDNEY	Adenoma: tubular cell	0	0	0	1	0.2857	0.2347	IN
URINARY BLADDER	Lipoma	1	0	0	0	1.0000	0.9611	IN
URINARY BLADDER	Papilloma: transitional c	0	1	0	0	1.0000	0.9192	IN
TESTIS	Adenoma: interstitial cel	0	0	6	4	0.0206	0.0191	IN
SEMINAL VESICLE	Leiomyoma	0	1	0	0	1.0000	0.9192	IN
SUBCUTANEOUS TISSUE	Fibroma	3	6	2	2	0.6718	0.6831	MX
SUBCUTANEOUS TISSUE	Lipoma	0	0	1	1	0.0682	0.0440	MX
SUBCUTANEOUS TISSUE	Osteosarcoma	0	0	1	0	0.4167	0.5000	FA
SUBCUTANEOUS TISSUE	Rhabdomyosarcoma	0	0	0	1	0.0909	0.0554	FA
SUBCUTANEOUS TISSUE	Leiomyoma	0	0	0	1	0.2083	0.1391	FA
SUBCUTANEOUS TISSUE	Squamous cell carcinoma:	0	1	0	0	1.0000	0.9245	FA
SUBCUTANEOUS TISSUE	Hemangioma	0	1	0	0	1.0000	0.9160	IN
PITUITARY	Adenoma: pars distalis	26	27	26	22	0.9843	0.9834	MX
PITUITARY	Adenoma: pars intermedia	0	0	0	1	0.2895	0.2303	IN
THYROID	Adenoma: C-cell	1	2	2	2	0.6272	0.6341	IN
THYROID	Carcinoma: C-cell	1	3	3	3	0.5192	0.5254	IN
THYROID	Adenoma: follicular cell	0	0	0	1	0.2857	0.2347	IN
PARATHYROID GLAND	Adenoma	0	2	0	1	0.7056	0.7219	IN
ADRENAL	Malignant pheochromocytom	4	0	1	2	0.7143	0.7227	MX
ADRENAL	Adenoma: cortical	1	0	0	1	0.5030	0.5113	IN
ADRENAL	Benign pheochromocytoma	0	5	8	7	0.0775	0.0760	MX
HEMOLYM. TISSUE	Malignant lymphoma	1	2	1	0	1.0000	0.9453	FA
HEMOLYM. TISSUE	Histiocytic sarcoma	2	0	0	0	1.0000	0.9738	FA
MAMMARY GLAND	Adenocarcinoma	2	0	0	0	1.0000	0.9600	MX
MAMMARY GLAND	Adenoma	0	0	1	0	0.4359	0.5893	IN
MAMMARY GLAND	Fibroma	0	1	0	0	1.0000	0.9488	FA
SKIN MISCELLANEOUS	Keratoacanthoma	3	2	0	3	0.7575	0.7623	MX

SKIN MISCELLANEOUS	Fibroma: dermal	1	0	0	0	1.0000	0.9199	IN
SKIN MISCELLANEOUS	Polyp	1	0	0	0	1.0000	0.9154	IN
SKIN MISCELLANEOUS	Fibroma	1	1	0	1	0.7576	0.7672	IN
SKIN MISCELLANEOUS	Fibrosarcoma	0	0	1	0	0.4412	0.5948	IN
SKIN MISCELLANEOUS	Adenoma: sebaceous	0	0	1	0	0.6250	0.6960	IN
SKIN MISCELLANEOUS	Papilloma: squamous cell	0	1	1	0	0.8644	0.8797	IN
SKIN MISCELLANEOUS	Carcinoma: squamous cell	0	0	0	1	0.2917	0.2363	IN
THORAX	Hibernoma: benign	0	1	0	0	N/A	N/A	FA
THORAX	Hibernoma: malignant	0	1	0	0	N/A	N/A	FA
ABDOMEN	Leiomyosarcoma	0	0	1	0	N/A	N/A	FA
JEJUNUM	Adenoma	0	0	1	0	0.5941	0.6838	FA
JEJUNUM	Leiomyosarcoma	0	1	0	0	1.0000	0.9493	FA

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Executive CAC
Date of Meeting; December 4, 2001
Rat Carcinogenicity Study

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Timothy McGovern, Ph.D., HFD-170, Alternate Member
David Morse, Ph.D. Supervisory Pharmacologist, HFD-150
Lilliam Rosario, Ph.D., Pharm-Tox Reviewer, HFD-150

Author of Draft: Lilliam Rosario, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21,344
Drug Name: Faslodex (Fulvestrant; ICI 182,780
Sponsor: Astra Zeneca Pharmaceuticals

Mouse Carcinogenicity Study: Not conducted

Background
This 2-year carcinogenicity study in rats was submitted to NDA 21,344. This NDA proposes the use of ICI 182,780 (fulvestrant) for the treatment of

DRAFT

The recommended dose of Faslodex is 250 mg to be administered intramuscularly (IM) monthly.

The Sponsor indicates fulvestrant is an antiestrogenic agent, which acts by downregulation of the estrogen receptor (ER). Fulvestrant binds ER in a competitive manner with a high affinity comparable to estradiol. Further, the Sponsor suggests that Fulvestrant is a non-agonist antiestrogen which blocks the uterotrophic action of estradiol in mice, rats and monkeys without itself having any partial agonist estrogen- like activity.

Genotoxicity
The mutagenic and clastogenic potential of ICI 182,780 has been studied in bacterial mutation assays in strains of *Salmonella typhimurium* and *Escherischia coli*, an *in vitro* cytogenetics assay in cultured human lymphocytes, a mouse lymphoma mutation assay, and an *in vivo* rat micronucleus test. ICI 182,780 has shown no evidence of genotoxic/clastogenic potential in this battery of tests.

Rat Carcinogenicity Study:

Study Design:

- Dose concurrence was obtained on July 28, 1998.
- The Sponsor selected the high dose level to represent the maximum possible dose by the IM route (maximum feasible dose).
- There were 6 groups (50 sex/group); Sprague Dawley rats [redacted]

Control-1 (C1):	Vehicle/15 days
Control-2 (C2):	Vehicle/30 days
Control-3 (C3):	Saline/15 days
Low Dose (LD):	15 mg/kg/30 days
Middle Dose (MD):	10 mg/rat/30 days
High Dose- (HD):	10 mg/rat/15 days

The following table shows the ~ actual dose (mg/kg) administered to Groups V (10 mg/rat/30days) and Group VI (10 mg/rat/15 days). For comparison purposes, these values have also been normalized for frequency of administration (from every 15 days to every 30 days)

		Group V 10 mg/rat/30 days		**Group VI 10 mg/rat/15 days**		
Sex	**Week**	**Body weight (g)**	**mg/kg/ 30 days**	**Body weight (g)**	**mg/kg/ 15 days**	**mg/kg/30 days**
Male	1	262.9	38	257.8	39	78
	96	793	13	781.5	13	26
Female	1	184.7	54	185.7	54	108
	96	580.3	17	574.4	17	34

Statistical Methods:

- All tests for tumor incidence were one-sided looking for an increase in response/incidence.
- The Haseman (1983) principle of statistical significance was adopted; a rare tumor (<1% spontaneous incidence) will be deemed statistically significant if $p<0.05$, and a common tumor shall be deemed significant if $p<0.01$.
- The statistical comparisons of interest were implemented using Peto's survival-adjusted trend test.
- Note that the significance values used by the Sponsor are in accordance with those employed by CDER when only a single carcinogenicity study is conducted. The probability levels for determining significance of tumor incidence has not been adjusted for multiple statistical comparisons as would be appropriate to maintain a constant error rate over multiple studies.

RAT TUMOR FINDINGS:

It appears that the IM administration of ICI 182,780 (fulvestrant) for 24 months increased the incidence of ovarian granulosa cell tumors and testicular Leydig cell tumors in female and male rats, respectively.

Ovaries:

- A 14% increase in the incidence of a rare ovarian granulosa cell tumors in the high dose female animals (7/50 rats at 10 mg/rat/15d; p=0.01887).
- Spontaneous incidence of granulosa cell tumors for this strain of rat is 0.06% (n=1729) (Giknis and Clifford, 2001 [redacted]
- The conducting laboratory reports background instances varying from 0/120 to 1/120 (0.2%).
- Another study (n=4493) with the same strain and source reports 0.3% (Gregson and Abbott, 1984).

Testes:

- There was increase incidence (2-12%) of interstitial Leydig cell tumors (adenomas-common) in drug-treated animals.
- These tumors were present at a low incidence (4%) in the saline control group and absent in the vehicle control groups. The incidence in the high dose group was similar to controls (2%) while slightly increased (8-12%) in the two low dose groups.
- In Group 4 (15 mg/kg/30 days), interstitial cell tumors were increased significantly (p=0.01922)
- Spontaneous incidence for this strain of rat is 2.35% [redacted]

The reviewer proposed 3 questions for the EXEC CAC committee:

1. Are the survival rates observed in control and drug-treated groups adequate to determine the carcinogenic potential of ICI 182,780 (fulvestrant)?
   - Even though survival rates appear lower than expected for control males, the Committee agreed that the rate of mortality is adequate to determine the carcinogenic potential of ICI 182,780.

2. Does the Committee agree that administration of ICI 182,780 increases the incidence of granulosa cell tumors and interstitial Leydig cell tumors?

   The Committee
   - agreed that administration of ICI 182,780 increases the incidence of both granulosa cell tumors and interstitial Leydig cell tumors, in females and males, respectively.
   - recommended the statistical evaluation of these results take into consideration that only one carcinogenicity study was submitted.
   - recommended to carefully examine the pharmacological data submitted to support the claim that ICI 182,780 is a "non-agonist" antiestrogen. The increase incidence of interstitial Leydig cell tumors in males may suggest a drug-induced estrogenic effect.
   - noted that while the carcinogenicity study was acceptable, the Sponsor did not perform the defining studies for an anti-estrogen to determine if the compound is non-genotoxic.

The Committee suggested that a ^{32}P post labeling study to determine whether ICI 182,780 induces DNA adducts.

3. Does the Committee agree that these findings should be included in the product labeling for ICI 182,780 (fulvestrant)?
   The Committee agreed that the increase incidence of both granulosa cell tumors and interstitial Leydig cell tumors, in females and males, respectively be included in the product labeling for ICI 182,780 (fulvestrant).

Additional comments from the Committee:

The Committee

- pointed out that, unlike tamoxifen, the incidence of liver tumors was not changed in ICI 182,780-treated rats.
- suggested that, since male rats in the high dose group lost weight, the mid-dose male group should also be considered in evaluation of carcinogenic response.

Executive CAC Recommendations and Conclusions:

1) Fulvestrant increases the incidence of ovarian granulosa cell tumors in female rats, and the incidence of interstitial Leydig cell tumors in male rats.
2) The increase incidence of granulosa and Leydig cell tumors should be included in the product labeling for fulvestrant.
3) The Committee recommended that the Sponsor be asked to perform ^{32}P post-labeling study to determine if fulvestrant and/or its' metabolites may form adducts with cellular DNA.

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Joseph DeGeorge, Ph.D.
Chair, Executive CAC

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/Division File, HFD-150
/David Morse, Ph.D. Supervisory Pharmacologist, HFD-150
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Joseph DeGeorge
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