VI. CARCINOGENICITY:

Study title: A 2 YEAR INTRAMUSCULAR CARCINOGENICITY STUDY OF ICI 182,780 IN THE ALBINO RAT.

Key study findings:

- ICI 182,780 increases the incidence of ovarian granulosa cell tumors and testicular interstital Leydig ademomas.
- ICI 182,780 decreases the incidence of uterine endometrial stromal polyps, mammary tumors (adenoma, fibroadenoma, adenocarcinoma) in females, and pituitary adenomas in females. Reductions in mammary gland and pituitary tumors may have contributed to the increase in longevity of animals administered ICI 182,780.

Study number: TCR/2683
Volume #, and page #: \N_000\2001-10-29\TCR2683 Complete Report

Conducting laboratory and location:

Test Facility:	Test Site:	Test Site:
(*in vivo* study)	(Pharmacokinetics)	(Electron Microscopy)
[redacted]	AstraZeneca UK Ltd	AstraZeneca UK Ltd
	DMPK Mereside Alderley Park	Safety Assessment Alderley
	Macclesfield, Cheshire England	Mereside Alderley Park Macclesfield, Cheshire England

Date of study initiation: 10 November 1998
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity:

ICI 182,780	Bulk Drug	Bulk Drug	LA (IM) Injection	LA (IM) Injection	Vehicle	Vehicle
Batch #	C169/4	C177/2	P/1465/22A	P/1359/4	P/1465/19	P/1359/17
ADM #	00193A98	39679H96	62181D99	39454G97	62077F99	01184F98
Date of Manufacture	12/18/97	11/11/1996	5/19/1999	11/12/1997	5/12/1999	3/11/1998
Date of Analysis	2/18/98	1/13/1997	7/8/1999	2/5/1998	6/25/1999	6/3/1998
Strengh (HPLC)					-	-

CAC concurrence: Yes

Study Type: 104 weeks in albino rats; IM administration to the lateral compartment of the thigh (dose was divided in two parts (up to 0.1 mL) and administered on the right and left side).
Species/strain: male and female Sprague Dawley (Crl:CD(SD)BR) rats (Rattus norvegicus) from [redacted]

Number/sex/group; age at start of study: 50/sex; 28±1 days old

Animal housing: Individual

Formulation/vehicle: Long acting formulation

Ingredients	Drug %w/v
ICI 182,780	5
Ethanol	10
Benzyl Alcohol	10
Benzyl Benzoate	15
Castor Oil	to 100

Drug stability/homogeneity:

Data from the primary stability studies indicate that fulvestrant is stable at the proposed long term storage condition of [redacted]. In addition no significant change (as defined by ICH guideline Q1A) has been observed after 6 months storage at the accelerated storage condition of [redacted] nor after 12 months storage at the intermediate accelerated storage conditions of [redacted] and [redacted].

Methods:

Doses:

Group No. Identification	Dose Levels	Dose Volume	Animal number	
			Males	Females
1 Vehicle control	0 mg/kg/15 days	0.2 mL/rat	1001-1029, 1031-1051	1501-1550
2 Vehicle control	0 mg/kg/30 days	0.2 mL/rat	2001-2050	2501-2550
3 Saline control	0 mg/kg/15 days	0.2 mL/rat	3001-3050	3501-3550
4 ICI 182,780	15 mg/kg/30 days[a]	0.3 mL/kg	4001-4050	4501-4550
5 ICI 182,780	10 mg/rat/30 days	0.2 mL/rat	5001-5050	5501-5550
6 ICI 182,780	10 mg/rat/15 days	0.2 mL/rat	6001-6050	6501-6550
7 Health screen	-	-	7001-7010	7501-7510

a Dosage limited by maximum injection volume of 0.2 mL/rat
* Control Male 1030 replaced by Male 1051 following mortality during replacement period

The following shows the ~ actual dose (mg/kg) administered to Groups V (10 mg/rat/30days) and Group VI (10 mg/rat/15 days).

	Male					Female				
	BW (g)	~Actual dose	BW (g)	~Actual dose	~Actual dose	BW (g)	~Actual dose	BW (g)	~Actual dose	~Actual dose
Week	10 mg/rat/ 30 days	mg/kg/ 30 days	10 mg/rat/ 15 days	mg/kg/ 15 days	mg/kg/ 30 days	10 mg/rat/ 30 days	mg/kg/ 30 days	10 mg/rat/ 15 days	mg/kg/ 15 days	mg/kg/ 30 days
0	192.3	-	187.5	-	-	152.9	-	153.2	-	-
1	262.9	38	257.8	39	78	184.7	54	185.7	54	108
48	830.5	12	787.3	13	26	487.8	21	507.3	20	40
96	793	13	781.5	13	26	580.3	17	574.4	17	34
104	795.8	-	782.3	-	-	559.6	-	577.4	-	-

Basis of dose selection: According to the Sponsor, the dose levels selected represent the maximum possible doses by the intramuscular (IM) route based on strength of the formulation and injection volumes.

Restriction paradigm for dietary restriction studies: n/a

Route of administration: IM injection
Frequency of drug administration: every 15 or 30 days
Dual controls employed: Vehicle and saline controls included
Interim sacrifices: n/a
Satellite PK or special study group(s): None
Deviations from original study protocol: Occasional minor deviations from the protocol occurred and were documented in the raw data and/or text. The Sponsor reports these deviations had no impact on the outcome of the study or upon the interpretation of the results.

Statistical methods:
First the Levene's test was used to assess the equality of the group variances followed by ANOVA if this test was not significant. If the Levene's test was significant, then the statistical analyses were performed on the ranked transformed data.
Survival Analysis: An overall test for homogeneity was performed on the survival functions of all 6 groups.
Tumor Data: All tests for tumour incidence were one-sided looking for an increase in response/incidence. The Haseman (1983) principle of statistical significance was adopted in the formal assessment of statistically significant effects. One-sided 5% tests for decreasing response/incidence were also performed.
The statistical comparisons of interest were implemented using Peto's survival-adjusted trend test. Statistical comparisons were performed in three phases:
Phase 1: Vehicle effect with dosing every 15 or 30 days: Both the 15-day and 30-day vehicle groups (Groups 1 and 2) were compared to the saline control group (Group 3).
Phase 2: Treatment effect for each dosing frequency: Two vehicle groups (Groups 1 and 2) and the two 10 mg/kg groups at 15 and 30 days frequency (Groups 5 and 6, respectively). Treatment groups were then compared to the appropriate vehicle separately for each dosing frequency.
Phase 3: Dose effect over the 30 day dosing regimen: Group 2 (vehicle/30 days) was compared with the 15 mg/kg/30 days treatment group (Group 4).

Observations and times:

Clinical signs:	Twice daily for mortality and clinical signs. A complete physical examination was performed once during the pretreatment period and weekly during the treatment period. In addition, from Week 26 onwards, all animals were examined for the presence of palpable masses during the detailed examination.
Body weights:	Weekly.
Food consumption:	Weekly for the first 13 weeks of treatment, then monthly, thereafter.
Hematology:	Red blood cell counts and total and differential white blood cell counts were performed at 12 and 18 months and at terminal necropsy.
Clinical chemistry:	Not obtained
Organ weights:	Not obtained

Gross pathology: A gross pathological examination was performed on all animals on this study.

Histopathology: Tissues, as defined in the protocol, were examined histopathologically for all animals on this study. See addendum.

Toxicokinetics:

Groups 4 and 5 (n=3/sex) were bled at 2, 4, 8, 12, 16 and 24 days post dose after the 12th dose. Samples were also taken from 6 rats/sex (Groups 4 and 5) prior to the the 2nd, 4th, 7th and 10th dose.
Group 6 (n=3) were bled at 2, 4, 8, 12, 16 and 24 days after the 23th dose. Samples were also taken from 6 rats/sex from the same group prior to the 3rd, 7th, 13th and 19th dose.

Results:

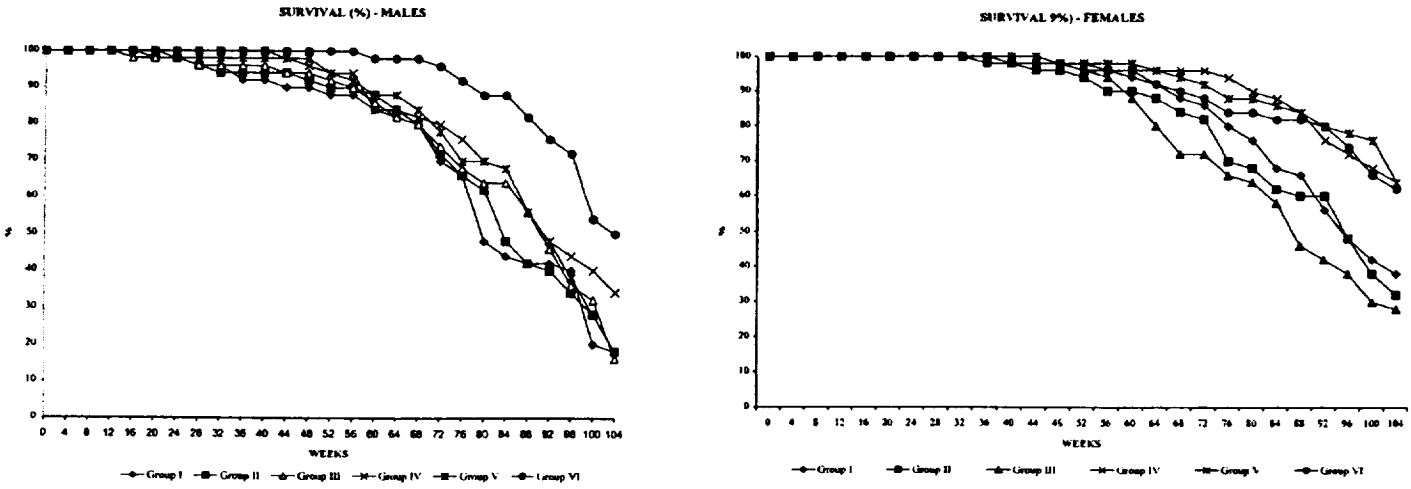
Mortality:

	Group	Dose	Dose * (mg/kg/30 days)	Frequency (days)	Survival			
					Males (n=50)	% Survival	Females (n=50)	% Survival
1	Vehicle Control	0 mg/kg	0	15	9	18	19	38
2	Vehicle Control	0 mg/kg	0	30	9	18	16	32
3	Saline Control	0 mg/kg	0	15	8	16	14	28
4	ICI 182,780	15 mg/kg	15	30	17	34	32	64
5	ICI 182,780	10 mg/rat/	♂:76 ♀:104	30	13	26	32	64
6	ICI 182,780	10 mg/rat/	♂:78 ♀:104	15	25	50	31	62

* The ~ actual dose administered for group V and VI was calculated based on the average weight for males and females on day 1.

For control males, survival rates appear lower than expected. In 1997, according to the [redacted], the % surival for male and female SD rat ranged 31.7-61.9% and 31.7-61.4%, respectively. In this study, the overall survival rate ranges between 17.1-62.9 and 24-61.4% for male and females rats, respectively.

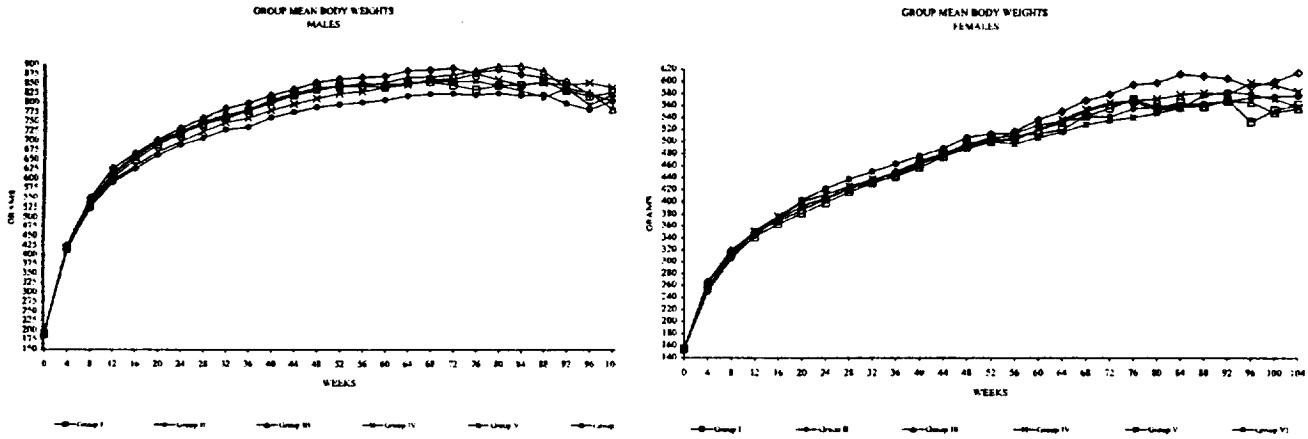
Percent survival as a function of time (weeks) in ♂ and ♀ SD rats.



Clinical signs: There were no treatment-related clinical signs, however a number of animals from all treated groups and from control animals in Groups 1 and 2 (vehicle), exhibited cysts at the injection sites.

Body weights: Overall body weights throughout the study were not affected by treatment. Occasional statistically significant variations in body weight gain across all groups (both sexes) were considered incidental.

Body weight (g) as a function of time (weeks) for ♂ and ♀ SD rats.



Food consumption: A statistically significant reduction (7-14%) in food consumption was observed in both male and female animals from all treated groups, the effect being most pronounced in female rats. Effects were noted from Week 2 for females but did not become apparent in male rats until Week 20. In neither sex did the reduction in food consumption result in a decrease in terminal body weight.

Hematology: RBC levels were elevated in drug-treated females. *p<0.05

RBC x $10^3/mm^3$	Week 52	Week 78	Week 105
veh/15d	7.08	6.06	5.77
veh/30d	6.97	6.52	5.82
saline	6.97	6.75	6.35
15 mg/kg	7.32 (↑5%)*	6.64 (↑2%)*	6.66 (↑14%)*
10 mg/rat/30d	7.53 (↑8%)*	7.2 (↑10%)*	6.84 (↑18%)*
10 mg/rat/15d	7.7 (↑9%)*	7.35 (↑21%)*	6.78 (↑18%)*

There were no changes in hematology parameters that were considered to be related to treatment with ICI 182,780.
Minor differences of some parameters, occasionally statistically significant, were considered incidental and unrelated to treatment with ICI 182,780

Clinical chemistry: No clinical chemistry was included.

Organ weights: Organs were not weighed

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