Study title: ICI 182,780: One Month Intramuscular Toxicity Study in Rats.

Key study findings:

- Females exhibit histological changes in the ovaries (absent or reduced corpora lutea, multiple follicular cysts, luteal cysts, hemorrhagic Graafian follicles and hemorrhagic corpora lutea), uterus (atrophy), cervix (atrophy) and vagina (atrophy).
- There are no differences in the incidence or severity of the histological changes observed in rats administered ICI 182,780 alone or in combination with sulphone. These changes appear to be related to the anti-estrogenic activity of the compound.

Study no: TAR/2972
Volume #, and page #: N_000\2001-03-28\pharmtox\tox\Dose\ TAR/2972

Conducting laboratory and location: AstraZeneca UK Limited Safety Assessment Alderley Alderley Park Macclesfield Cheshire SK10 4TG England
Date of study initiation: April 21, 1999
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Batch # P/1465/28, P/1465/26, P/1465/29, 99.9% w/w
Formulation/vehicle:

Ingredients	Strength placebo	Strength 2 % w/v	Strength 1.96 % w/v
	% w/v	% w/v	% w/v
ICI 182780	-	2.0	1.96
ICI 182780 sulphone	-	-	0.04
Poloxamer 407 USNF	1.0	1.0	1.0
Ethanol 96 % BP	10.0	10.0	10.0
Water for Injection Ph Eur	8.0	8.0	8.0
Propylene glycol	to 100 %	to 100 %	to 100 %
Formulation batch reference	P/1465/28	P/1465/26	P/1465/29

Methods: This study compares the toxicity of ICI 182,780 2% SA (short acting) formulation and a ICI 182,780 1.96% (with 0.04% sulphone) SA formulation administered intramuscularly to the rat once daily for 28 days. Note: The sulphone derivative is a degradation product of ICI 182,780 formulations and is a minor metabolite in the rat after IM administration. The results of this study are intended to support the final specification for sulphone content in ICI 182,780 parenteral formulations. The dose level selected for the study of 5 mg/kg/day (30 mg/m^2) x 28 days = 140 mg/kg (840 mg/m^2) is ~ 30x-(5x) the proposed human dose of 250 mg/30 days (4.17 mg/kg or 154.3 mg/m^2).

Dosing:

Species/strain:	Alpk: APfSD -Wistar derived rats
#/sex/group or time point (main study):	10/sex/group
Satellite groups used for toxicokinetics:	3/sex/group
Age:	37-41 days old
Weight:	127-217 g
Doses in administered units:	0, 5 mg/kg/d, and 5 mg/kg/d ICI 18270 + 0.4 mg/ml sulphone. Daily x 28 days

Route and volume:	IM; 0. 025 ml/100 g

Observations and times:

Clinical signs:	Twice daily
Body weights:	Day -7, pre- study, first day of dosing and then weekly for the remainder of the study.
Food consumption:	Daily
Ophthalmoscopy:	Pre-study and week 4
Hematology:	At scheduled necropsy. Blood samples for coagulation analyses were taken from designated 5/animals/group at scheduled necropsy (day 29)
Clinical chemistry:	At scheduled necropsy (day 29)
Urinalysis:	At scheduled necropsy (day 29)
Gross pathology:	Day 29
Organs weighed:	Adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate gland, spleen, testes (including epididymides), thymus and uterus.
Histopathology:	Day 29
Toxicokinetics:	Pre-dose and 1, 3, 6, 12, and 24 hours on day 28. The AUC_{0-24} of ICI 182,780 and the AUC_{0-12} of the circulating metabolites (ZM208,917 sulphone and ZM366,472 17- ketone) for the male and female rats were compared within and between each dose group.

Results:

Mortality:	One ♂ animal dosed 5 mg/ kg ICI 182,780 with Sulphone, from the pharmacokinetic sub- group, died (day 5) as the result of an accident. The Sponsor did not indicate the nature of the accident. Necropsy findings included minimal focal acute myositis and minimal multifocal adjacent tissue acute inflammatory cell infiltration at the injection site. Also, mild unilateral hydronephrosis and minimal focal cortical tubular basophilia
Clinical signs:	Clinical observations included swelling of the hind limbs with associated transient limping in several animals in all groups including controls from day 3 to 24. The Sponsor considers this effect a consequence of exposure to the excipients and not ICI 182,780.
Body weights:	Males from both groups dosed with ICI 182,780 showed an approximate 10% body weight gain reduction when compared to control group. All females gained weight at a similar rate throughout the dosing period.
Food consumption:	Unremarkable (UR)
Ophthalmoscopy:	UR
Hematology:	Values represent percent change from control.

	Males			Females		
	Control	II[A]	III[A]	Control	II[A]	III[A]
Hemoglobin (g/dl)	15.3		↓4*	14.6	↑7*	
RBC ($x10^{12}$/l)	8.2		↓4*	7.6	↑8*	↑7*
Reticulocytes (%)	3.05		↑5*	3.29	↓11	↓8
Hematocrit (l/l)	0.48		↓4*	0.45	↑7	↑4*
MCV (fl)	59.6			59.3		↓4*
MCH (pg)	19			19.2		↓5*
Platelets (10^9/l)	974	↑11*	↑9*	938	↑9	
WBC (10^9/l)	8.6		↑14*	7.4		↑11
Neutrophil (%)	1.5	↑19	↑35*	1.53	↑10	↑56

[A] Group II-drug + sulphone; Group III-drug alone
*P<0.05

Clinical chemistry: Values represent percent change from control.

	Males			Females		
	Control	II[A]	III[A]	Control	II[A]	III[A]
Glucose (mmol.l)	14.6	↓16	↓18*	12.3		
Urea (mmol/l)	6.3			6.6	↓9	↓11*
Albumin (g/l)	30		↓7*	32	↓6*	↓9*
A/G Ratio	1		↓12*	1.1	↓16*	↓15*
T. calcium (mmol/l)	3.28		↓7*	3.14		1
ALP (IU/l)	344		↓8*	182	↑60*	↑41*
Triglycerides (mmol/l)	1.05		↓23*	0.68	↑19	↑35*

[A] Group II-drug + sulphone; Group III-drug alone
*P<0.05

Urinalysis: UR

Organ weights: At necropsy, there was a decrease in median body weight of male rats in Group II (11%) and in Group III (16%) given ICI 182,780. Thus, some absolute organ weights for male rats in these groups showed significant differences from the control values. The Sponsor considers these changes to be of no toxicological importance.
Median relative uterine weight was decreased by 79% for females in Group II and III given ICI 182,780.

Gross pathology:

Gross pathology findings	Group II[A]	Group III[A]
ovaries showed pale discoloration with red foci	5/10	8/10
cervix were thin/ small	4/10	3/10
uterus were thin/ small	10/10	9/10

[A] Group II-drug + sulphone; Group III-drug alone

Histopathology:

Females	**Control**	**II[A]**	**III[A]**
Cervix: Severe Atrophy		10/10	10/10
Ovaries			
No corporea lutea		5/10	7/9
Reduced corporea lutea		5/10	1/9
Follicular Cysts		9/10	8/9
Luteal Cysts			1/9
Hemorrhagic Corporea Lutea			1/9
Hemorrhagic Graafian follicles		2/10	9/9
Uterus: Severe Atrophy		10/10	10/10
Vagina: Epithelial Severe Atrophy	0/10	10/10	9/9
Estrus	5/10	0/10	0/9

Injection site-acute myositis Adjacent tissue acute inflammatory cell infiltration	5/10 0/10	5/10 4/10	5/10 7/10
Sciatic nerve-adjacent acue inflammatory cell infiltration	0/10	5/10	7/10
Males	**Control**	**II[A]**	**III[A]**
Epididymides-Chronic epididymitis	4/10	0/10	3/10
Injection site-acute myositis Adjacent tissue acute inflammatory cell infiltration	3/10 1/10	4/10 4/10	5/10 5/10
Sciatic nerve-adjacent acue inflammatory cell infiltration	0/10	0/10	2/10

[A] Group II-drug + sulphone; Group III-drug alone

Toxicokinetics:

	ICI 182,780		ZM 208,917[A]				ZM 366,472[B]			
	Group II*	Group III	Group II*	Group II*	Group III	Group III	Group II*	Group II*	Group III	Group III
	Combined	Combined	♂	♀	♂	♀	♂	♀	♂	♀
AUC $_{(0\text{-}12,24)}$** (ng*h/ml)	3300	3270	205	333	122	194	NC	104	NC	92.0
C_{min} (ng/ml)	48.2	43.4	3.76	4.52	<2.00	<2.00	NC	7.43	NC	5.07
C_{max} (ng/ml)	337	251	25.4	38.0	12.4	24.9	NC	15.6	NC	13.2
T_{max} (h)	1.00	3.00	1.00	1.00	6.00	3.00	NC	3.00	NC	3.00

*with 0.04% sulphone; ** ICI 182.780 was measured 0-24 and ZM 208,917 and ZM 366,472 were measured 0-12

[A] ZM208,917 is a sulphone metabolite

[B] ZM366,472 is a 17-ketone metabolite only demonstrated in females.

- There was no difference in exposure to ICI 182,780 between the sexes or between the groups given ICI 182,780 alone or in combination with sulphone.
- Absorption appeared faster in animals given ICI 182,780 and sulphone compared to administration of the drug alone. That is, on day 28, C_{max} for ICI 182,780 occurred at 1 h post-dose (t_{max}) for Group II (drug + sulphone) compared to 3 h post-dose for Group III (drug alone).
- Exposure to ZM208,917 (sulphone metabolite) was slightly greater in females compared to males (Group II and III : 62% and 59%, respectively).
- Exposure to ZM208,917 (sulphone metabolite) was approximately 70% greater in animals given ICI 182,780 in combination with sulphone than in animals given ICI 182,780 alone.
- There was a significant difference between the sexes in the $AUC_{0\text{-}12}$ of ZM366,472 (ketone metabolite) with male rats showing no systemic exposure. However, there was no difference between the $AUC_{0\text{-}12}$ of ZM366,472 of Groups II and III females.

Summary of individual study findings:

Study TAR/2972 compares the toxicity of the ICI 182,780 formulation (2% ICI 182,780-SA) and a ICI 182,780 formulation (SA) spiked with sulphone (1.96% ICI 182,780 with 0.04% sulphone), when administered intramuscularly to the rat once daily for 28 days. The sulphone derivative is the main degradation product of ICI 182,780 formulations and is a minor metabolite in the rat.

Pharmacokinetic monitoring demonstrated no difference in exposure to ICI 182,780 between the sexes or between the groups given ICI 182,780 alone or in combination with sulphone. Exposure to ZM208,917 (sulphone metabolite) was greater in females compared to males and ~ 70%

greater in animals given ICI 182,780 in combination with sulphone than in animals given ICI 182,780 alone (the increase in exposure probably due to administered ZM208,917). Exposure to ZM366,472 (ketone matebolite) was observed only in females.

Changes seen in animals given ICI 182,780 (alone or in combination with sulphone) were related to the anti-estrogenic activity of the compound. The changes seen included a 10% reduction in body weight gain in males and histological changes in the ovaries (absent or reduced corpora lutea, multiple follicular cysts, luteal cysts, hemorrhagic Graafian follicles and hemorrhagic corpora lutea), uterus (atrophy), cervix (atrophy) and vagina (atrophy). There were no differences in the incidence or severity of histological changes between the two groups.

Study title: ICI 182,780 : SIX MONTH INTRAMUSCULAR TOXICITY STUDY IN RATS.

Key study findings:

- Atrophy of the female reproductive tract; a specific constellation of ovarian alterations with increased late stage and cystic Graafian follicles, loss of mature corpora lutea and reduced vacuolation of the interstitial cells.
- A loss of spermatozoa from the seminiferous tubules with an accompanying dilatation, seminiferous tubular atrophy with some associated degenerative changes in the epididymides.
- Conversion of specific tissues in females to the morphology normally seen in males including mammary gland structure, splenic hemosiderosis, pituitary gonadotroph vacuolation and reduced hair loss and an earlier appearance of adrenal cortical congestion with hemocyst formation.

Study no: TPR/2042.
Volume #, and page #: N_000\2001-03-28\pharmtox\tox\Dose\ TAR/2972\TPR/2042.
Conducting laboratory and location: ICI Pharmaceuticals Safety of Medicines Department Alderley Park Macclesfield Cheshire England
Date of study initiation: April 2, 1992
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: ICI 182,780; ADM 44010/89; 98.8%
Formulation/vehicle: Sustained release LA formulation

Ingredients	Strength w/v%	Placebo w/v%
ICI 182,780	5.0	0
Ethanol 96% v/v	10.0	10.0
Benzyl Alcohol	10.0	10.0
Benzyl Benzoate	15.0	15.0
Castor Oil	To 100	To 100
Batch number	PH/6731/41	PH/6731/40
Analytical Number	ADM 48027/90	ADM 48026/90

Methods:
Dosing:

Species/strain: CR1:(WI)BR Wistar rats

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