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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-344

Pharmacology Review(s)

Pharmacology/Toxicology Review of NDA 21-344

Date: 5 Mar. 2002

From: David E. Morse, Ph.D.
Supervisory Pharmacologist
Div. of Oncology Drug Products, HFD-150

To: Robert Temple, M.D.
Director, Office of Drug Evaluation I

Through: Richard Pazdur, M.D.
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Cc: Grant Williams, M.D., Dep. Dir., DODP (HFD-150)
Lilliam A. Rosario, Ph.D., Pharm./Tox., DODP (HFD-150)

Subject: NDA 21-344
FASLODEX®® Injection (fulvestrant)
Secondary Review of Pharm./Tox. Information and Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-344, written by Lilliam A. Rosario, Ph.D.

II. Background

The sponsor (AstraZeneca Pharmaceuticals, LP.) is seeking approval of FASLODEX® (injection) for use in Draft

FASLODEX® (fulvestrant) is a modified steroid, which binds competitively to the estrogen receptor (ER), with an affinity approximately comparable to that of estradiol. Fulvestrant acts as a competitive inhibitor of the activation of the ER by estradiol, and thereby inhibits the growth of ER+ dependent tissues.

III. Comments and Conclusions

1. A review of NDA 21-344, FASLODEX® Injection (fulvestrant), indicates the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies (including: acute and repeat-dose (IM) toxicology studies up to 6 and 12 months in rats and dogs), reproductive toxicity tests in rats and rabbits (Segments I-III; ICH endpoints A-F), genotoxicity tests (in vitro and in vivo), and in two carcinogenicity bioassays (in mice and rats), for approval in the treatment of postmenopausal women with locally advanced or metastatic breast cancer who have previously been treated with endocrine therapy. It should be noted that the carcinogenicity testing and full spectrum of reproductive toxicity studies performed by the sponsor were not deemed necessary by the Review Division for potential product use in a postmenopausal patient population with advanced neoplastic disease.

2. Specific comments pertaining to the product review follow.

Genotoxic and Carcinogenic Potential:

In a 2-year carcinogenesis study in rats (male and female), an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-estrogen. Fulvestrant showed no antigenic, mutagenic, or clastogenic potential in a standard battery of genotoxicity tests when evaluated at doses or concentrations appropriate to the assay.

Following review of the carcinogenicity data by the Executive Committee of the CAC (Carcinogenicity Assessment Committee), it was recommended by the executive committee that the sponsor be asked to conduct a P32 post-labeling assay for the formation of DNA adducts by fulvestrant (or its' metabolites). This request was apparently based on previous experience with tamoxifen (a related competitive inhibitor of the ER), which when tested for carcinogenic potential yielded positive results in multiple hormonally dependent tissues and caused an increased incidence of hepatic tumors (which could not be explained as dependent upon ER activity). When subsequently tested in the P32 post-labeling assay, it was found that exposure to tamoxifen resulted in the formation of DNA adducts (a likely explanation for the increased incidence of hepatic tumors).

As stated above, dosing with fulvestrant for up to 2 years resulted in an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. There was no evidence in the study of fulvestrant for the increased induction of tumors in any non-hormone dependent/sensitive tissue. Furthermore, fulvestrant showed no mutagenic or clastogenic potential in a standard battery of genotoxicity tests. Based on this data, it does not appear that further testing of the genotoxic potential of fulvestrant is necessary for product approval.

Mechanism of Action:

Fulvestrant binds ER in a competitive manner, with a high affinity comparable to that of estradiol. The Sponsor claims that "Fulvestrant is a potent antiestrogenic agent, which acts by down-regulation of the estrogen receptor (ER) inducing a rapid loss of ER protein from breast cancer cells. Preclinical studies demonstrated that fulvestrant is a potent, reversible inhibitor of the growth of estrogen- sensitive human breast cancer cells and of tamoxifen- resistant breast cancer cells in vitro. The sponsor appears to be intending to use this data as support for defining fulvestrant as a new class of antiestrogen, one that acts via a new mechanism. However, several issues, which should be considered as part of this topic, are outlined in the following paragraphs.

A) In a study by Robertson et. al. (2001), it was found that immuno-reactive ER was reduced in tissues taken from postmenopausal women with breast cancer, who were treated with either fulvestrant or tamoxifen prior to surgery. While the dosing interval was limited in duration, this data does not appear to support the sponsor's contention that fulvestrant functions via a new and unique mode of action (dissimilar to the mode of action of tamoxifen).

B) Throughout the MOA studies conducted by the sponsor, ER protein levels were measured by an indirect immuno-reactive assay methodology, as compared to direct receptor isolation/purification and protein analysis. Furthermore, the sponsor did not provide affinity data for the specificity of the ER antibodies, or data for effects of conformational changes that might occur with bound fulvestrant, tamoxifen or estradiol, and how this might alter antibody binding to the ER. It is therefor recommended that the product label clearly specify that ER protein was measured via an immuno-reactive assay (vs. direct protein measurement).

Taken together, these data do not appear to support the sponsors' contention that fulvestrant functions through a unique mode of action (i.e., ER protein down-regulation), which is independent of the mode of action of tamoxifen.

3. Specific comments pertaining to the product label follow.

   A review of the draft product label suggests that it adequately reflects the non-clinical safety profile of fulvestrant injection.

IV. Summary

A review of the action package for NDA 21-344, FULVESTRANT® Injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for potential approval in the [redacted] There are no unresolved issues or requests to be directed to the sponsor for this indication.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Morse
4/22/02 12:52:35 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY COVER SHEET

Executive Summary

I. Recommendations

A. Recommendation on Approvability: The non-clinical studies adequately support the use of fulvestrant (FASLODEX), by the intramuscular route, for

B. Recommendation for Nonclinical Studies: None

C. Recommendations on Labeling: Please refer to Appendix B on page for 144 for labeling recommendations on the Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy, Nursing Mothers, and Warning sections of the product label.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Multiple non-clinical toxicity studies of up to 6 and 12 months duration in rats and dogs, genotoxicity, carcinogenicity, antigenicity, and local tissue irritancy effects were submitted to support the use of fulvestrant (IM) in the treatment of locally advanced and metastatic breast cancer in post-menopausal women.

The high doses used in the long-term studies in rats (10 mg/rat/15d for 6 months) and dogs (40 mg/kg/28d for 12 months), based on body surface area conversion were approximately 4 fold higher than the proposed clinical dose of 250 mg/month. Drug exposure ($AUC_{0\text{-}28,\ 30\ days}$) ranged from 4-10 fold and C_{max} ranged from 9-38 fold higher in the longest duration toxicology studies than the values observed in clinical testing.

Fulvestrant was well absorbed and widely distributed following IM administration in rats. Metabolism was qualitatively similar in rats, dogs, and human with the primary route of elimination in feces. Fulvestrant crosses the placenta following single intramuscular doses of 6.0 mg/m^2 in rats and 3 mg/m^2 in rabbits resulting in fetal tissue drug concentrations 2 hours after dosing of 76 and 97% compared to maternal plasma, respectively. Fulvestrant is found in rat milk at levels significantly higher than in rat plasma (12-fold after administration of 12 mg/m^2). The maximal drug exposure in rat pups from ICI 182,780-treated lactating dams was estimated as 10.3% of the administered dose.

In all the intramuscularly dosed toxicology studies, effects upon the reproductive tract and other organs sensitive to estrogens were observed, consistent with the proposed mechanism of action of fulvestrant. In female rats and dogs, atrophy of the uterus, cervix, and vagina with a loss of normal cyclical estrous activity was observed. In the ovary increased late stage and cystic Graafian follicles, loss of mature corpora lutea,

and reduced vacuolation of the interstitial cells were observed. There was some evidence of reversibility of these ovarian changes (but not complete recovery) following dose cessation up to 20 weeks duration. In male rats, after 6 months dosing, a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides were seen. There was an incomplete recovery of changes in the testes and epididymides after a 20-week recovery period.

In female rats, fulvestrant (≥0.06 mg/m^2/day) administered prior to mating and until day 7 of gestation, caused a reduction in female fertility and embryonic survival. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.006 mg/m^2/day. Restoration of female fertility was evident following withdrawal of dosing at 12 mg/m^2/day. Further, a dose of 12 mg/m^2/day during organogenesis resulted in maternal vaginal bleeding, and delay and prolongation of parturition in rats. There was an increase incidence of post-implantation loss in rabbits receiving levels of ≥3 mg/m^2/day during organogenesis.

Fulvestrant caused an increased incidence of fetal abnormalities in rats. Tarsal flexure of the hindpaw at 12 mg/m^2/day and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses ≥ 0.6 mg/m^2/day were observed when fulvestrant was administered during the period of organogenesis. Fulvestrant also caused an increased incidence of fetal abnormalities in rabbits (backwards displacement of the pelvic girdle, extra 13th ribs, and 27 pre-sacral vertebrae at 3 mg/m^2/day) when administered during the period of organogenesis. This study in rabbits was considered inadequate to fully define possible adverse effects on fetal development due to the lack of maternal toxicity at the highest dose (3 mg/m^2/d) and incomplete fetal assessment at the low and intermediate doses tested.

Fulvestrant showed no antigenic, mutagenic, or clastogenic potential. However, in a 2-year carcinogenesis study in female and male rats, an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-estrogen.

B. Pharmacologic Activity

Pharmacology studies show that fulvestrant binds to estrogen receptors in a competitive manner, with affinity comparable with that of estradiol. The drug's mode of action appears to lead to downregulation of estrogen receptor protein. Fulvestrant is a reversible inhibitor of the growth of estrogen-sensitive human breast cancer (MCF-7) cells and tamoxifen-resistant MCF-7 cells *in vitro.* Fulvestrant blocks the uterotropic actions of endogenous and exogenous estrogens in rodents and monkeys, and of tamoxifen in the rat. In a series of *in vivo* xenograft studies, fulvestrant prevents the establishment of tumors from xenografts of human breast cancer (MCF-7) cells in nude mice, inhibits the growth of established estrogen-sensitive MCF-7 xenografts and-inhibits the growth of tamoxifen-resistant breast tumors.

C. Nonclinical Safety Issues Relevant to Clinical Use:

The Sponsor's description of the mechanism of action of fulvestrant is adequately supported by the data submitted. However, it is noteworthy that both *in vitro* (Brunner et al., 1997) and *in vivo* (Osborne et al. 1995), it has been shown that tumors which eventually develop resistance to fulvestrant will not subsequently respond to tamoxifen. Thus, a treatment sequence in which ICI 182,780 precedes tamoxifen may not be indicated. It is recommended that this information be included in the label since it has repercussions for indications in which patients may be treated first with fulvestrant.

In meeting to discuss the carcinogenic potential of Fulvestrant (December 4, 2001), the Executive Carcinogenicity Assessment Committee noted that while fulvestrant appears to have a negative profile for genotoxicity potential on a standard battery of tests, the Sponsor did not perform all of the defining studies (similar to Tamoxifen) to determine fulvestrant is not genotoxic. 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. We agree that a ^{32}P post-labeling study will be valuable in assessing possible genotoxic potential of Fulvestrant. However, given that the current indication for Fulvestrant Draft [redacted], the request for this study may be postponed. If the indication for Fulvestrant was to change to include any other population, the Sponsor is strongly recommended to conduct a ^{32}P post-labeling study to ensure that Fulvestrant is non-genotoxic.

III. Administrative

/S/

A. Reviewer signature: Lilliam A. Rosario, Ph.D.
Pharmacology-Toxicology Reviewer

B. Supervisor signature: Concurrence - David Morse, Ph.D.
Supervisory Pharmacologist
Non-Concurrence - /S/
(see memo attached)

C. cc: list:
brossp
morsed
rosariol

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21,344

Review number: 1

Sequence number/date/type of submission: 000/3-28-2001/NDA

Information to sponsor: Yes (x) No ( )

Sponsor:
IPR Pharmaceuticals, Inc
1800 Concord Pike P 0 Box 8355
Wilmington, DE 19803-8355

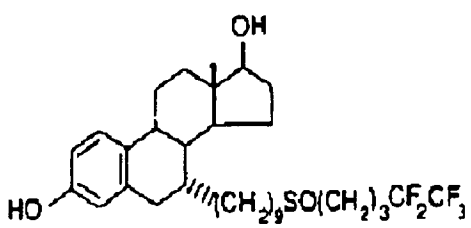
US Agent:
AstraZeneca Pharmaceuticals LP
1800 Concord Pike P 0 Box 8355
Wilmington, DE 19803-8355

Manufacturer for drug substance : AstraZeneca UK Limited
Silk Road Business Park
Macclesfield Cheshire SK10 2NA UK

Reviewer name: Lilliam Rosario, Ph.D.
Division name: Oncology Drug Products
HFD #: HFD-150
Review completion date: December 20, 2001

Drug:

Trade name: Faslodex
Generic name: Fulvestrant
Code name: ICI 182,780, ZD9238
Chemical name: 7α-[9-(4, 4, 5, 5, 5- pentafluoropentylsulfinyl) nonyl] estra-1,3,5(10) triene- 3, 17β-diol.
CAS registry number: 129453-61-8
Mole file number: Not provided
Molecular formula/molecular weight: $C_{32}H_{47}F_5O_3S$ / 606.8
Structure:



Relevant INDs/DMFs: IND [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted]

Drug class: Anti-estrogen

Indication: FASLODEX is indicated for [redacted] Draft

Clinical formulation:

Table 2 Qualitative composition of FASLODEX

Ingredient	Function	Reference to standards
Fulvestrant	Drug substance	See 'Specification of the Drug Substance'
Alcohol	[redacted]	USP
Benzyl alcohol	[redacted]	USNF
Benzyl benzoate	[redacted]	USP
Castor oil	[redacted]	USP

Route of administration: Intramuscular (IM)

Proposed use: FASLODEX™ is a sterile oily solution for deep intramuscular (IM) injection. It is presented in one 5 ml or two 2. 5 ml pre-filled syringes to deliver, as a long acting (LA) injection, the required dose of 250 mg over a 1 month period. FASLODEX contains 50 mg/ml fulvestrant and is administered once monthly.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Primary pharmacodynamics:

Mechanism of action:

The Sponsor claims that "Fulvestrant is a potent antiestrogenic agent, which acts by downregulation of the estrogen receptor (ER), a mechanism that induces a rapid loss of ER protein from breast cancer cells. Fulvestrant binds ER in a competitive manner, with a high affinity comparable to that of estradiol. Preclinical studies demonstrated that fulvestrant is a potent, reversible inhibitor of the growth of estrogen- sensitive human breast cancer cells and of tamoxifen- resistant breast cancer cells in vitro. Fulvestrant prevents the establishment of tumors from xenografts of human breast cancer cells in nude mice, inhibits the growth of established estrogen- sensitive xenografts and inhibits the growth of tamoxifen- resistant breast tumors in vivo. 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. In studies with immature female rats, fulvestrant blocked the uterotrophic action of estradiol and the estrogenic (partial agonist) effect of tamoxifen."

Drug activity related to proposed indication:

- Downregulation of the estrogen receptor (ER) inducing a rapid loss of ER protein from breast cancer cells (from review Wakeling, 2000).

"*"In contrast to the partial agonists, studies of the mode of action of the pure antioestrogens, ICI 164384 and ICI 182780, have produced a consensus that the ability of the ER to activate or inhibit transcription in a ligand-dependent or -independent manner in vivo is completely attenuated by ICI 1643S4 and ICI 182780 (Wakeling 1995). Multiple changes in ER function following pure antioestrogen treatment appear to contribute to this complete abrogation of oestrogen action (see Fig. 3). These include impaired dimerisation (Fawell et al. 1990, Chen et al. 1999), increased receptor degradation (Dauvois et al. 1992, Nicholson et al. 1995, Borras et al. 1996, Pink & Jordan 1996) and disrupted nuclear localisation (Dauvois et al. 1993, Htun et al. 1999). The rapid loss ('down-regulation') of ER following ICI 164384- or ICI 182780-treatment of cells in culture (Dauvois et al. 1992, Nicholson er al. 1995, Borras er al. 1996, Pink & Jordan 1996), or from the uterus after in vivo treatment (Gibson et al. 1991), is likely to play a major role in abrogating oestrogen action. ER down-regulation would account for the ability of pure antioestrogens to block the activation of ER by other mediators such as dopamine, cAMP and growth factors (Aronica & Katzenellenbogen 1993, Ignar-Trowbridge et al. 1993, Smith et al. 1993, Newton et a!. 1994, El-Tanani & Green 1997)"*

"*...As a consequence of the 'down-regulation' of ER by ICI 164384 or ICI 182780, the transcription of ER-regulated genes should be completely blocked. This has proved to be the case in cells, in animal models, and in man. In the rat uterus, oestradiol and tamoxifen stimulate the expression of a number of genes, including complement component C3 (Galman et al. 1990), calbindin-D (Blin et al. 1995), IGF-I (Huynh Bc Pollack 1993), and vascular endothelial cell growth factor and c-fos (Hyder et at. 1997). In each case, ICI 164384 or ICI 182780 showed no induction of transcripttion and, when adminstered with oestradiol or tamoxifen, completely blocked oestrogen or tamoxifen induction of these genes. Similarly, these two compounds act as pure anti- oestrogens on the transcription of oestrogen inducible genes in human breast cancer cells in vitro (May et al. 1989, Wise- man et al. 1989, Nicholson et al. 1995), in vivo (Osbome et al. 1995), and in patients with breast cancer (DeFriend et al. 1995)".*

Drug activity related to proposed indication:

Estrogen receptor binding	Displacement curves RBA from the rat uterus	• IC_{50} ICI 182, 780 =9.35 x10^{-9}M; IC_{50} Estradiol=8.32 x 10^{-9} M • Relative Binding Affinity (RBA) ICI 182.780 = 0.89 compared to estradiol RBA=1; RBA tamoxifen= 0.025 (Wakeling and Bowler, 1988). • ICI 182,780 is a competitive inhibitor of estradiol binding to ER (Wakeling et al, 1991) • The RBA of ICI 182,780 for ER was similar to that of estradiol (0. 89 cf estradiol = 1) and exceeded that of tamoxifen by approximately 35-fold.
Inhibition of breast cancer cell growth	MCF-7 (ER positive) and BT 20 (ER negative) cell growth inhibition. Flow cytometric analysis of cell cycle and population distribution of MCF-7 cells.	• ICI 182,780 inhibited the growth of MCF-7 cells in a concentration dependent manner (mean IC_{50} 3.1 x 10^{-10} M from 7 experiments). • Estradiol (10^{-10} -10^{-8} M) reversed the growth inhibitory effect of 10^{-8} M ICI 182,780 in a dose-dependent and complete manner. • ICI 182,780 was more potent than ICI 164,384 (non-agonist antiestrogen; IC_{50} values 0.3 vs 1.6 x 10^{-9}) or 4- hydroxytamoxifen or tamoxifen (partial agonist antiestrogens). • BT 20 cells were unaffected by ICI 182,780 (10^{-10} to 10^{-6} M). • ICI 182,780 was not cytotoxic at a concentration 1000-fold greater (1 x 10^{-5} M) than that required for full antiestrogenic activity (1 x 10^{-8} M). • The maximum reduction in cells with ICI 182,780 or ICI 164,384 =80%; tamoxifen or 4-hydroxytamoxifen= 50%. • Analysis of the population distribution of MCF-7 cells after 5 days of exposure to the tamoxifen or ICI 182,780 showed that in tamoxifen-treated cells, the proportion which continued to synthesise DNA was reduced from 82% (control) to 37%, whereas in ICI 182,780-treated cultures, this was reduced to 7 %. • The Sponsor cites studies showing that tamoxifen-resistant cells remain sensitive to the growth inhibitory effect of ICI 182,780 (Brunner et al, 1993; Hu et al, 1993; Wiseman et al, 1993; Lykkesfeldt et al, 1994), whereas ICI 182,780-resistant cells are cross resistant to tamoxifen (Brunner et al, 1997). • It is important to note that given the cross resistance to tamoxifen, tumors which have relapsed during ICI 182,780 treatment may not respond to treatment with tamoxifen, thus, this treatment sequence is not indicated.

<table>
<tr>
<td>Anti tumor effects</td>
<td>Anti- tumor activity in mice bearing tumors derived from grafts of the MCF-7 human breast cancer cell line, or from explants of the human breast tumor-derived solid tumor, Br10 (Ref Wakeling et al 1991).</td>
<td>

Single sc injection of 5 mg of ICI 182,780 blocked the growth of MCF-7-derived human breast tumor xenografts in nude mice for at least 4 weeks.

(Values are mean percent ± SEM, n ≥ 5, of tumor area normalised by reference to the initial area of each tumor preceeding the 4-week treatment period)
<table>
<tr><th>Treatment</th><th>Week 1</th><th>Week 2</th><th>Week 3</th><th>Week 4</th></tr>
<tr><td>Control</td><td>118 ± 9</td><td>114 ± 10</td><td>148 ± 29</td><td>174 ± 35</td></tr>
<tr><td>Tamoxifen</td><td>86 ± 8</td><td>78 ± 8</td><td>56 ± 5</td><td>53 ± 8</td></tr>
<tr><td>ICI 182,780</td><td>90 ± 8</td><td>87 ± 4</td><td>74 ± 4</td><td>82 ± 6</td></tr>
</table>

The magnitude of this effect was comparable with that in animals treated daily with a high dose of tamoxifen (10 mg/kg/day po).
The growth of transplants of the Br10 human breast tumor was suppressed by ICI 182,780 treatment. A single sc injection of 5 mg of ICI 182,780 on the day of tumor implantation, reduced tumor growth compared with controls. This effect was comparable with continuous daily treatment with tamoxifen (10 mg/kg/day po) for 8 weeks.

(Values are mean ± SEM tumor area mm^2 (n = 6-8) for all tumors attaining measurable size by day 50 post-implantation).
<table>
<tr><th>Measurement day</th><th>Control</th><th>Tamoxifen</th><th>ICI 182,780</th></tr>
<tr><td>53</td><td>38 ± 7</td><td>28 ± 5</td><td>17 ± 4</td></tr>
<tr><td>73</td><td>72 ± 16</td><td>37 4</td><td>35 ± 14</td></tr>
<tr><td>80</td><td>86 ± 19</td><td>46 ± 8</td><td>44 ± 10</td></tr>
<tr><td>87</td><td>104 ± 25</td><td>59 ± 7</td><td>50 ± 12</td></tr>
<tr><td>94</td><td>114 ± 28</td><td>66 ± 7</td><td>58 ± 16</td></tr>
<tr><td>OVARIECTOMY</td><td></td><td></td><td></td></tr>
<tr><td>115</td><td>95 ± 25</td><td>63 ± 9</td><td>60 ± 21</td></tr>
</table>

The Sponsor cites studies showing that ICI 182,780 inhibits the growth of tamoxifen-stimulated MCF-7 tumors in nude mice (Osborne et al 1994).
The efficacy of tamoxifen and ICI 182,780 in the treatment of established MCF-7 derived tumors in nude mice, and in preventing the growth of tumors from grafts of MCF-7 cells was compared by Osborne et al (1995). Established tumors were treated either by withdrawal of

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		exogenous estrogen alone, or by estrogen withdrawal and addition of tamoxifen (daily sc 0.5 mg) or ICI 182,780 (weekly sc 5 mg LA). • ICI 182,780 suppressed the growth of established tumors for twice as long as treatment with tamoxifen or estrogen withdrawal. • The median time to progression with estrogen withdrawal alone or with tamoxifen was 97 and 104 days, respectively). The median time to progression with ICI 182,780 was 200 days. • Tumor formation was delayed in ICI 182,780-treated mice compared to tamoxifen-treated mice. • Tamoxifen delayed tumor growth in estrogen-treated mice for 2 months; tumors grew slowly or not at all in mice treated with ICI 182,780. • The tumors which eventually grew out in some ICI 182,780-treated mice were transplanted into new recipient mice and tested for cross-resistance to tamoxifen. These tumors grew independently of estrogen supplementation and in some mice tamoxifen slightly reduced tumor growth rate. Thus, most mice resistant to ICI 182,780 showed cross-resistance to tamoxifen. These results predict that tumors which eventually develop resistance to ICI 182,780 will not subsequently respond to tamoxifen. • Using the mouse MXT M1. 7 mammary carcinoma, ICI 182,780 demonstrated superior efficacy compared with tamoxifen (Parczyk and Schneider, 1996).
Uterotropic and antiuterotropic activity in immature rat	Treatment effects on the weight of the uterus. Treatment effects in neonatal rats on premature opening of the vagina.	• Treatment with exogenous estradiol alone stimulates an up to 5-fold reproducible increase in the wet weight of the uterus with maximum response after 3 days of dosing. The estrogenic potency of ICI 182,780, measured by their uterotropic action, can be compared with estradiol. Similarly, a reduction of uterine weight, in animals treated concurrently with estradiol and test compounds, measures antiestrogenic activity. • In immature rats, ICI 182,780 administered parenterally (2 mg/ kg sc) or orally (5 mg/ kg po) reduced the weight of the uterus below that in vehicle treated controls. • ICI 182,780 had no tropic action on the immature rat uteri. • The same dose(s) of ICI 182,780, when co- administered with a maximally stimulating dose of estradiol (0. 5mg), completely blocked the tropic action of estradiol in a dose- dependent and complete manner. • The parenteral ED_{50}= 0.066 mg/kg sc and the oral ED_{50} was 0. 9 mg/kg. • Tamoxifen, partial agonist, stimulated the growth of the immature rat uterus but to a lesser extent than did estradiol. The uterotropic action of tamoxifen was blocked in a dose-dependent and complete manner by co-administration of ICI 182,780.

		• Estrogen agonists cause premature opening of the vagina and disrupts normal reproductive development in neonatal rats. Estradiol or tamoxifen treatment in the first week of life brought forward the time at which the vagina opens, from ~ the fifth week of life to the second or third week. ICI 182,780 alone had no effect indicating a lack of estrogenic activity in this test. • When co- administered with tamoxifen, ICI 182,780 blocked premature vaginal opening in 9 of 13 rats.
Uterotropic and antiuterotropic activity in mature ovariectomized rat	Treatment effects on the weight of the uterus. Assessment of vaginal cornification	• ICI 182,780 alone did not promote any growth of the uterus. • When co-administered with estradiol, there was a dose- dependent and complete blockade of estrogen-induced uterine growth (ICI 182,780 ED $_{50}$ = 0.07 mg/kg sc; 0.7 mg/kg po). • Since many steroids administered parenterally in oil have a sustained duration of action, the effect of ICI 182,780, as a single sc bolus dose in arachis oil, was tested in ovariectomized rats. • Vaginal cornification in ovariectomized, estrogen (0.5mg)-treated rats was blocked for more than 6 weeks by a single injection of 10 mg of ICI 182,780. • Single 2.5 mg ICI 182,780 im injection blocked vaginal cornification for ~ 4 weeks in ovariectomized rats treated daily with 0.5 mg of estradiol benzoate. • The Sponsor cites reports confirming thecomplete absence of estrogen-like effects of ICI 182,780 on the rodent uterus (Wade et al 1993; Branham et al 1996; Dao et al 1996; Dipippo and Powers 1997; Pillai et al 1999). For example, Wade et al (1993) showed that ICI 182,780 has no uterotropic activity, blocked the uterotropic effect of tamoxifen and had no estrogenic effects on food intake, body weight or estrous behavior. Branham et al (1996) demonstrated that ICI 182,780 blocked tamoxifen-induced developmental toxicity associated with the estrogenic effect of tamoxifen on the rat uterus. Also, showed that ICI 182,780 does not affect postnatal uterine development in the rat.
Uterotropic and antiuterotropic activity in mature ovariectomized mouse	Treatment effects on the weight of the uterus.	• ICI 182,780 alone did not promote any growth of the uterus. • When co-administered with estradiol, there was a dose- dependent and complete blockade of estrogen- induced uterine growth (ICI 182,780 ED_{50} = 0.36 mg/kg sc; ›4 mg/kg po).
Antiestrogenic effects in intact female rats	Treatment effects on the weight of the	• ICI 182,780 reduced the weight of the uterus in a dose-dependent manner (ED_{50} ~ 0.12 mg/kg. • At the highest daily dose used in this study (1 mg/kg), involution of the uterus after 14 days approached that following ovariectomy (90% effect). The maximum involution of the uterus

	uterus. Effects on on cyclical vaginal cornification, body weight gain, serum gonadotrophins and bone density	after 2 or 4 weeks treatment with ICI 182,780 was less than that in rats ovariectomized for a similar period. • Cyclical vaginal cornification was blocked partially (0.1 mg/ kg) or completely (0.3 mg/ kg), but body weight gain and plasma gonadotropin concentrations were largely unaffected by ICI 182,780 treatment. The anticipated increase in body weight gain, plasma LH and FSH and decrease in plasma PRL clearly evident in ovariectomized rats, were not observed in ICI 182,780- treated rats. • ICI 182,780 (castor oil formulation) IM x 28 days of treatmen reduced the weight of the uterus in a dose- dependent manner (ED_{50} = 0.11 mg/kg). • The maximum antiuterotropic effect of ICI 182,780 after 28 days approached ovariectomy (90% and 86% with 1 and 3 mg/kg doses; OVX control). • Cyclical cornification of the vagina was blocked at the 0.3 mg/kg dose, although sporadic examples of fully cornified smears were occasionally observed at this dose, but never at the higher 1 or 3 mg/ kg doses. • The absence of any effect of ICI 182,780, at doses up to 3 mg/kg/d, on body weight gain and plasma LH was in contrast to the increase in these parameters in rats ovariectomized at the beginning of the experiment. Similarly, at a daily dose of up to 3 mg/kg, ICI 182,780 had no effect on bone gross density or mineral density, whereas there was a significant decrease in bone density in ovariectomized rats.
Antiestrogenic activity in ovariectomized, estrogen-treated monkeys	Visual scoring of perineal swelling. Quantitative MRI to measure the volume of the endometrium and myometrium.	• Based on the scoring of perinal swelling, it was shown that ICI 182,780/kg (daily x 10 days; 0.1, 0.5 or 1 mg), prior to estrogen treatment, delayed the onset of perineal swelling by~ 1, 2, and 5 weeks, respectively. • A single dose of 10 mg ICI 182,780 sc was similarly effective for 3 to 4 weeks. • ICI 182,780 antagonizes estrogen-stimulated growth of the endometrium and myometrium in the adult ovariectomized monkey as measured with MRI. • Single ICI 182,780 (2.5 to 5 mg/kg IM LA) blocked the uterotropic action of exogenous estradiol for 2 to 5 weeks. • Measurements of plasma ICI 182,780 showed that inhibition of the tropic effect of estradiol required drug concentrations in the range 1 to 2 ng ICI 182,780/ml or greater. Extrapolation of this data to humans predicts a monthly IM injection of 200 to 300 mg of ICI 182,780 (50 to 75 kg patient) to achieve therapeutic utility. • Daily dose of 0.1 mg ICI 182,780/kg im (SA) or a monthly dose of 4 mg ICI 182,780/ kg im

		(LA) completely blocked estrogen-stimulated growth of the primate endometrium and myometrium. • Following a 7-day dosing period, the recovery of uterine growth response to estradiol was equally rapid after cessation of treatment with either the 0.1 or 1 mg doses. • In monkeys where the uterus was stimulated with estrogen before beginning ICI 182,780 treatment, a daily dose of 0.2 mg ICI 182,780/kg IM SA, produced involution of the endometrium at the same rate as following estrogen withdrawal.
Antiestrogenic and endocrine effects in adult female monkeys with normal menstrual cycles	MRI measurements of the uterus, in early, mid and late cycle in untreated monkeys Endocrine effects were monitored by the analysis of plasma estradiol, progesterone, and FSH concentrations.	• Ovulation was blocked in 7 of 10 animals treated with ICI 182,780 (0. 1 or 0.2 mg/kg/d SA) and 8 of 12 treated with the long-acting formulation (2.5 or 4 mg/kg monthly). • In monkeys rendered anovulatory by ICI 182,780, treatment decreased endometrium volume to a level comparable with that measured in ovariectomized monkeys suggesting that ICI 182,780 completely blocked the tropic action of endogenous estrogens. In these animals, continued monitoring of plasma estradiol after treatment (days 3 to 27), revealed ovulatory peaks between 3 and 17 days after the final dose of ICI 182,780 (mean 8.4 ± 1.4 days) suggesting that the endocrine effects of ICI 182,780 are reversible. • An estrogen withdrawal-like action on the myometrium was also recorded, where the small decrease in volume of the myometrium in the follicular phase in untreated monkeys was significantly enhanced by ICI 182,780, and was similar in extent to that seen following estrogen withdrawal in ovariectomized monkeys. Myometrial shrinkage was sustained through the luteal phase. • Single IM injection of 4 mg ICI 182,780/ kg LA at the beginning of the menstrual cycle, caused regression of the endometrium and myometrium to the same extent as SA formulation administered daily. The lower dose of 2.5 mg ICI 182,780/kg was also effective, but to a lesser extent than the higher 4 mg dose. • With both formulations of ICI 182,780, antiuterotropic efficacy in monkeys that ovulated during treatment was more variable and generally smaller than in anovulatory animals, but still substantial in the majority (5/7) of individuals. • Endocrine effects: In the majority of treated cycles (26 of 36; 72%), the mid cycle peak of estradiol, characteristic of a normal ovulatory cycle, was absent and blockade of ovulation was confirmed by the absence of normal luteal phase progesterone secretion and, in some individuals, further confirmed by the absence of a mid cycle peak of FSH. • There was a trend for the higher doses of either formulation to be more effective in ovulation

		blockade; for the SA formulation 10/14 monkeys treated with 0.1 mg/kg, and 4/5 treated with 0.2 mg/kg, were anovulatory, and for the LA formulation 7/11 and 5/6, treated with 2.5 and 4 mg respectively, were anovulatory. The differences in ovulation rate between dose groups did not reach statistical significance in these studies. • There is an intrinsic differential sensitivity between individual monkeys, to ovulation blockade by the same dose(s) of ICI 182,780. • An increase in plasma estradiol concentration was measured immediately following ICI 182,780 treatment; this 2 to 3-fold increase was sustained throughout the cycle and was observed in both ovulatory and anovulatory cycles. Such an increase might be a consequence of antagonism by ICI 182,780 of the negative feedback effects of estradiol on gonadotropin secretion mediated by estrogen receptors in the hypothalamus. If this was the case, a compensatory rise in plasma gonadotropin concentration would be anticipated. Measurements of plasma FSH revealed similar concentrations in treated and control monkeys, but other workers have reported a small but significant increase in serum LH and/ or estradiol during the follicular phase of the estrous cycle in ICI 182,780- treated monkeys (Ref Ördög et al 1998; Ref Fraser et al 1999). This was attributed to antagonism of the negative feedback effect of estradiol on the pituitary gland (Ref Ördög et al 1998). • In monkeys, the apparent stimulation of the ovarian estrogen secretion by ICI 182,780 treatment did not lead to ovarian hypertrophy. In this study, groups of 5 monkeys received either no treatment or injections of 4 mg of the LA formulation of ICI 182780/ kg IM on the third day of the menstrual cycle, either once, twice or three times at 28 day intervals. Ovaries were removed on day 12 or 13 from controls or on the 12th -14th day after the last dose of ICI 182,780. Teatment for up to three months with ICI 182,780, did not promote a statistically significant increase the weight of the primate ovary.

Pharmacology summary:
ICI 182,780 (Fulvestrant; FASLODEX™)

- Downregulates the estrogen receptor (ER) inducing a rapid loss of ER protein from breast cancer cells (Wakeling, 2000 review).
  ICI 182,780 inhibits receptor dimerization, reduces nuclear localization of ERα, completely blocks the activity of AF1 and AF2, and, reduces the biological half- life of ERα to less than 1 hour. In breast cancer cells exposed to ICI 182,780, there is a decrease in ERα protein.
- Binds ER in a competitive manner, with a high affinity comparable to that of estradiol.
- Inhibits breast cancer cell growth. ICI 182,780 is a reversible inhibitor of the growth of estrogen-sensitive human breast cancer cells and of tamoxifen-resistant breast cancer cells *in vitro*.
- Prevents the establishment of tumors from xenografts of human breast cancer cells in nude mice, inhibits the growth of established estrogen-sensitive xenografts and-inhibits the growth of tamoxifen-resistant breast tumors *in vivo*.
- Is a non-agonist antiestrogen that blocks the uterotrophic action of estradiol in mice, rats, and monkeys without having significant partial agonist estrogen-like activity.

Secondary pharmacodynamics: n/a

Pharmacology conclusions:
The Sponsor's description of the mechanism of action of ICI 182,780 is supported by the data submitted. However, it is noteworthy that both *in vitro* (Brunner et al., 1997) and *in vivo* (Osborne et al. 1995), it has been shown that tumors which eventually develop resistance to ICI 182,780 will not subsequently respond to tamoxifen. Thus, a treatment sequence in which ICI 182,780 precedes tamoxifen may not be indicated. This information should be included in the label and has repercussions for indications in which patients may be treated first with ICI 182,780.

II. SAFETY PHARMACOLOGY:

Study number/ Species	Study type	**Method/model**	**Number of animals/dose formulation**	**Salient findings**
TSM/1161 Mouse (CD-1(ICR) BR VAF/ plus)	'Primary Observation Test' to detect effects on the gross behavioral and physiological state of the animals	Following administration of ICI 182,780, vehicle control or positive control, mice were observed between 30 and 300 min post dose	6 ♂/group 0 (vehicle), 1, 5 and 20 mg/ kg sc ICI 182,780 (LA); clonidine HCl (1 mg/kg orally).	ICI 182,780 (1, 5 and 20 mg/kg SC) produced mild effects on behavior (e.g. change in pupil diameter , ↑ group cage dispersion, apathy, ↓ group locomotor activity, and vocalization) similar to vehicle. Effects seen with clonidine HCl were consistent with the pharmacology of the compound (i.e, ↓ locomotor activity, etc.).
TSM/1162 Mouse (CD-1 (ICR) BR VAF/ plus)	Effect on hexobarbital-induced sleeping time	Following administration of ICI 182,780, vehicle and positive control, the animals were given hexobarbital (80 mg/kg; IP). The time to loss and regaining of righting reflex and the sleeping time were measured.	8 ♂/group 0 (vehicle), 1, 5 and 20 mg/ kg ICI 182,780 (SC; LA) chlorpromazine HCl (20 mg/kg orally)	ICI 182,780 (1, 5 and 20 mg/kg; SC) had no effect on the duration of hexobarbital induced sleeping time suggesting the drug does not modify the anaesthetic actions of hexobarbital in mice. Chlorpromazine prolonged the sleeping time in mice compared to vehicle-treated animals
TSM/ 1163 Mouse (CD-1(ICR) BR VAF/ plus)	Anti- and pro-convulsant effects using pentylenetetrazole seizure test.	Following administration of ICI 182,780, vehicle, and positive control, the animals were infused with pentylenetetrazole (10 mg/ml IV; 6ml/h) and monitored for seizure activity	8 ♂/group 0 (vehicle), 1, 5 and 20 mg/kg (SC; LA) (*d*-amphetamine sulphate, 30 mg/kg orally; proconvuls. Phenytoin, 40 mg/kg orally-anticonvuls.	ICI 182,780 (1, 5 and 20 mg/kg) did not alter the dose of pentylenetetrazole required to cause convulsions compared to the vehicle control showing the compound did not display any proconvulsant or anticonvulsant activity. Phenytoin sodium (40 mg/kg) increase the dose of pentylenetetrazole required to cause convulsions compared to the vehicle *d*-Amphetamine sulphate (30 mg/ kg) decrease the dose of pentylenetetrazole required to cause convulsions compared to the vehicle.

TSR/3026 Rat (Sprague Dawley)	Effects on motor activity	Total ambulatory and rearing activity was measured after administration of ICI 182,780, vehicle or positive control	8 ♂/group 0 (vehicle), 1, 5 and 20 mg/ kg (IM; LA) Chlorpromazine HCl (20 mg/kg orally) .	ICI 182,780 (20 mg/kg; IM) increased total locomotor activity, ambulatory, and rearing activity starting at 60 min post-drug administration. ICI 182,780 (1 and 5 mg/kg; IM) did not affect total locomotor activity or ambulatory activity but significantly increase rearing activity 60 min post administration of at 1 mg/kg ICI 182,780. Chlorpromazine HCl (20 mg/kg) decreased total locomotor, ambulatory, and rearing activity compared to vehicle.
TSR/3027 Rat (Sprague-Dawley)	Effects on nociception using a tail flick test	Tail flick latency was measured after administration of ICI 182,780, vehicle or positive control up to 150 min post-dose.	8♂/group 0 (vehicle), 1, 5 and 20 mg/ kg (IM LA) morphine HCl (20 mg/kg orally)	ICI 182,780 (1, 5 and 20 mg/kg IM) had no marked effects on tail flick latency compared to the vehicle. Morphine HCl (20 mg/kg) significantly increased tail flick latencies compared to vehicle consistent with the pharmacology of an opioid agonist.
TSZ/7 Sheep In- vitro	Potential to prolong QT interval by examining effects on intracellularly recorded cardiac action potential in sheep isolated Purkinje fibers	Isolated Purkinje fibers from ♂ and ♀ sheep were stimulated at 1 Hz. APD_{60} and APD_{90}, MRD, UA, and DMP were measured.	0 (DMSO), 1, 10 and 100 ng/ml ICI 182,780 in DMSO *dl*-Sotalol HCl (30 µM for ~ 30 min).	In sheep isolated cardiac Purkinje fibres, paced at a stimulation frequency of 1 Hz, ICI 182,780 (1, 10 and 100 ng/ml), had no significant effects on any of the action potential parameters measured. *dl*-Sotalol hydrochloride (30 µM, 30 min; positive control) caused a prolongation of the action potential duration (↑ APD_{60} and ↑ APD_{90}).
TSD/1092 Dog (Beagle)	Effects on cardiovascular hemodynamics and respiration rate	Arterial blood pressure and heart rate, femoral arterial blood flow and blood conductance, left ventricular pressure, cardiac output, stroke volume, total peripheral resistance, ECG, ECG waveform analysis, respiration parameters, arterial blood gases (pCO_2 and pCO_2), base excess, HCO_3 -, $\%O_2$ saturation and pH were monitored in anaesthetized, spontaneously respiring dogs up to 120 minutes post dose:	4 ♂/group 0 and 1 or 20 mg/kg (IM LA)	ICI 182,780 (1 and 20 mg/kg IM) had no physiologically significant effects on any of the cardiovascular parameters measured or on respiration rate. Heart rate was significantly increased (~7%; 10 to 15 min post dose) and pH values significantly decreased (0.5%; 5 min post-dose) in ICI 182,780-treated dogs compared to vehicle-treated animals but these changes were not considered to be physiologically important.

TSR/3028 Rat (Sprague-Dawley)	Effects on respiration rate and body core temperature in conscious animals	Following administration of ICI 182,780, vehicle or positive control, respiration rate, tidal volume, inspiration and expiration rate, and core temperature were measured up to 120 min post dose.	8 males per group 0 (vehicle), 1, 5 and 20 mg/kg (IM LA) Chlorpromazine HCl (20 mg/kg/orally)	ICI 182,780 (1, 5 and 20 mg/kg IM) had no effect on respiration rate or core body temperature. Chlorpromazine HCl resulted in a significant decrease in respiration rate and core body temperature.
TSR/3029 Rat (Sprague-Dawley)	Effects on urinary pH, urinary volume, and urinary excretion of sodium, potassium and chloride	Animals were oral volume loaded with 20 ml/kg 30 minutes prior to dosing with ICI 182,780, vehicle or positive control.	8 ♂/group 0 (vehicle), 1, 5 and 20 mg/kg (IM LA) Furosemide (20 mg/kg orally).	ICI 182,780 (1, 5 and 20 mg/kg IM) had no effect on renal function compared to the vehicle. Furosemide (20 mg/ kg), a diuretic, increased urine volume and output of sodium, potassium and chloride compared to the vehicle control
TSM/1164 Mouse (CD-1(ICR) BR VAF/ plus)	Effect on GI transit of a charcoal meal	Following administration of ICI 182,780, vehicle or positive control, the animals were given a charcoal suspension by gavage. The distance that the charcoal meal had traveled along the intestine in 30 min. was measured.	8♂/group 0 (vehicle), 1, 5 and 20 mg/ kg (SC; LA) Morphine HCl(20 mg/kg orally)	ICI 182,780 (1, 5, and 20 mg/kg; SC) had no significant effect on GI transit in mice. ICI 182,780 (1 and 20 mg/kg; SC) had no significant effect on gastric emptying in mice; however at 5 mg/kg, stomach weight was increased compared to vehicle indicating a reduction in gastric emptying. Morphine HCl (20 mg/ kg) reduced GI transit and increased stomach weight indicating a reduction in gastric emptying.
TSG/211 Guinea- pig (Dunkin-Hartley) In-vitro	Effects on basal tone and the responses to acetylcholine, histamine, 5- hydroxy tryptamine, and barium chloride in isolated ileum	Isolated ileum segments exposed to each spasmogen, washed out and then, in turn exposed to ICI 182,780 at different dose levels and any effects on baseline tension recorded.	Ileum segments n=4 ♂ Organ bath: 1, 10 and 100 ng/ml ICI 182,780 in DMSO	ICI 182,780 (1, 10, and 100 ng/ ml) had no effect on basal tone of the ileum. No signignificant effects on the contractile responses to acetylcholine, 5-HT, histamine, and barium chloride in *in vitro* guinea-pig gastrointestinal smooth muscle suggesting no intereaction with these specific receptors.
TSR/3029 Rat (Sprague-Dawley)	Effects on urinary pH, urinary volume, and urinary excretion of sodium, potassium and chloride	Animals were oral volume loaded with 20 ml/kg 30 minutes prior to dosing with ICI 182,780, vehicle or positive control.	8 ♂/group 0 (vehicle), 1, 5 and 20 mg/kg (IM LA) Furosemide (20 mg/kg orally).	ICI 182,780 (1, 5 and 20 mg/kg IM) had no effect on renal function compared to the vehicle. Furosemide (20 mg/ kg), a diuretic, increased urine volume and output of sodium, potassium and chloride compared to the vehicle control

Safety pharmacology summary:
The Sponsor provided the following relationships between doses administered in the animal studies and possible clinical exposure.

Test	ICI 182,780 concentration	Dose relationship
In vitro	1, 10 and 100 (0.17 mM) ng/ml	Highest concentration (100 ng/ml equivalent to 0.17 mM) is ~ 10 times the peak plasma concentration (C_{max} - 9.7 ng/ml, trial 9238IL/ 0020) in humans at the clinical dose (250 mg/month).
In vivo/ rodent studies	1, 5, and 20 mg/kg mouse: 3, 15, and 60 mg/m^2 rat: 6, 30, and 120 mg/m^2	The expected human dose is ~6 mg/m^2/day for a 50 kg person receiving 250 mg/month. The low dose (3 or 6 mg/m^2) is ~ the expected human dose. The middle dose (15 or 30 mg/m^2) provides a 3-5 fold margin. The high dose (60-120 mg/m^2) is ~ 10-20 fold the therapeutic dose.
In vivo/ dog studies	1 and 20 mg/kg 20 and 400 mg/m^2	The low dose (20 mg/m^2) is a small multiple of the expected human dose. The high dose (400 mg/m^2) was ~ 67-fold the therapeutic dose.

Neurological effects: The effects of ICI 182,780 were determined on neuromuscular coordination, gross behavior, depressant activity, convulsant activity, pain perception, sleeping time, and locomotor activity, in mice and/or rats. With the exception of increased locomotor activity and increase rearing in rats after administration of 20 mg/kg and 1 mg/kg ICI 182,780/kg, respectively, no effect was seen on any other measured parameters.

Cardiovascular effects: Effects of ICI 182,780 on cardiovascular function were measured in anaesthetized spontaneously respiring dogs. ICI 182,780 (1 or 20 mg/ kg IM), had no effects on any of the cardiovascular parameters measured. Data from a Purkinje fiber preparation indicate that at plasma concentrations up to 100 ng/ml, ICI 182,780 is unlikely to affect QT interval or QRS duration of the ECG.

Pulmonary effects: The effects of ICI 182,780 on pulmonary function were assessed in in conscious rats treated with 1, 5 or 30 mg ICI 182,780/ kg. At doses of 1, 5 or 20 mg/kg IM, ICI 182,780 had no effect on respiratory function.

Renal effects: The ability of a ICI 182,780 to affect urine production, and its effects on the excretion of electrolytes in urine, were determined following dosing with 1 mg/kg IM. ICI 182,780 had no effect on urine volume, osmolarity, sodium, potassium or chloride output.

Gastrointestinal effects: The effects of ICI 182,780 on gastro-intestinal motility was assessed in the mouse by measuring the distance travelled by a charcoal meal. ICI 182,780 had no effect on GI mobility at doses up to 20 mg/kg (SC). Although not a dose-related finding, ICI 182,780 appear to reduce gastric emptying at 5 mg/kg SC.

Safety pharmacology conclusions:
ICI 182,780 does not produce ataxia, has no CNS stimulant activity, has no pro-or anti-convulsant potential, and does not modify any other observable indices of CNS function. Also, the drug has no cardiovascular effects, as measured in anesthetized dogs and in a sheep Purkinje fiber preparation. Further, ICI 182,780 does not affect respiratory or renal function. Gastro-intestinal motiliy does not appear to be significantly affected although gastric emptying was reduced after administration of ICI 182,780 (5 mg/kg SC) in mice.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK parameters:

Single dose PK parameters

Report #	Species/ Duration	Dose and Route (Formulation)[A]	C_{max} (ng/ml)	$AUC_{(0-t)}$[B] (ng.h/ml)	t_{max} (h)	$t_{1/2}$ (h)
KMR/005	Rat/Single dose	2.5 mg/kg IM (SA)	101	678	4	4.3
KKR/0041	Rat/Single dose ♀ bw=~160 g ♂ bw=~200 g	15 mg/kg (♀) (LA) 10 mg/rat (♀:~63 mg/kg) 10 mg/rat (♀:~63 mg/kg; ♂:~50 mg/kg) x2 (♂)	47.1 106 86.7(♂) 48.7 (♀) 48.7	5880 21600 29664 16392	1 1 1 1	9.1 days 10.8 days ND ND
KMD/006	Dog/Single	2.5 mg/kg IM (SA)	145	3454	0.25	33 days
KPD/051	Dog/Single	10 mg/kg IM (LA) 20 mg/kg 30 mg/kg	23.5 47.7 58.8	7824 17808 28080	1 to 6 1 to 3 3 to 9	13.1 days 27.2 days 23.1 days
KKP/081	Monkey/Single	5 mg/kg IM (SA)	1100	7370	2	38.7

[A] SA denotes short-acting and LA denotes long-acting formulation
[B] $AUC_{(0-t)}$ t=24 h for SA and t=28/29 days for LA

Multiple dose PK parameters

Report #	Species/ Duration	Dose and Route (Formulation) [A]	# doses	C_{max} (ng/ml)				AUC_{0-t} (ng.day/ml)				T_{max} (h)			
				First dose		Last dose		First dose		Last dose		First dose		Last dose	
TAR/1801	Rat/1 month	2.5 IM (SA)	30	218		238		43.8		42.4		2		2	
		5 IM	30	524		574		104.6		101.3		2		2	
		[B]		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
TPR/2042	Rat/6 months	15 mg/kg/30 days	6	53.3	62.4	56.3	60.2	326	483	719	998	1.29	1.13	2	4
		10 mg/rat/30 days	6	94.5	125	82.3	194	1207	2083	638	1235	2	11	1.3	1.13
		10 mg/rat/15 days (LA)	12	70.2	129	88.3	208	705	1352	963	1684	2	7	2	1.13
TAD/583	Dog/1 month	1 mg/kg IM + SC	1	35.1		66		12.9		42.3		4		2	
		2.5 mg/kg IM + SC	14	87.6		209		53.2		139.6		4		4	
		4 mg/kg IM + SC (SA)	14	150		407		68.8		286.6		1		4	
TPD/628	Dog/6 months	10 mg/kg/28 days	6	27.8		23.1		270.4		389.6		2 to 7 days		3h to 7 days	
		20 mg/kg/28 days	6	42.3		51.6		468.9		845.3		2 to 7 days		3h to 7 days	
		30 mg/kg 28 days IM (LA)	6	95.4		95		947.8		2341.3		2 to 4 days		3h to 7 days	
TFD/913	Dog/12 months	10 mg/kg/28 days	9	13.3		20.9		154		353		3		1	
		20 mg/kg/28 days	9	36		35		369		685		3		3	
		40 mg/kg/28 days IM (LA)	9	55.5		87.9		683		1500		3		3	

[A] SA denotes short-acting and LA denotes long-acting formulation

[B] In groups 10 mg/rat/30 days and 10 mg/rat/15 days,♂ rats (~210 g) received ~47 and 96 mg/kg at the beginning of the study and ~ 17 and 35 mg/kg, respectively by the end of the study. Similarly, ♀ rats (~160 g) received ~63 and 123 mg/kg at the beginning of the study and 34 and 67 mg/kg, respectively by the end of the study.

Absorption, Distribution, Metabolism, and Excretion:

<table>
<tr><th>STUDY TYPE/Number</th><th>SPECIES (Number/Sex))</th><th>DOSE/ROUTE mg/kg</th><th>ASSAY</th><th>PRINCIPAL FINDINGS</th></tr>
<tr><td>ADME and PK (single dose) KMR/005</td><td>Wistar Rat (3M/3F/group</td><td>Single administration 2.5 mg/kg IV IM (SA) ^{14}C radiolabelled material (Batch 1R2A)[A]</td><td>Liquid Scintillation Counting, RIA, & [redacted]</td><td>
<table>
<tr><th>PK</th><th>IM</th><th>IV</th></tr>
<tr><td>Cmax (ng/ml)</td><td>101</td><td>569</td></tr>
<tr><td>T max (h)</td><td>4</td><td>0.08</td></tr>
<tr><td>AUC (ng.day/ ml)</td><td>678</td><td>478</td></tr>
<tr><td>T ½ (d)</td><td>4.3</td><td>4.5</td></tr>
</table>
<table>
<tr><th>Excretion (%) dose in 120h</th><th>IM</th><th>IV</th></tr>
<tr><td>Feces</td><td>91.6</td><td>95.1</td></tr>
<tr><td>Urine</td><td>0.07</td><td>0.07</td></tr>
<tr><td>Cagewash</td><td>0.04</td><td>0.03</td></tr>
<tr><td>Carcass</td><td>1.7</td><td>1.2</td></tr>
<tr><td>Total</td><td>93.4</td><td>96.4</td></tr>
</table>
No gender difference
ICI 182,780 and, mainly, metabolites were confirmed in feces.
There were several unknown metabolites that were not identified.
</td></tr>
<tr><td>Pharmacokinetics KKR/041</td><td>Wistar Rat 3F/ 3M/time point</td><td>Long acting IM formulation 10 mg/ rat (F) 15 mg/ kg (F) 10 mg/ rat (M/ F) (2 doses 15 days apart)</td><td>[redacted]</td><td>
<table>
<tr><th></th><th>Females 15mg/ kg</th><th>Females 10 mg/ rat</th><th>Females 10 mg/ rat*</th><th>Males 10 mg/ rat*</th></tr>
<tr><td>Cmax (ng/ml)</td><td>47.1</td><td>106</td><td>86.7 (81.9)</td><td>48.7 (49.1)</td></tr>
<tr><td>T max (d)</td><td>1</td><td>1</td><td>1.0 (1.0)</td><td>1.0 (1.0)</td></tr>
<tr><td>AUC(0-28/29d) (ng. day/ ml)</td><td>245</td><td>900</td><td>1236</td><td>683</td></tr>
<tr><td>AUC (0-14/15 d) (ng. day/ ml)</td><td>NC</td><td>NC</td><td>623</td><td>330</td></tr>
<tr><td>T ½ (d)</td><td>9.1</td><td>10.8</td><td>NC</td><td>NC</td></tr>
</table>
*2 doses 14 d apart.
NC=not calculated
Gender differences in C_{max}, (males < females) AUC (males < females), and number of metabolites (males > females).
Lower exposure than obtained previously in a toxicokinetic study using RIA (TPR 2042)
</td></tr>
</table>

[A] The radiolabel was incorporated in the carbon atom "alpha" to the ring structure [14C]-ICI 182,780 7α-(9-(4,4,5,5,5-pentafluoropentyl-sulfinyl) [1-14C]nonyl]estra-1,3,5(10)-triene-3,17β-diol.

<table>
<tr>
<td>ADME and Pharmacokinetics (single dose) KMD/006</td>
<td>Beagle Dog 3M</td>
<td>Single administration 2.5 mg/kg IV; IM (SA) ^{14}C radiolabelled material (Batch 1R2A)</td>
<td>Liquid Scintillation Counting, RIA, & TLC</td>
<td>
<table>
<tr><th>PK</th><th>IM</th><th>IV</th></tr>
<tr><td>Cmax (ng/ml)</td><td>145</td><td>2175</td></tr>
<tr><td>T max (h)</td><td>0.25</td><td>0.08</td></tr>
<tr><td>AUC (ng.day/ ml)</td><td>3454</td><td>1881</td></tr>
<tr><td>T ½ (h)</td><td>33</td><td>1.94</td></tr>
</table>
<table>
<tr><th>Excretion (%) dose in 168 h</th><th>IM</th><th>IV</th></tr>
<tr><td>Feces</td><td>74.1</td><td>82.5</td></tr>
<tr><td>Urine</td><td>1.68</td><td>1.12</td></tr>
<tr><td>Cagewash</td><td>10.2</td><td>6.49</td></tr>
<tr><td>Total</td><td>86.0</td><td>90.1</td></tr>
</table>
ICI 182,780 and, mainly, metabolites were confirmed in feces. There were several unknown metabolites.
</td>
</tr>
<tr>
<td>ADME KMD/015</td>
<td>Bile-cannulated Beagle Dog 3M</td>
<td>Single administration 4 mg/kg IM (SA) ^{14}C radiolabel (Batch 1R2A)</td>
<td>Liquid Scintillation Counting, TLC</td>
<td>Up to 78 % dose excreted via bile in 48 h.
Glucuronide conjugates of ICI 182,780 (80%) plus at least 10 other metabolites, little unchanged ICI 182,780</td>
</tr>
<tr>
<td>ADME KMD/047</td>
<td>Beagle Dog 3F</td>
<td>Single administration 2 mg/ kg oral and IM (SA) crossover design ^{14}C radiolabelled material (Batch IR4)</td>
<td>Liquid Scintillation Counting, TLC HPLC</td>
<td>About 77% was recovered in the bile after IM dose.
After oral administration up to 26% of the dose was recovered in the bile indicating at least 26% absorption.
At least ten radiolabelled components were present in addition to parent compound.(IM. 10%)
The profiles were qualitatively similar after oral dosing.
The proportion of each were not quantified due to complexity of profile.
A number of phase 1 and 2 metabolites were identified, including formation of a sulphone and a 17- keto analogue of parent, oxidation at the C- 3 position of the aromatic ring. Conjugation to produce either sulfates (at C- 3) or glucuronides (at C- 3 and C- 17).</td>
</tr>
</table>

<table>
<tr>
<td>PK (single dose)
KPD/051</td>
<td>Beagle dog
(3M)</td>
<td>Single administration
10 mg/ kg
20 mg/ kg
30 mg/ kg
IM (LA)</td>
<td>[redacted]</td>
<td>
<table>
<tr><th>Dose (mg/kg)</th><th>10</th><th>20</th><th>30</th></tr>
<tr><td>C_{max} (ng/ml)</td><td>23.5</td><td>47.7</td><td>58.8</td></tr>
<tr><td>T_{max} (h)</td><td>1-6</td><td>1-3</td><td>3-9</td></tr>
<tr><td>AUC (ng.day/ ml)</td><td>326</td><td>742</td><td>1170</td></tr>
<tr><td>T ½ (h)</td><td>13.1</td><td>27.2</td><td>23.1</td></tr>
</table>

Small but significant difference between the RIA and HPLC [redacted] (AUC_{0-28} with RIA 82.2 % of AUC value with HPLC-MS-MS). (TPD 628)
Following IM administration of the racemic mixture of ICI 182,780, the two diastereomers, ZM208,926 and ZM208,927 were found in the same ratio at which they had been dosed (~ 50: 50).

</td>
</tr>
<tr>
<td>ADME and PK
(single dose)
KKD/066</td>
<td>Beagle dog
(3F)</td>
<td>Single Administration
2.5 mg/kg IM
(SA) 14C radiolabeled material (Batch IR5)</td>
<td>HPLC
Liquid Scintillation Counting,
[redacted]</td>
<td>Radiolabelled material in whole plasma obtained by solvent extraction co-chromatographed with unchanged parent compound at all time points.
Extraction efficiency decreased (from ~ 80% to 40%) at later sample times, due to co-precipitation of the radiolabel with plasma protein.
Solvent extraction following enzyme digestion by incubation with Subtilisin carlsberg, gave increased extraction recoveries of radioactivity in the region of 83 to 95%.
HPLC analysis of these extracts showed that all of the radioactivity co-eluted with ICI 182,780 standard and [redacted] confirmed the identity of this peak as ICI 182,780.</td>
</tr>
<tr>
<td>ADME
KMB/036</td>
<td>New Zealand White Rabbit
3F</td>
<td>Single administration
0.26 mg/ kg
IM (SA) ^{14}C radiolabeled material (Batch IR5)</td>
<td>HPLC and Liquid Scintillation counting</td>
<td>
<table>
<tr><th>Excretion (%) Dose in 168 h</th><th>IM</th></tr>
<tr><td>Feces</td><td>94.83</td></tr>
<tr><td>Urine</td><td>0.42</td></tr>
<tr><td>Cagewash</td><td>0.006</td></tr>
<tr><td>Total</td><td>95.32</td></tr>
</table>
</td>
</tr>
</table>

ADME KMB/036	New Zealand White Rabbit 3F	Single administration 0.26 mg/ kg IM (SA) ^{14}C radiolabeled material (Batch IR5)	HPLC and Liquid Scintillation counting	Elimination was rapid with approximately 77% of the recovered dose eliminated within 48 hours. ICI 182,780 was apparently excreted largely unchanged in feces (>70% dose) together with 2 minor components (<11%) corresponding to the sulphone and 17- keto analogues of ICI 182,780.
ADME (Distribution) KMR 007.	2 ♂ albino rats, 4 ♀albino rats and 3 ♂hooded rats.	[^{14}C]-ICI 182,780 (2.5 mg/kg) IM	Whole body autoradiography	• Two hours after administration, highest levels of radioactivity were in the stomach, gastro-intestinal tract and liver, then lower levels in the adrenal gland, kidney, lung, brown fat and pituitary. The lowest tissue levels of radioactivity were in the blood and thymus.. No radioactivity was detected in the brain and spinal cord. • Radioactivity in intestinal contents and liver bile suggest rapid biliary secretion. However the sections also show that radioactive material was secreted into the digestive tract via the saliva and the gastric mucosa. • Drug-derived material was cleared rapidly from the tissues and excreted largely in feces. Although high concentrations of radioactivity were initially seen in kidney there was no indication that drug-derived material was secreted in urine.

<table>
<tr>
<td>ADME
(Distribution)
KMR049
(cross reference
182780 K.MR007).</td>
<td>4 ♀ and 2 ♂
albino rats and
3 ♂ hooded
rats</td>
<td>2.5 mg/kg
[^{14}C]- ICI
182,780 IM</td>
<td>Quantitative
whole body
autoradiogra
phy</td>
<td>

Highest levels were detected in the small intestine mucosa, liver, and mesenteric lymph glands.
Lower levels were apparent in the adrenal, pancreas, kidney, lung, heart, brown fat, glandular tissue, and blood. Levels were not detected in the CNS.

<table>
<tr><th></th><th>Female Albino</th><th>Male albino</th><th>Male pigmented</th></tr>
<tr><td>Small Intestine Mucosa</td><td>3.308</td><td>0.588</td><td>2.465</td></tr>
<tr><td>Liver</td><td>2.193</td><td>2.073</td><td>2.983</td></tr>
<tr><td>Mesenteric lymph nodes</td><td>0.962</td><td>0.746</td><td>0.666</td></tr>
<tr><td>Pancreas</td><td>0.844</td><td>0.563</td><td>0.748</td></tr>
<tr><td>Stomach Mucosa (fundus)</td><td>0.796</td><td>0.34</td><td>0.402</td></tr>
<tr><td>Adrenal</td><td>0.754</td><td>0.615</td><td>0.995</td></tr>
<tr><td>Kidney</td><td>0.742</td><td>0.684</td><td>0.782</td></tr>
<tr><td>Lung</td><td>0.714</td><td>0.887</td><td>0.575</td></tr>
<tr><td>Heart</td><td>0.57</td><td>0.492</td><td>0.51</td></tr>
<tr><td>Pituitary</td><td>0.477</td><td>0.422</td><td>0.527</td></tr>
<tr><td>Fat (brown)</td><td>0.47</td><td>0.493</td><td>0.825</td></tr>
<tr><td>Spleen</td><td>0.419</td><td>0.304</td><td>0.536</td></tr>
<tr><td>Blood</td><td>0.417</td><td>0.288</td><td>0.359</td></tr>
<tr><td>Salivary glands</td><td>0.402</td><td>0.346</td><td>0.636</td></tr>
<tr><td>Ovary</td><td>0.319</td><td>-</td><td>-</td></tr>
<tr><td>Uterus</td><td>0.31</td><td>-</td><td>-</td></tr>
<tr><td>Bone marrow</td><td>0.304</td><td>0.35</td><td>0.344</td></tr>
<tr><td>Thryoid</td><td>0.3</td><td>0.382</td><td>0.557</td></tr>
<tr><td>Uveal tract</td><td>0.282</td><td>0.417</td><td>0.403</td></tr>
<tr><td>Harderian gland</td><td>0.264</td><td>0.205</td><td>0.263</td></tr>
<tr><td>Skin (non pigmented)</td><td>0.184</td><td>0.185</td><td>0.219</td></tr>
<tr><td>Thymus</td><td>0.176</td><td>0.164</td><td>nq</td></tr>
<tr><td>Skin (pigmented)</td><td>-</td><td>-</td><td>0.284</td></tr>
<tr><td>Large intestine mucosa</td><td>nq</td><td>0.362</td><td>0.465</td></tr>
<tr><td>Seminal vesicles</td><td>-</td><td>0.238</td><td>nq</td></tr>
<tr><td>Prostrate</td><td>-</td><td>0.2</td><td>0.229</td></tr>
<tr><td>Preputial gland</td><td>-</td><td>0.171</td><td>0.351</td></tr>
<tr><td>Eye</td><td>nq</td><td>0.141</td><td>nq</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>ADME (Distribution) KMR050</td>
<td>27 ♂rats were administered a 3 rats/time point</td>
<td>Single IM dose of 2.5 mg/kg [^{14}C]-ICI 182,780 (35.5 µCi/ kg).</td>
<td>Autoradiography at the injection site.</td>
<td>
<table>
<tr><th>Time Points (h)</th><th>Mean muscle concentration (µg equiv/g)</th><th>Mean peak muscle concentration (µg equiv/g)</th><th>Plasma Mean concentration (ng equiv/g)</th></tr>
<tr><td>0.08</td><td>66.6±27.6</td><td>254.5±141.8</td><td>Nq</td></tr>
<tr><td>0.25</td><td>72.4±6.6</td><td>243.8±52.4</td><td>26.2±9.3</td></tr>
<tr><td>0.5</td><td>69.3±6.2</td><td>261.2±38.8</td><td>65.5±19.3</td></tr>
<tr><td>1.0</td><td>77.8±19.7</td><td>368.8±41.3</td><td>94.5±18.4</td></tr>
<tr><td>2.0</td><td>57.0±16.9</td><td>319.4±139.6</td><td>96.3±12.3</td></tr>
<tr><td>4</td><td>14.2±6.7</td><td>87.1±46.1</td><td>35±14.2</td></tr>
<tr><td>12</td><td>14.8±5.2</td><td>66.2±22.5</td><td>26.7±14.8</td></tr>
<tr><td>24</td><td>4.2±2.0</td><td>30.1±15.8</td><td>15.5±0.9</td></tr>
<tr><td>48</td><td>1.4±0.4</td><td>5.8±2.2</td><td>30.4±22.6</td></tr>
</table>

The mean amount of dose recovered at the injection site up to 2 h post- dose was very variable ranging from 27 to 38% of the administered dose.
The Sponsor argues that the lower than expected % of dose detected may be due to the practical problems associated with dosing a small volume to a small target injection site and/ or the handling and manipulation of the muscle during assay procedures. Therefore the data may provide unrealistically low estimates of injection site exposure to [^{14}C]-ICI 182,780 at early time points.
By 48 h, the radioactivity at the injection site declined to ~ 1% of the dose by 48 hours indicating that dosed material had been removed from the injection site.
The difference between peak and mean concentrations indicates localization of the dose at the injection site.
Concentrations of radioactivity in plasma were not quantifiable (LOQ = [redacted] ng equiv./g) 5 minutes post- dose, but increased to a~ 95 ng equivalents of ICI 182,780/ g at 1 to 2 h post- dose. The plasma concentrations of radioactivity declined in parallel to concentrations of radioactivity at the injection site, which may indicate that the plasma concentration is primarily dependent on the rate of release of dosed material from the injection site.

</td>
</tr>
</table>

ADME Transplacental tranfer KMR\037	4 ♀ Alpk: ApfSD rats; 16 days pregnant	Single IM dose of [^{14}C]- ICI 182,780 at 1.03 ± 0.07 mg/kg incorporating 15.4 ± 0.81µCi. (batch 1R5)	Liquid scintillation counting	• Administration of ICI 182,780 (1 mg/kg IM) to pregnant female rats resulted in the detection of radioactive material in fetuses at 2 hour after dosing. • Fetal tissue concentrations of drug-related material were approximately 76% of those in maternal plasma. • These results indicate that placental transfer of drug related material occurs at this dose level.
ADME Transplacental tranfer KMB\038	4 ♀ New Zealand White hybrid rabbits; 11 days pregnant	Single IM dose of [^{14}C]- ICI 182,780 at 0.25 mg/kg ± 0.003, incorporating 33.78 ± 0.74 µCi. (batch 1R5)	Liquid scintillation counting	• Administration of ICI 182,780 (0.25 mg/kg IM) to pregnant female rabbits resulted in the detection of radioactive material in embryos 2 hours after dosing. • Fetal tissue concentrations of drug- related material were approximately 97% of those in maternal plasma. • These results indicate that placental transfer of drug related material occurs at this dose level.
ADME Excretion into milk KMR\078	6 pregnant Alpk: A$_f$fSD rats	Single IM dose of [^{14}C]- ICI 182,780 at 2.38 ±0.13 mg/kg incorporating 103.89 ±5.74 µCi/ kg (batch 1R7).	Liquid scintillation counting	• [^{14}C]-ICI 182,780 (2 mg/kg IM) was administered to lactating rats and drug-related material was excreted in milk with peak concentrations of 859.03±180.73 ng.equiv/g 6 h post dose. • The maximal concentrations of ICI 182,780 in the milk was ~12 times higher compared to the drug concentration in blood. • The maximal drug exposure in pups from drug-treated lactating dams was estimated as 10.3% of the administered dose (2 mg/kg). • In milk, the presence of ICI 182,780, sulphone, 17- ketone, and 17- keto-sulphone was confirmed with HPLC and .

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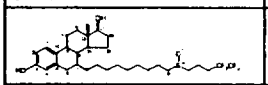
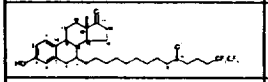
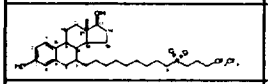
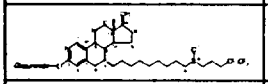
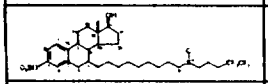
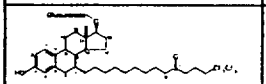
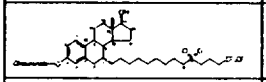
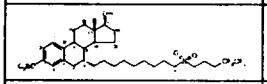
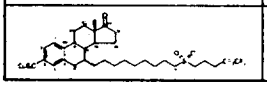
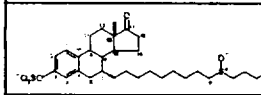
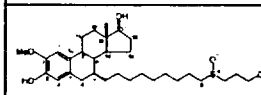
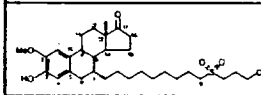
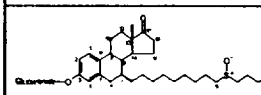
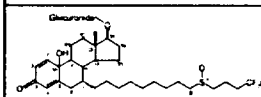
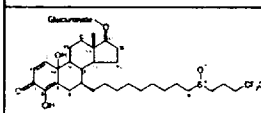
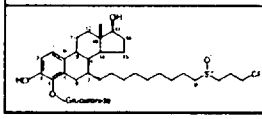
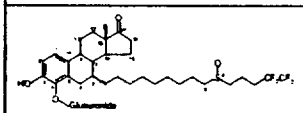
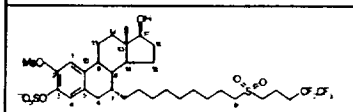
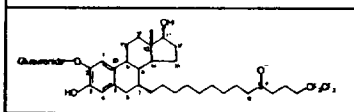
Metabolism

Metabolites of ICI 182,780 identified in vitro and/ or in vivo in the rat, dog, rabbit and human

Structure	Descriptive name	Source
	ICI 182,780	
	ICI 182,780-17-ketone (ZM 366,472)	human hepatocytes rabbit feces
	ICI 182,780-9'-sulphone (ZM 208,917)	human hepatocytes rabbit feces
	ICI 182,780-3-glucuronide	rat bile human hepatocytes dog bile
	ICI 182,780-3-sulphate (ZM 366,479)	human hepatocytes dog hepatocytes dog bile
	ICI 182,780-17-glucuronide	dog hepatocytes dog bile
	ICI 182,780-9'sulphone-3-glucuronide	dog bile
	ICI 182,780-9'sulphone-3-sulphate	human hepatocytes dog bile
	ICI 182,780-17-ketone-9'sulphone-3-sulphate	rat bile dog bile

Structure	Descriptive name	Source
	ICI 182,780-17-ketone-3-sulphate	dog bile
	2-methoxy-ICI 182,780	rat bile
	2-methoxy-ICI 182,780-17-ketone-9'sulphone	rat bile
	ICI 182,780-17-ketone-3-glucuronide	dog bile
	ICI 182,780-10-hydroxy-1,4 diene-3-one-17-glucuronide	dog bile
	ICI 182,780-4,10-dihydroxy-1,4 diene-3-one-17-glucuronide	dog bile
	ICI 182,780-4-glucuronide	rat bile

Structure	Descriptive name	Source
	ZM 366472 - 4 - glucuronide	rat bile
	ZM 208917- 3-sulphate with methoxy at C2	rat bile
	ICI 182,780-2-glucuronide	rat bile

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Summary metabolite profile extracted from feces after IM dosing (percentage of total)

Peak	Reference name[1]	Rat	Dog	Human Male	Human Female
1		0.95	0.13	2.94	5.88
2*		17.32	4.01	9.11	17.28
3	3-sulphate	3.34	0.96	0.70	3.40
4		13.29	12.81	5.81	11.40
5		3.91	1.04	1.91	5.46
6		3.88	0.79	1.43	1.64
7		2.05	0.33	1.32	1.46
8	3-glucuronide	2.64	0.59	1.95	2.73
9		1.80	1.04	2.76	2.79
10	17-glucuronide	1.78	0.86	2.06	1.76
11		2.63	1.01	1.47	4.24
12		2.47	1.16	2.28	1.39
13		3.62	3.22	4.04	4.91
14		4.85	1.85	6.32	1.64
15	Sulphone	3.21	8.47	1.69	8.31
16	ICI 182,780/ ketosulfone	9.15	47.87	6.36	11.40
17	17-Ketone	2.18	4.44	7.17	0.55
18		10.60	3.82	20.07	4.43
19		2.60	0.64	8.97	2.12
20		1.75	0.60	4.15	1.27
21		0.19	0.05	0.62	1.76
Total		94.2	95.7	93.1	95.8

[1]: derivatives of the ICI 182,780 structure
*: broad band multiplet

PK/TK summary:
ICI 182,780 has been presented in two formulations. A short- acting (SA) formulation was used for metabolism and pharmacokinetic studies using single intramuscular doses. Toxicokinetic data from multiple doses were obtained using the SA formulation as well as the long-acting formulation (LA) intended for once- monthly intramuscular injection. The LA formulation is the proposed commercial formulation.

In rats, after single IM dosing of the SA formulation (2.5 mg/kg), there was an absorption and distribution phase during which plasma concentrations rose to a plateau lasting between 4 and 12 hours after dosing. Thereafter, concentrations declined with an apparent elimination half-life of

4.3 hours. Following multiple daily IM dosing of SA formulation (2.5 and 5 mg/kg), C_{max}, t_{max}, and $AUC_{0\text{-}24\ h}$ values were similar for both males and females in all dose groups.

In IM studies in rats using the LA formulation (6-month), ICI 182,780 was generally released slowly from the formulation throughout the 30 day measurement period, and t_{max} was very variable (between 3 hours and 11 days after dosing). Following the peak, serum concentrations declined slowly with compound still measurable at all dose levels 30 days after dosing. $AUC_{(0\text{-}30\ days)}$ was ~ 2- fold higher than after a single low dose (15 mg/kg). However, only slight accumulation (~25%) was observed in the high-dose group (10 mg/rat/15 d) and no accumulation in the mid-dose group (10 mg/rat/30 d). There was a significant difference between the sexes in serum ICI 182,780 concentrations, possibly reflecting the lower body weights of female rats, compared to male rats, given a fixed dose (10 mg/rats). When body weight was taken into account, however, there was still a trend towards higher exposure in female rats. It is noteworthy that at the beginning of this 6-month study, male rats (~210 g) in groups 10 mg/rat/30 days and 10 mg/rat/15 days, received ~47 and 96 mg/kg, respectively. By the end of the study, they were receiving ~ 17 and 35 mg/kg. Similarly, at the beginning of the study, female rats (~160 g) were receiving 63 and 123 mg/kg and by the end they were receiving 34 and 67 mg/kg. Thus, as the body weight increases (~2-3 fold) with time, the actual dose administered decreases in both male and female rats.

In dogs, after IM dosing of the SA formulation, there was an absorption and distribution phase during which plasma concentrations rose to a plateau lasting between 4 and 12 hours after dosing. Thereafter, concentrations declined with an apparent elimination half-life of 33 hours. The long apparent half-life in the dog probably reflects continued slow absorption of ICI 182,780 from the site of injection, rather than the terminal half- life of ICI 182,780. Repeated daily administration of the SA formulation by both IM and SC routes for at least 4 weeks showed a degree of accumulation at all dose levels (1, 2.5, and 4 mg/kg/day). By Day 14 of the study, all animals had higher serum concentrations. Mean C_{max} values had increased by between 1.8- and 2.3- fold and $AUC_{(0\text{-}24h)}$ by 2.5- to 3.2- fold. The majority of the accumulation took place during the first two weeks of dosing with levels increasing thereafter by only about 20%.

Intramuscular administration of the LA formulation gave dose proportional increases in the group mean $AUC_{(0\text{-}28\ days)}$. In common with the rat, the time to C_{max} (t_{max}) varied, occurring between 2 and 7 days after dosing. Monthly IM injections of the LA formulation to dogs resulted in accumulation (1.4 to 2.5- fold over 6 months and 1.8 to 2.2- fold over 9 months) as demonstrated by the increase in AUC and Day 29 serum ICI 182,780 concentrations. There was no evidence of an increase in C_{max} following multiple dosing; however, positive pre-dose concentrations were measured for all dose groups before the final dose, reflecting the slow decline in serum concentrations following the peak.

The exposures to ICI 182,780 in rats and dogs were compared to drug exposure in humans. PK values were obtained from the rat 6- month study(TPR/ 2042 -10 mg/rat/15 days dose group), 12-month dog study (TFD/913-40 mg/kg/28 days dose group), and at the highest dose administered clinically to women (Study IL0020-250 mg/month).

	Rat (♂)	Rat (♀) [A]	Dog (both)	Human (♀) [B]
	10 mg/rat/15 days (~36 mg/kg/15 days)	10 mg/rat/15 days (~67 mg/kg/ 15days)	40 mg/kg/28 d	250 mg/montly
	216 mg/m^2/15 days	402 mg/m^2/15 days	800 mg/m^2/28 days	185 mg/m^2/month[C]
	432 mg/m^2/30 days	804 mg/m^2/30 days	800 mg/m^2/28 days	185 mg/m^2/month[C]
Dose ratio	2	4	4	1
AUC (ng.h/ml)	46,656	92,688	36,000	8887
AUC ratio	5.2	10.4	4.1	1
C_{max} (ng/ml)	105	372	88	9.7
C_{max} ratio	10.8	38	9.1	1

[A] Rats were administered ICI 182,780 on a 1 dose/15 days regimen and the pharmacokinetic parameters used were calculated over the penultimate dose interval (highest observed values). For comparison with dog and human data, the $AUC_{(0\text{-}15\ days)}$ was multiplied by 2 to estimate the 30 day exposure.

[B] Limited accumulation (x2.3) was demonstrated in this study; therefore, the $AUC_{(0\text{-}28\ days)}$ value obtained after the first dose was multiplied by a factor of 2.3 to represent the 0 to 28 day exposure at steady state. The exposure ratios ranged from 4 to 10 for AUC and 9 to 38 for C_{max}.

[C] Estimated dose for a 50 kg human.

Distribution:

Distribution of radiolabeled ICI 182,780 (SA) after IM administration was measured in rats using whole body autoradiography. There was no sex-or pigmentation difference in the distribution of radiolabeled material. Quantitative whole body autoradiography confirmed that, by 2 hours after single IM, radioactivity was widely distributed in rats. The highest levels of radioactivity were detected in the small intestine mucosa, liver, and mesenteric lymph glands. Lower levels of radioactivity were quantifiable in the adrenal, pancreas, kidney, lung, heart, brown fat, glandular tissue, and blood. There was no quantifiable level of radioactivity distributed within the central nervous system. Drug related material was rapidly cleared such that by 7 days after administration of the dose, radioactivity was quantifiable only in the liver.

Direct measurement of radioactivity at the site of injection, following administration of [^{14}C]-ICI 182,780 as a single IM dose to rats, showed that the percentage of the dose remaining at the injection site up to 2 hours postdose ranged from 27% to 38%. Radioactivity was localized in the injection site muscle, and the injection site and other muscle concentrations declined in parallel. Plasma concentrations of radioactivity were always lower than, and also declined in parallel to, concentrations in muscle.

There was transplacental transfer of radioactivity following administration of a single IM dose of [^{14}C]- ICI 182,780 to female rabbits (0.25 mg/kg) and to female rats (1.0 mg/kg). At 2 hours after dosing, fetal tissue concentrations of drug-related material were ~ 76% and ~97% of maternal plasma concentrations in rats and rabbits, respectively, indicating that placental transfer of drug related material occurred. Drug-related radioactivity was also excreted in milk with peak observed concentrations at 6 hours post dose. Concentrations of ICI 182,780 in the milk were around 12 times higher than in the blood. The estimated exposure to the pups is ~10% from an administered dose of 2 mg/kg ICI 182,780.

Metabolism: Note: All metabolism and excretion studies were carried out using the SA formulation, as the rate of elimination of the LA formulation precludes collection and analysis of drug related material in excreta.

In vitro
A comparison of metabolites formed by rat, dog, and human hepatocytes demonstrated rapid and extensive metabolism of [^{14}C]-ICI 182,780. Rat hepatocytes produced several components, dog hepatocytes formed 2 major metabolites, while human hepatocytes appeared to metabolize [^{14}C]-ICI 182,780 more slowly, producing 4 components. With one exception, *in vitro* metabolites identified in all species appeared to be ICI 182,780 3-sulphate, , the 17-β-glucuronide of ICI 182,780 (not in human), and ICI 182,780 sulphone. These findings suggested that, in humans, sulfation may represent a principal way to metabolize ICI 182,780.

In vivo metabolism:
The composition of the profiles from all species was generally similar. Chromatographic analyses of rat and dog bile or feces extracts showed that [^{14}C]-ICI 182,780 is extensively metabolized. Bile samples contained at least 12 or more metabolites and minimal amounts of unchanged compound. The metabolism of ICI 182,780 appears to include oxidation, aromatic hydroxylation, and conjugation with glucuronic acid and sulphate at the 2, 3 and 17 positions of the steroid nucleus. These metabolites may undergo subsequent metabolism, in addition to phase 2 conjugation. In contrast, there appeared to be limited metabolism after intramuscular administration to rabbits, with ICI 182,780 apparently excreted largely unchanged in feces (>70% dose), together with two minor components (<11%) corresponding to the side chain sulphone and 17- keto analogues of ICI 182,780. There was a significant sex difference in pathways of metabolism in that males produced at least 5 additional metabolites not detected in samples from females.

The major excretory metabolites in the rat, dog, and man were ICI 182,780 and its keto and/or sulphone analogues (rat and man 15 to 20%, dog 61%) together with material corresponding to sulphate conjugates (up to 16%). Consistent with the *in vitro* data, these data indicate that the primary routes of metabolism in each species include formation of the 17-ketone and sulphone metabolites.

Excretion
In rat (both sexes), dog (male), and rabbit (female), ICI 182,780 (SA) IM was excreted primarily in feces (~90%). Urinary recovery accounted for ≤2% of the dose. The rate of excretion of the radiolabeled material was faster in the rat than in the dog. The 0 to 24 hour recovery of the radiolabeled dose was ~ 70% in rat and 30% in dog, indicating good availability of ICI 182,780 from the site of intramuscular injection in both species. In bile duct cannulated rats or dogs, the majority of the dose was recovered in bile within 24 to 48 hours after dosing. In the rabbit, elimination was also rapid with ~ 77% of the recovered dose eliminated within 48 hours.

PK/TK conclusions:
The disposition of ICI 182,780 was investigated in rat and dog, the primary toxicology species, using a metabolically stable radiolabeled form to characterize the pharmacokinetics and metabolism of the compound. ICI 182,780 was well absorbed and widely distributed following IM administration. ICI 182,780 is eliminated almost entirely in feces in rats and dogs. Metabolism was qualitatively similar in rats, dogs, and man. Adequate exposure to ICI 182,780 was achieved in the rat and dog relative to man. Overall, the data indicate that the disposition of ICI 182,780 in the animal species used for toxicity studies is similar to that found in humans.

IV. GENERAL TOXICOLOGY:

Study title: ICI 182,780 : ACUTE TOXICITY (LIMIT) STUDY IN MICE: INTRAMUSCULAR ADMINISTRATION.

Key study findings:

- ICI 182,780, administered intramuscularly to mice as a single dose of approximately 200 mg/kg body weight caused no deaths and no compound related signs of systemic toxicity.
- The abnormal gait and edema followed by bruising of hind limbs was indicative of a reaction to the vehicle since it was present in both the control and drug-treated animals.
- Histopathological examination of injection sites showed a similar degree of chronic inflammatory cell infiltration in both groups of mice.

Study no: TLM/645
Volume #, and page #: N_000\2001-03-28\pharmtox\tox\Dose\ TLM/645
Conducting laboratory and location: ICI Pharmaceuticals Safety of Medicines Department Alderley Park Macclesfield Cheshire England
Date of study initiation: February 21, 1989
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot # and % purity: ADM 44026/88; 99.5%
Formulation/vehicle:

Ingredients	Placebo mg % w/v	ICI 182,780 mg 2 %w/v
ICI 182,780	-	2.0
Pluronic F127	1.0	1.0
Ethanol 96% BP	10.0	10.0
Water for injection	8.0	8.0
Propylene Glycol	to 100%	to 100%
Bulk-drug analytical reference number		ADM 44026/88
Formulation Batch Reference Number	PH 6124/118	PH 6124/122
Formulation Analytical Reference Number	ADM 49061/88	ADM 49009/89

Methods:
Dosing:

Species/strain:	APfCD-1 (AP) mice
#/sex/group or time point:	10/sex/group
Age:	33 days old
Weight:	18-26 g
Doses:	0, ~200 mg/kg (achieved doses ranged from 154-211 mg/kg) Single dose, observation for 14 days
Route, form, and volume:	IM; 0.2 ml (0.1 ml to each hind leg)

Observations and times:

Clinical signs:	Daily
Body weights:	Pre-dose on day 1, on day 8, and prior to necropsy on day 15.
Gross pathology:	Day 15
Histopathology:	Day 15

Results:

Mortality: No mortality observed.

Clinical signs: Clinical signs included subdued behavior, hunched posture and partially closed eyes, and edema at the injection site in both groups of mice. The edema was followed by bruising of the hind limbs in 7/10 animals in both groups. The bruising was present for between 1 to 5 days. The hind limbs of all the mice were stiff, causing abnormal gait, which persisted from dosing to day 14 of the observation period in five animals in Group I. In Group II the observation of abnormal gait was more sporadic, disappearing and re-appearing in the latter days of the study.

Body weights: Unremarkable (UR)

Gross pathology: No abnormal tissues were found in the thoracic and abdominal cavities.

Histopathology:

- Chronic inflammatory cell infiltration was observed at the injection sites in both groups.
- Resultant chronic myositis, neuritis, arteritis and pigment deposits occurred.
- Chronic myositis was observed in all animals (minimal to moderate), neuritis (minimal to moderate) in all except 1 Group II animal, arteritis in 2 animals only and pigment deposits in 2 Group I animals.
- Three injection sites (all Group I females) were contaminated with bacterial cocci.

Study title: ICI 182,780 : ACUTE TOXICITY (LIMIT) STUDY IN RATS: INTRAMUSCULAR ADMINISTRATION.

Key study findings:

- There was a similar degree of chronic inflammatory cell infiltration in both control and drug-treated rats. The Sponsor suggests that this reaction was due to the alcohol components of the vehicle and not the test material.

Study no: TLR/1802
Volume #, and page #: N_000\2001-03-28\pharmtox\tox\Dose\TLR/1802
Conducting laboratory and location: ICI Pharmaceuticals Safety of Medicines Department Alderley Park Macclesfield Cheshire England
Date of study initiation: January 26, 1989
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: ADM 44026/88, 99.5%
Formulation/vehicle:

Ingredients	Placebo mg % w/v	ICI 182,780 mg 2 %w/v
ICI 182,780	-	2.0
Pluronic F127	1.0	1.0
Ethanol 96% BP	10.0	10.0
Water for injection	8.0	8.0
Propylene Glycol	to 100%	to 100%
Bulk-drug analytical reference number		ADM 44026/88
Formulation Batch Reference Number	PH 6124/118	PH 6124/122
Formulation Analytical Reference Number	ADM 49061/88	ADM 49009/89

Methods:
Dosing:

Species/strain:	Alpk: APfSD (Wistar derived) (AP) rats
#/sex/group or time point (main study):	15 sex/group
Age:	39-43 days old
Weight:	114-146 g
Doses in administered units:	8 mg/rat-The achieved doses ranged between 55 and 70 mg/kg. Single dose; observation for 14 days.
Route, form, volume:	IM, 0.4 ml (0.2 ml/each hind leg)

Observations and times:

Clinical signs:	Twice daily
Body weights:	Pre-dose on day 1, on day 8, and prior to necropsy on day 15.
Gross pathology:	Day 15
Histopathology:	Day 15

Results:

Mortality: All animals survived.

Clinical signs:

		0 min-3 h		3 h-7h		Days 2-14	
Group	Observation	♂	♀	♂	♀	♂	♀
Control	No abnormalities detected	5	5	5	4	5	5
	Bruised hind limb				1		
ICI 182,780	No abnormalities detected	5	2	4	4	5	5
	Bruised hind limb/edema		3	1	1		

Body weights: Unremarkable (UR)

Gross pathology: No abnormal tissues were found in the thoracic and abdominal cavities.

Histopathology:

Group	Observation	♂	♀
Control	Chronic inflammatory cell infiltration (minimal to mild)	3	4
	Chronic myositis (minimal to mild)	1	1
	Mononuclear cell infiltration	4	2
ICI 182,780	Chronic inflammatory cell infiltration (minimal to mild)	4	5
	Chronic myositis (minimal to mild)	3	3
	Mononuclear cell infiltration	2	2

Pigment deposits, myocyte atrophy, acute inflammatory cell infiltration and mineralization occurred in all animals.

Study title: ONE MONTH INTRAMUSCULAR BRIDGING STUDY IN RATS

Key study findings:

- Animals receiving 10 mg/rat gained less weight than those given 15 mg/kg.
- At necropsy small cervix and uterus were observed in females from each group. Histologically, there was also evidence of ovarian cysts and dilated prostate glands.
- Transient swelling, inflammation, and muscle necrosis was observed at injection sites. Small depots of injected material were present in muscle and associated tissue with some associated fibrosis.
- Pharmacokinetic analyses showed that exposure of rats to ICI 182,780 was maintained for at least 29 days following doses of 15 mg/kg or 10 mg/animal.

Study no: TKR/1917
Volume #, and page #: N_000\2001-03-28\pharmtox\tox\Dose\TKR/1917
Conducting laboratory and location: ICI Pharmaceuticals Safety of Medicines Department Alderley Park Macclesfield Cheshire England
Date of study initiation: February 26, 1992
GLP compliance: Yes
QA report: yes ( ) no (x)
Drug, lot #, and % purity: ADM 44026/89, 98.5%

Formulation/vehicle:

Ingredients	ICI 182,780 5 %w/v
ICI 182,780	5
Ethanol 96% v/v	10.0
Benzyl alcohol	10.0
Benzyl benzoate	15.0
Castor oil	To 100.0
Bulk-drug analytical reference number	ADM 44009/88
Formulation Batch Reference Number	PH 6731/36
Formulation Analytical Reference Number	ADM 48015/90

The material was formulated as a sterile solution containing 50 mg/ml of ICI 182,780 and supplied in 5 ml glass ampoules.

Methods: This study was designed to assess toxicities and pharmacokinetic profile resulting from the administration of a sustained release formulation of ICI 182,780.

Dosing:

Species/strain: Alpk:APfSD (Wistar derived) (Alderley Park) rats (AP rat)

#/sex/group: 9 sex/dose

Satellite groups used for toxicokinetics or recovery: Same animals as in main study

Age: 43-45 days old

Weight: 174-207 g

Doses: Single dose; no control group in this study

Group	Dose	♂	♀
I*	15 mg/kg	9	9
II*	10 mg/rat	9	9
III**	10 mg/rat	9	9

* Group I and II received a single dose

** Group III received 2 doses 2 weeks apart

Route, form, volume: IM using a plastic syringe and an hypodermic needle. Volume not indicated.

Observations and times:

Clinical signs: Twice daily

Body weights: Days -7 and -3 pre-study, on the first day of dosing and then weekly for the remainder of the study.

Food consumption: One week pre-study and weekly for the remainder of the study.

Gross pathology: 14 days to interim necropsy and 28 days to terminal necropsy

Histopathology: 14 days to interim necropsy and 28 days to terminal necropsy. In the animals from the interim kill, only the injection sites and abnormal tissues were taken for histopathological examination.

Toxicokinetics: Day -5 (pre-dose) at 3, 7 and 24 hours after the first dose and on days 4, 7, 11, 15 (Group III only at 3, 7 and 24 hours after

the second dose; Groups I and II just a single time point), 20, 24 and 29 to define the blood level profile.

Results:

Mortality: There were no deaths during the study.

Clinical signs: Swelling of the injection site in 8 animals from all the groups.

Body weights: Values indicate % increase in weight from day 1 to day 29. Number is parenthesis indicate % change from values obtained in rats administered 15 mg/kg.

Sex	15 mg/kg (once)	10 mg/animal (once)	10 mg/animal (twice)
♂	98.7	80.6 (↓18%)	90.1 (↓9%)
♀	42.7	37.6 (↓12%)	36.1 (↓15%)

- Rats given 10 mg/animal gained less (9-18%) weight than those given 15 mg/kg.
- The absence of a control group in this study precludes further assessment of effects upon growth.

Food consumption: UR

Gross pathology: Small cervix and uterus were seen in some females from each group with a higher incidence in rats given two doses of 10 mg/rat.

Histopathology: Severity findings ranged from minimal to mild, except unilateral nephrosis in 10 mg/rat which ranged from mild to moderate.

	Male			Female		
Dose	15 mg/kg	10 mg/rat	10 mg/rat X2	15 mg/kg	10 mg/rat	10 mg/rat X2
Cervix (small)				1/6	7/8	9/9
Uterus (small).				5/9	9/9	9/9
Ovary cysts				0/6	5/8	9/9
Prostate interstitial fibrosis	0/7	1/6	2/9			
Mammary hyperplasia	0/1	0/1		0/6	2/6	1/8
Hydronephrosis; unilateral	0/6	3/6	7/9	2/7	1/7	2/9
Tubular basophilia	2/6	1/6	4/9	1/7	3/7	2/9
Transitional epithelial - hyperplasia	0/6	0/6	1/9	0/7	0/7	0/9
Mandibularlymph node reactive lymphoid hyperplasia	1/1		2/2			2/2
Injection site fibrosis	0/9	2/9	2/8	0/9	3/9	4/9

- Histopathological changes included a reduction in the size of the uterus and cervix (without any morphological change), ovarian cysts, and dilatation of prostate glands. These changes were most marked animals receiving 10 mg/animal.
- The injection sites showed inflammation associated with muscle necrosis (minimal). Small depots of injected material were occasionally present in the muscle and adjacent tissue with some associated fibrosis.

Toxicokinetics:

Dose	C_{max} (ng/ml)	T_{max} (hr) Day 1	AUC_{0-29} (ng d/ml)	Serum Conc. (ng/ml) (Day 29)
15 mg/kg	37.3±6.32	3	431	13.9±1.14
10 mg/rat	93.9±20.3	3	764	11.8±0.89
10 mg/rat Dose1	101±21	7	1417	37.5±3.38
10 mg/rat Dose2	77.1±14.9	7	1417	37.5±3.38

- There was no discernible sex difference in serum concentrations for animals in Group I (15 mg/kg). However, female rats from Group II (10 mg/rat) and III (10 mg/rat twice) showed higher serum concentrations than males following this fixed dose volume probably due to their lower body weight.
- At the end of the study (day 29), ICI 182,780 was still detectable in serum showing exposure to the compound throughout the one month period.

Study title: ICI 182,780 (Depot formulation) : INTRAMUSCULAR BRIDGING STUDY IN DOGS.

Key study findings:
- Data is not provided in this study, only a summary of findings.
- Foreign body granulomata associated with the depot formulation and chronic myositis were seen in the muscles used for dose administration even after one month of recovery.
- The severity (unknown) of these findings was not dose related according to the narrative.
- No other changes were seen which were considered to be associated with drug administration.

Study no: TKD/627
Volume #, and page #: N_000\2001-03-28\pharmtox\tox\Dose\ TKD/627
Conducting laboratory and location: ICI Pharmaceuticals Safety of Medicines Department Alderley Park Macclesfield Cheshire England
Date of study initiation: 3/27/92
GLP compliance: Yes
QA report: yes ( ) no (x)
Drug, lot #, radiolabel, and % purity:
Formulation/vehicle: Sustained release formulation contained 5% w/v ICI 182,780, ethanol (10/ w/v), benzyl alcohol (10/ w/v) and benzyl benzoate (15% w/v) which were made up to 100% with castor oil

Methods: This study was designed to assess the tolerance to a sustained release (depot) formulation of ICI 182,780.
Dosing:

Species/strain:	Alderley Park beagle dogs
#/sex/group or time point (main study):	2/sex/group
Age:	Not indicated
Weight:	Not indicated

Doses: 35, 15, and 30 mg/kg/month. Dosed on day 1 and observed for 28 days

Route and volume: IM

Group	Dose (mg/kg/month)	Dose volume (ml/kg)		
		Hind legs	Back	Forelegs
I	35	0.2 x 2	0.1 x 2	0.05 x 2
II	15	0.075 x 2	0.075 x 2	
III	30	0.15 x 2	0.15 x 2	

Observations and times:

Body weights: Weekly
Food consumption: Weekly
Histopathology: Selected tissues were taken at necropsy
Toxicokinetics: Blood concentrations of ICI 182,780 were measured on samples taken on day 1 and pre-dose on a number of days during the observation period.

Results:

Body weights: UR
Food consumption: UR
Histopathology: Foreign body granulomata associated with the presence on the depot formulation and chronic myositis were seen in the muscles used for dose administration. The severity of these findings did not appear to be dose related..
Toxicokinetics: Systemic exposure of dogs to ICI 182,780 reflected by the area under the concentration time curve showed a less than proportional increase with increasing dose. The mean AUC's following 35, 30 and 15 mg/kg were 1190, 1193 and 820 ng.d/ml respectively. Interanimal variability was substantial throughout the study.

Summary of individual study findings:

Data is not provided in this study, only a summary of findings. Administration of the formulation was tolerated, but foreign body granulomata and myositis (not dose related) were still present one month after dose administration. The severity (unknown) of these findings was not dose related according to the narrative. No other changes were seen which were considered to be associated with drug administration.