CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20753

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

A. Staton
OCT 20 1999

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-753
Priority: 1 S
AROMASIN® (Exemestane)
Tablets (25 mg)

SUBMISSION DATES: DEC. 21, 1998
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PHARMACIA & UPJOHN

REVIEWERS: Emmanuel O. Fadiran, Ph.D.
John Duan, Ph.D.

TYPE OF SUBMISSION: Original NME

SYNOPSIS:

This is the review of the clinical pharmacology and biopharmaceutics studies submitted to NDA 20-753 for exemestane tablets. The sponsor has studied the human pharmacokinetics (single and multiple dose), metabolism, and excretion of exemestane, an irreversible steroidal aromatase inhibitor. Exemestane is proposed for the treatment of advanced breast cancer (ABC) in women with natural or artificially induced postmenopausal status failing standard hormonal therapy. The recommended daily dose is 25 mg (approximately 0.4 mg/kg for a 60 kg woman), preferably given after a meal.

Exemestane was well absorbed from the gastrointestinal tract. The evaluation of the absolute bioavailability in humans was not possible due to the absence of a suitable intravenous formulation; however, indirect evidence indicates that bioavailablility is likely limited by a relatively high first-pass effect. Coadministration of exemestane with a standard high fat meal increased the C_{Max} by 59% and AUC by 39%. Absorption of intact drug was rapid, with peak concentrations typically achieved within 2 hours and followed by a polyexponential decline with a terminal half-life of approximately 24 h. Exemestane binds non-specifically to plasma proteins; albumin and α_1-acid glycoprotein contributing equally to the binding (93-95%). Exemestane distributes extensively into tissues (reflecting the high lipophilicity of the compound) and it is cleared rapidly and extensively by metabolism from the systemic circulation. The metabolic profile, although showing some quantitative differences, is qualitatively similar between man and other animal species. Biotransformation involves an initial oxidation of the methylene group in position 6 and reduction of the 17-keto group. Urinary excretion of the parent drug is extremely low, with less than 1% of the dose excreted as unchanged exemestane in urine. Following administration of [^{14}C]-exemestane to healthy postmenopausal women, the cumulative amounts of radioactivity excreted in urine and feces were similar (42 ± 3% in urine and 42 ± 6% in feces over a 1-week collection period).

The pharmacokinetics of exemestane did not show marked dose or time-dependencies. A three-fold increase in AUC was observed in subjects with liver and renal impairment compared to healthy postmenopausal women. The pharmacokinetics of exemestane does not appear to be influenced by gender.

Exemestane is extensively metabolized. In vitro studies using human liver preparations showed that CYP3A4 is the major enzyme involved in the oxidative metabolism of exemestane. Other CYP forms including CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYPE1 do not appear to be significantly involved in the biotransformation of exemestane. Exemestane does not inhibit the common CYP isoenzymes involved in the xenobiotics metabolism and is not a major inducer of CYP3A. The selective inhibition of CYP3A4 (by ketoconazole), the cytochrome P450 most likely involved in one of the initial pathways of exemestane metabolism, does not appear to have any significant impact on the pharmacokinetics of the intact drug. No metabolites of exemestane identified to date have shown significant aromatase inhibition with the exception of the 17-hydroexemestane (FCE 25071), which was 2.6 times less potent than intact exemestane.

A population PK-PD analysis was conducted on the data from Study 94-OEXE-012. A two compartment model best described the PK data and the analysis showed that bioavailability was influenced by both food and formulation while formulation influenced the absorption rate. The PD (suppression of Estrone Sulphate) was fitted to an indirect inhibitory model and simulations showed that the PD model predicted the onset and off set of estrogen suppression by exemestane.

The sponsor conducted a study to establish the bioequivalence between the clinical formulation (formulations A2 and A3) and the to-be-marketed formulation (A4). Division of Scientific Investigation audit revealed that the study is unacceptable because of the violation of CFR 320.63 (Retention of Bioequivalence Samples). However, according to the current Scale-Up and Post-Approval Changes (SUPAC) requirements, the multiple changes (scale-up, manufacturing process, and site-change) made in the development of of the to-be marketed formulation do not require a bioequivalence study. Comparability of the dissolution profiles is adequate to establish a link between the two formulations. The dissolution profile comparisons passed the similarity test (f_2 dissolution test). Therefore the two formulations should be considered bioequivalent.

An *in vitro* dissolution method has been provided but the recommended dissolution specification has been changed from NLT % at minutes to Q= % at minutes.

COMMENTS TO BE SENT TO THE SPONSOR:

1. It is strongly recommended that the sponsor submit the full study report for Study 95-OEXE-015 and Study 95-OEXE-016 with the assay validation data (this has been previously communicated to the sponsor). The free drug concentrations from these two studies should be determined (at least a few samples per subject). Subsequently the data should be analyzed to compare free drug concentrations in healthy volunteers and patients with renal or hepatic impairment.

2. The sponsor stated that the assays for Study 95-OEXE-022 and Study 95-OEXE-028 were validated but did not provide the assay validation data. Please, provide assay validation data for Study 95-OEXE-022 and Study 95-OEXE-028.

3. The bioequivalence study (Study 97-OXE-035) linking the clinical formulation with the to-be-marketed formulation was unacceptable because of the violation of CFR 320.63 code. However, the changes (scale-up, manufacturing process, and site-change) made in the development of the to-be-marketed formulation from the clinical formulation require establishment of dissolution profile similarity between the formulations. The dissolution profiles of the clinical and the to-be-marketed formulations passes the test for similarity (f_2 dissolution test). Therefore, the two formulations are bioequivalent from the Clinical Pharmacology and Biopharmaceutics point of view.

4. Food enhances the bioavailability of the drug by approximately 40%. There is no absolute bioavailability information in humans is available. Animal data indicated about 5% absolute bioavailability. There is an extensive first-pass effect in humans. Food has a significant role in increasing the exposure to the drug, which may be essential for the activity of the drug. A 40% increase in bioavailability is considered to be significant from the Clinical Pharmacology and Biopharmaceutics perspective. Therefore, exemestane should be given after a meal. The pivotal clinical trial protocol required exemestane to be given with food.

5. Based on the dissolution data submitted by the sponsor, the following dissolution specifications are recommended for Aromasin 25 mg tablets.

Dissolution Apparatus:	USP, Apparatus 1 (basket)
Speed of Rotation:	100 rpm
Medium:	0.5% (w/v) sodium lauryl Sulfate aqueous solution
Temperature:	37^0 C
Amount:	Q of % in minutes

6. LABELING COMMENTS: Please, edit the Pharmacokinetics Section [deleted page

number] Special Population Section [deleted page number] and the Dosage and Administration Section of the labeling as shown below:

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pages of trade

secret and/or

confidential

commercial

information

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I reviewed the sponsor's NDA 20-753 and finds that the submission adequately addresses the clinical pharmacology and biopharmaceutics requirements. Please forward the general and labeling comments above to the sponsor.

/S/ 10/20/99

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

/S/ 10/20/99

John Duan, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Rahman, Ph.D. /S/ 10/20/99

Biopharm Day - 10/15/99: MehtaM, HuntJ, MartinA, RahmanA, DuanJ, IbrahimS, MishinaE, KiefferL, WilliamsG, BoothB, LeightonJ

cc: NDA 20-753, HFD-150 (MartinA, BeitzJ, StatenA), HFD-850 (LeskoL), HFD-860 (FadiranE, DuanJ, MehtaM), HFD-340 (VISHWANATHAN), BIOPHARM - CDR

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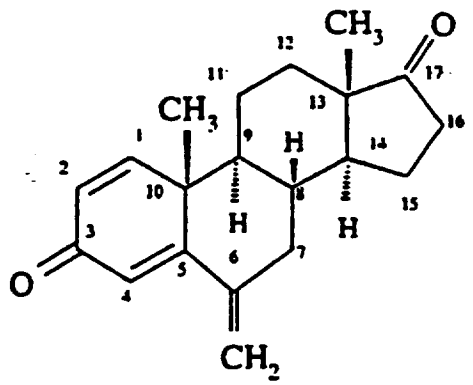
Appendix (Study Summaries)

**Reviewed by John Duan*

BACKGROUND: Exemestane is a neutral compound with steroidal structure characterized by high lipophilicity (Figure 1). Exemestane is an irreversible inhibitor of aromatase enzyme, which is responsible for the conversion of androgens into estrogens. Inhibition of postmenopausal estrogen production by aromatase inhibitors is an established treatment modality for postmenopausal breast cancer. Exemestane is a low-solubility, high lipophylic drug. It is proposed for the treatment of advanced breast cancer (ABC) in women with natural or artificially induced postmenopausal status failing standard hormonal therapy. The recommended daily dose is 25 mg (approximately 0.4 mg/kg for a 60 kg woman), preferably given after a meal. Hot flashes, nausea, fatigue, pain, increased sweating and increased appetite are some of adverse effects that have been reported. The sponsor has submitted 15 pharmacokinetics / pharmacodynamics studies and 3 *in vitro* studies in support of the NDA and all the studies were reviewed.

FIGURE 1. Structural Formula of Exemestane



USAN : exemestane

Chemical Name : 6-methylenandrosta-1,4-diene-3,17-dione;
androsta-1,4-diene-3,17-dione-6-methylene

Molecular Formula: $C_{20}H_{24}O_2$

Molecular Weight : 296.41

Laboratory Code : FCE 24304, PNU-155971

CAS Registry Number : 107868-30-4

Physical and Chemical Characteristics of Exemestane

Physical appearance: White to white-yellowish crystalline powder

Solubility
Aqueous solvents: Practically insoluble in water. The exemestane pH-solubility profile, after stirring for 24 hours at 37°C, is reported in Table 1.

Organic solvents: Freely soluble in N,N-diethylformamide, soluble in methanol and ethanol and sparingly soluble in acetonitrile.

Table 1 : Exemestane pH-solubility profile

MEDIUM	pH	SOLUBILITY (µg/mL)
Water	—	80
Chloride buffer	1.5	86
Acetate buffer	5.5	79
Phosphate buffer	7.4	73

Polymorphism: No polymorphs have been observed.

Melting point: 194-194°C

Dissociation constant: Not determined (no acidic groups and practically insoluble in water)

Hygroscopicity: Not hygroscopic

Stereoisomerism: Contains five stereogenic centers (C-8, C-9, C-10, C-13 and C-14) but does not form diastereoismers. The final product does not show the presence of isomers.

Apparent partition coefficient: In octanol:water was not determined because exemestane is a lipophilic substance that is practically insoluble in water so that it is completely distributed in n-octanol and P_{app} tends to infinity.

SUMMARY OF BIOAVAILABILITY / PHARMACOKINETICS / PHARMACODYNAMICS

I. BIOAVAILABILITY/BIOEQUIVALENCE:

Absolute Bioavailability: The evaluation of the absolute bioavailability in humans was not possible due to the absence of a suitable intravenous formulation; however, indirect evidence indicates that bioavailability is likely limited by a relatively high first-pass effect. The high lipophilicity may be responsible for the high metabolic clearance and, therefore, for an extensive first-pass effect, which, in turn, reduces the absolute bioavailability. The average bioavailability of the exemestane sugar-coated tablet (25 mg) compared to the suspension formulation (25 mg) is 86% (Study 94-OXE-012) and two means of administration of exmestane caused similar inhibition of plasma estrone (E_1S). Preclinical data obtained in rats and dogs in which exemestane was given i.v. (formulated in polypropylene glycol and saline, 50:50, v/v), indicated that the absolute bioavailability was about 5%.

Bioequivalence: Bioequivalence was evaluated on log-transformed parameters and 90% confidence intervals (CI) were reported. In clinical pharmacokinetic studies, exemestane was given as hard-gelatin capsules (HGC), sugar-coated tablets (SCT) or as a suspension. Study 92-OEXE-008 was a relative bioavailability study that compared the 25 mg hard-gelatin capsules to the 25 mg sugar-coated tablets. The two formulations were bioequivalent with respect to AUC but bioinequivalent with respect to Cmax (CI=76-101) of exemestane but the two formulations had similar effect in decreasing plasma E_1S levels. Three manufacturing processes (designated A2, A3, and A4 processes) were optimized during the development of exemestane 25 mg sugar-coated tablets. These processes differed in manufacturing site, batch size and/or equipment used. A bioequivalence study was therefore performed to compare the bioavailability of the drug obtained using the three different processes (Study 97-OXE-035). Formulation A4 (to be marketed) was bioequivalent to the clinical formulation A2 (Table 2, Figure 2). Formulations A2 and A3 were bioequivalent with respect to AUC but bioinequivalent with respect to Cmax of exemestane (90% CI = 95-126). However, the marginal failure of the bioequivalence test is not likely to impact the safety and efficacy of exemestane since the aromatase inhibition (effect lasts for more than 1 week after a single dose) is unlikely to be related to peak concentration and repeated doses of exemestane as high as 600 mg/day have been administered without reaching a dose-limited toxicity. Formulations A2, A3 and A4 have the same composition and similar in vitro dissolution profiles.

The pivotal bioequivalence study linking the clinical formulation and the to-be-marketed formulation is therefore unacceptable because of the violation of CFR 320.63 (Retention of Bioequivalence samples). However, according to the current SUPAC requirements, the multiple changes (scale-up, manufacturing process, and site-change; no formulation changes) made during the development of the to-be-marketed formulation do not require a bioequivalence study. In this situation, comparability of the dissolution profiles of the two formulations is adequate to establish a link between the clinical and to-be-marketed formulation. The dissolution profiles passed the test for similarity (f2 dissolution test). Therefore, the two formulation should be considered bioequivalent. Formulation A2 has been linked to the hard gelatin capsules through Study 92-OEXE-008.

Table 2: Pharmacokinetic Parameters of exemestane after administration of three different formulations to healthy volunteers (mean±SD)

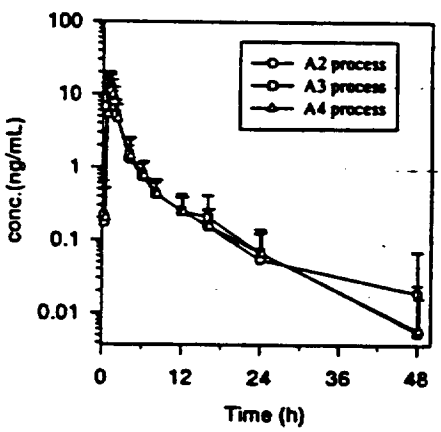
Parameter	Treatment A (Reference) A2	Treatment B (Test) A3	Treatment C (Test) A4	90% CI A3/A2	90% CI A4/A2
Cmax (ng/ml)	12.3±5.8	14.3±8.0	13.6±8.1	95-126	95-125
AUC_{0-t} (ng.h/ml)	25.1±12.1	28.1±12.2	25.7±11.9	104-124	94-113
$AUC_{0-\infty}$ (ng.h/ml)	28.4±17.3	29.6±12.1	27.4±11.9	99-120	92-112

Formulation A2 = Used for clinical development

Formulation A3 = Used for industrial scale validation for A2, also used for clinical development (different equipment too)

Formulation A4 = Scale-up for A2 and different manufacturing site (to be marketed formulation)

Figure 2: Plasma levels of exemestane following administration of a single 25 mg oral dose of exemestane obtained following three different processes to male subjects under fasting conditions; mean±SD (n=36).



Food effect: In most of the clinical studies, exemestane was given after a meal. Two studies formally assessed the effect of food on the pharmacokinetics of exemestane. The effect of a standard high fat meal on the absorption of exemestane administered as a single 25 mg dose of exemestane was evaluated (Study 94-OEXE-012). Co-administration of exemestane with this meal increased the Cmax by 59% and the AUC by 39% and caused a delay in the tmax of about 1 hour (Table 3, Figure 3). The two means of administration of exemestane (fast/fed) caused similar inhibition of E_1S (70-76%) which was reached at 2.5-2.7 days post-dosing and a similar inhibition during the 14-day observation period (AUC_{effect}). A longer duration of the inhibitory effect ($t_{1/2,effect}$) was observed when the drug was administered with food (fasted- 10.2 days, fed-12.2 days) which corresponds to the increased systemic exposure to exemestane when given with food. Preliminary evidence of a food effect was found in Japanese volunteers (Study 94-OEXE-023). Co-admistration of exemestane with a standard breakfast in Japanese volunteers led to (i) increase in Cmax and AUC of exemestane of 52% and 46% respectively, (ii) increase in Cmax and AUC of hydroexemestane of 42% and 135%, (ii) decrease in urinary excretion of exemestane and hydroexemestane of 25% and 45% respectively. The increase in the Cmax and AUC of exemestane are similar to those observed in Study 94-OEXE-012.The serum estrogen (E_1, E_2, and E_1S) suppression was similar (with and without food) and reached its maximum (22-39% of baseline) in 2 or 3 days after drug administration and almost disappeared at 2 weeks.

These pharmacokinetic findings may be related to a more efficient dissolution of the drug in the lipids present in food. In addition, meals may also increase splanchnic blood flow, allowing a larger fraction of the oral dose to evade first-pass metabolism and resulting in increased bioavailability. As a result, it is recommended to administer exemestane after a meal in the clinical practice. In the relative bioavailability studies described above and in the study evaluating the effect of food, no substantial modifications of the terminal half-life of the drug were observed indicating that the systemic disposition of exemestane is not absorption-rate limited.

Figure 3: Plasma levels of exemestane following administration of a single 25 mg oral dose of the drug as SCT given to postmenopausal subjects under fasting condition (SCT/fast) or after a meal (SCT/fed) during a crossover study; mean±SD (n=12).

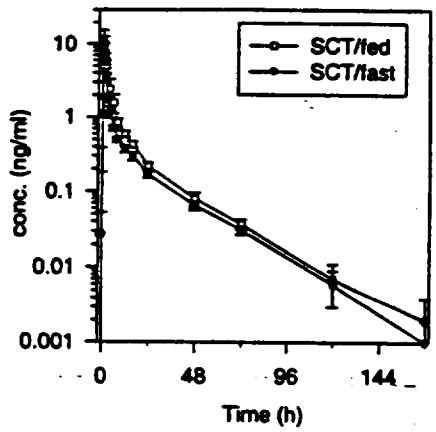


Table 3: Pharmacokinetic parameters of exemestane after administration of a single 25 mg oral dose of the drug as suspension under fasting condition or as sugar coated tablets under fasting condition (SCT/fast) or after a meal (SCT/fed) to postmenopausal subjects during a crossover study; mean ± SD (n=12)

Parameter	Suspension	SCT/fast	SCT/fed
C_{max} (ng/mL)	15.4 ± 8.1	11.1 ± 4.4	17.7 ± 15.6
t_{max} (h)	0.71 ± 0.26	0.97 ± 0.39	1.88 ± 1.64
AUC (ng.h/mL)	34.5 ± 11.3	29.7 ± 7.8	41.3 ± 11.8
$t_{1/2}$ (h)	21.90 ± 12.70	24.04 ± 9.58	21.45 ± 10.90

II. PHARMACOKINETICS:

Pharmacokinetics of exemestane were evaluated in several studies in healthy postmenopausal volunteers as well as in the target population of patients with advance breast cancer (ABC). Its physico-chemical properties have a substantial impact on the pharmacokinetic characteristics of the drug. Due to its high lipophilicity exemestane does not undergo permeability-rated limitation in absorption or distribution. As a result, the absorption is rapid and the drug has an extensive tissue distribution. The high lipophilicity is also responsible for the high metabolic clearance and, therefore, for an extensive first-pass effect, which, in turn, reduces the absolute bioavailability. In the pharmacokinetic studies single oral doses covered a range from 10 to 800 mg and multiple doses covered a range from 0.5 to 200 mg.

Plasma levels were detectable at the first sampling times (0.25-0.5 h post-dosing) and peak

levels (on average, 17 ng/mL after a single 25 mg oral dose given after a meal) were achieved approximately 2 h following the drug administration. After the peak levels were reached, plasma levels of the intact drug declined polyexponentially (Figures 2 and 3). Following a single oral dose of 25 mg, exemestane plasma concentrations declined rapidly to levels below 1 ng/mL within 12 h. Thereafter, the decline was slower, with a terminal half-life of approximately 24 h. The study with the radiolabelled drug showed the fraction of dose absorbed was 42%, as estimated from the amount of radioactivity excreted in urine as drug-related material (DRM) following oral dosing (Study PKEXEPHKI-011). This value represented an underestimate of the fraction absorbed, as the amount of drug absorbed and then eliminated through the bile is not taken into consideration (in rats, the amount of radioactivity excreted in the bile following oral dosing accounted for 52% of the dose *vs.* 70% eliminated in the feces in the same time period). Since the drug could not be given i.v. to humans, the volume of distribution terms were always affected by absolute bioavailability and only estimates of V_z/F could be obtained. Average values of V_z/F were approximately L, which are indicative of an extensive tissue distribution (Table 4). These findings in humans are consistent with those obtained in preclinical studies, in which the estimates of the volume of the central compartment calculated after i.v. dosing to rats and dogs were much higher than total body water (V_c: 4.8 and 1.8 L/kg, respectively). Tissue distribution studies in rats indicated tissue to plasma concentration ratios higher than one in all tissues, except brain and eyes. Thus, with the exception of brain tissue, exemestane appears to be widely distributed to tissues outside the plasma. The data obtained in the study with [^{14}C]-exemestane in humans showed that the blood to plasma ratio of total radioactivity was in the range 0.5-0.6, suggesting minimal distribution DRM into blood cells. Exemestane is rapidly and extensively converted to its metabolites, with plasma levels of intact exemestane accounting only for a minor proportion of the DRM even at the early time-points. For this reason, blood-to-plasma concentration ratio values of total radioactivity do not necessarily reflect the behavior of the intact drug.

After intravenous dosing to rats and dogs, the plasma clearance was about twice the hepatic blood flow, suggesting high hepatic extraction and indicating the occurrence of extrahepatic clearance. In humans, the true plasma clearance could not be determined, since the lack of a suitable intravenous formulation did not permit the assessment of absolute bioavailability. However, CL/F values of the order of 600 L/h were observed (Table 4). The magnitude of these values would suggest that exemestane clearance is as high in humans as it is in animals.

In a crossover study in postmenopausal women (Study 95-OEXE-014), the pharmacokinetics of exemestane were found to be linear at single oral doses ranging from 25 to 200 mg. Both C_{max} and AUC increased in direct proportion with dose and the terminal half-life was independent of dose (Table 4).

Table 4: Pharmacokinetic parameters of exemestane after oral administration of single doses of 25, 100 and 200 mg of the drug as sugar coated tablets affer a meal to postmenopausal subjects during a crossover study; mean ± SD (n=9).

		Dose (mg)		
Parameter		25	100	200
t_{lag}	(h) (median)	0.25	0.25	0.5
t_{max}	(h) (median)	1.5	1	1
C_{max}	(ng/mL)	19.55 ± 8.81	79.54 ± 30.57	158.19 ± 91.40
AUC(0-t_z)	(ng·h/mL)	47.54 ± 27.08	191.86 ± 85.60	390.09 ± 158.29
AUC	(ng·h/mL)	53.38 ± 29.44	197.04 ± 85.37	398.40 ± 159.03
$t_{1/2,z}$	(h)	29.6 ± 26.0	24.5 ± 18.6	32.2±17.9
MRT	(h)	18.8 ± 15.8	9.94 ± 3.82	10.9±3.8
CL/F	(L/h)	574 ± 244	574 ± 176	568±196
V_z/F	(L)	19023 ± 13106	16960 ± 7582	23855±10585

Additional evidence of dose-independent clearance was assessed by examining the systemic exposure (AUC after single dose or AUC after repeated dose calculated within the dosing interval, $AUC_{\tau,ss}$) in subjects who received exemestane as single (10 to 200 mg) or divided (repeated) daily doses (0.5 to 50 mg/day) in a number of clinical trials in postmenopausal healthy women. (Figure 4).

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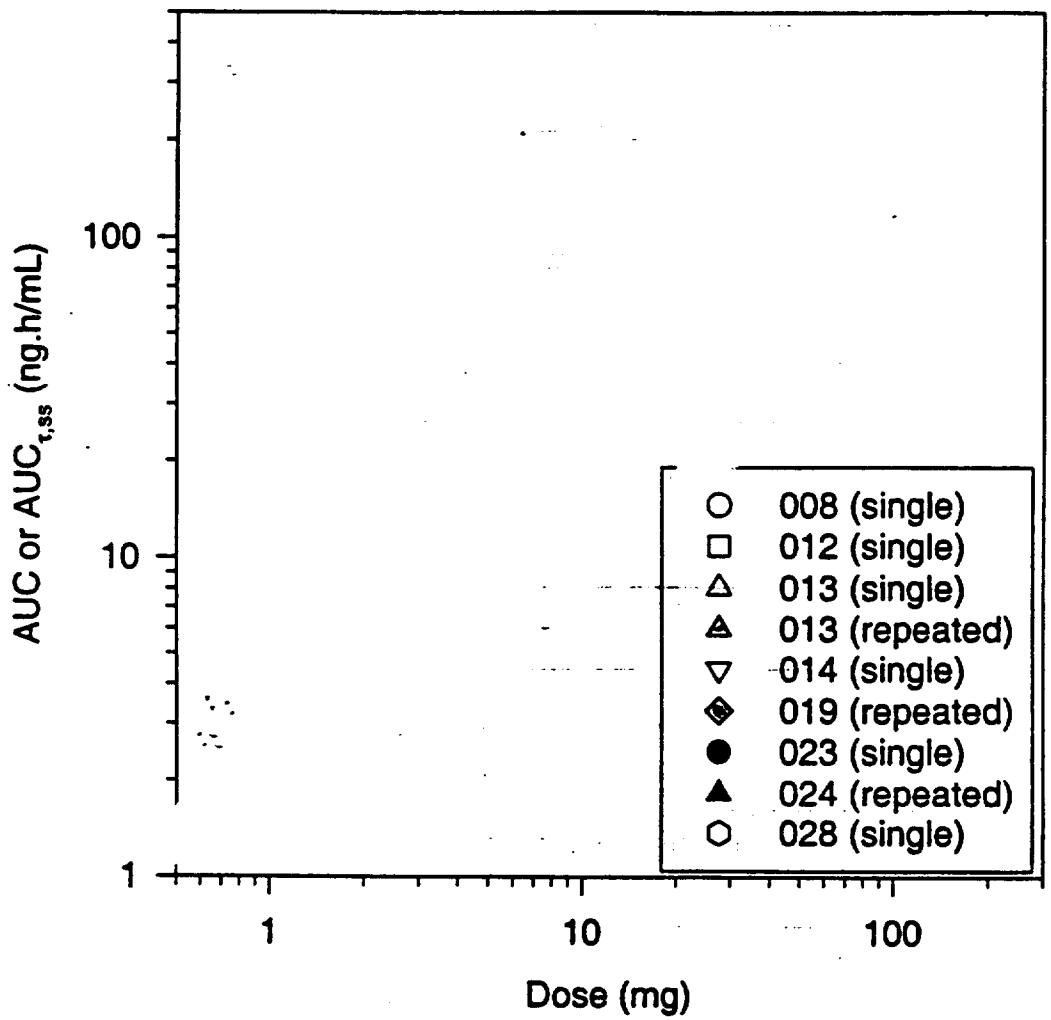
Figure 4. Log-log plot of individual AUC *versus* dose obtained in different studies following administration of single or repeated doses of exemestane to healthy volunteers (the dotted line has unitary slope). The numbers in the legend refer to the study protocol number.



Only in an early study (Study 89-OEXE-001) performed at doses up to 800 mg there was some signs of non-linearity, with the systemic exposure increasing less than in direct proportionality with the dose. However, the analytical method employed for this study only allowed exemestane plasma concentrations to be followed up to 8 h post-dosing, limiting the reliability of these results.

In a study aimed at evaluating the pharmacokinetics after single and repeated 25 mg doses in the same subjects (Study 95-OEXE-013), a decrease in systemic exposure (-28%, AUCτ vs AUC; -43%, Cmaxss vs Cmax after first dose) was observed after repeated dosing, possibly due to an increase in CL/F (38%). These findings could suggest autoinduction/activation of

some metabolic route. The urinary 6-β-hydoxycortisol to cortisol ratio was decreased by approximately 18% at steady state compared to baseline suggesting that the continuous exposure to exemestane did not substantially modify the activity of CYP3A4 which is responsible for the metabolism of exemestane. The observed effect could also be due to a decrease in biovailability (highly extracted drug administered orally undergoing prehepatic metabolism) or an increase in extrahepatic clearance (preclinical data showed that plasma clearance following I.V. dosing was higher than hepatic blood flow in rats and dogs suggesting extrahepatic metabolism occurring). The accumulation ratios (0.73 and 0.87 by Cmax and AUCτ respectively) were low and also reflect time-dependent pharmacokinetics. The terminal half-life was prolonged after repeated dosing (from 27 to 36 hours), Vz/F was increased by about 96%. Similar results were not found in advanced breast cancer patients (Study 95-OEXE-022). Comparison of the data obtained from Study 95-OEXE-022 with those obtained from healthy postmenopausal volunteers (Study 94-OEXE-012 and Study 95OEXE-013) show that: (a) Following single dose administration of 25 mg exemestane: (i) tmax is reduced from 2 h to 1 h; (ii) there is a 60% increase in Cmax; (iii) there is a 140% increase in AUC and (iv) a 30% decrease in CL/F in ABC patients compared to healthy postmenopausal volunteers; (b) Following repeated dosing of 25 mg exemestane: (i) tmax is reduced from 2.9 h to 1.2 h; (ii) there is an 80% increase in Cmax; (iii) there is a 160% increase in AUC; (iv) a 45% decrease in CL/F in ABC patients compared to healthy postmenopausal volunteers, (v) the accumulation index in ABC patients is 1.08 compared to 0.87 in healthy postmenopausal volunteers, suggesting the absence of autoinduction in ABC patients (Table 5).

Table 5: Pharmacokinetic parameters of exemestane after single and repeated daily oral doses of 25 mg of the drug as sugar coated tablets after a meal to ABC patients (n=6 and 9 for single and repeated dosing, respectively) and postmenopausal subjects (n=8); mean ± SD [range].

Parameter	ABC Patients	Postmenopausal Volunteers
	Single Dose	
t_{max} (h)	1.0 ± 0.8 [0.5-2.5]	2.3 ± 1.1 [1.5-4.0]
C_{max} (ng/mL)	40.4 ± 40.6 [13.2-119.4]	17.1 ± 12.2 [7.3-42.1]
AUC (ng·h/mL)	76.7 ± 44.7 [36.0-157.9]	57.8 ± 26.5 [27.5-102.8]
CL/F (L/h)	415 ± 202 [158-694]	517 ± 226 [243-909]
$t_{1/2,z}$ (h)	19.2 ± 10.2 [10.3-35.8]	26.6 ± 19.1 [11.3-65.6]
	Repeated Dose	
$t_{max,ss}$ (h)	1.16 ± 0.78 [0.5-2.0]	2.9 ± 1.2 [1.5-4.0]
$C_{max,ss}$ (ng/mL)	29.6 ± 24.9 [7.3-79.3]	11.4 ± 6.6 [4.8-20.5]
$AUC_{\tau,ss}$ (ng·h/mL)	75.4 ± 29.4 [34.7-125.5]	41.4 ± 18.5 [21.5-64.8]
CL/F_{ss} (L/h)	391 ± 184 [199-721]	715 ± 296 [386-1165]
$R_{A.Cmax}$	0.82 ± 0.42 [0.38-1.20]	0.73 ± 0.27 [0.50-0.96]
$R_{A.AUC(0-24\ h)}$	1.081 ± 0.17 [0.90-1.26]	0.87 ± 0.21 [0.69-1.05]

R_A = accumulation index

III. METABOLISM:

Exemestane is extensively metabolized. A large number of metabolites, each accounting for a limited proportion of the total measured radioactivity, have been observed in biosamples in all radiolabeled studies conducted in animals and humans (Study PKEXEPHKI-011). Exemestane is rapidly metabolized during the first-pass through the gastrointestinal tract and liver following oral administration. Even at the early sampling times, following oral administration to humans (Study PKEXEPHKI-011) plasma concentrations of radioactivity were much higher than corresponding plasma levels of intact exemestane, indicating the presence of substantial concentrations of metabolite(s) in the systemic circulation (Table 6). Multiple peaks were present in the plasma radioactivity time profiles, thus resulting in a broad plateau which occurred at later times than the peak time of intact exemestane.

Table 6. Pharmacokinetic parameters of exemestane and total radioactivity following oral administration of a single dose of 100 mg [^{14}C]-exemestane to healthy volunteers, mean ± SD, n=4.

Dosing	Substance	C_{max} (ng/mL)	t_{max} (h)	AUC (ng.h/mL)	$t_{1/2}$ (h)
Single 100 mg ^{14}C-exemestane dose	radioactivity	409 ± 272	34 ± 26	40658 ± 34364	38 ± 7
	exemestane	14 ± 5	3.5 ± 0.6	147 ± 31	26 ± 9

Following administration of [^{14}C]-exemestane to healthy postmenopausal women, the cumulative amounts of radioactivity excreted in urine and feces were similar (42 ± 3% in urine and 42 ± 6% in feces over a 1-week collection period). Only minor amounts (from about 0.1 up to 1% of the dose) were excreted in the urine as unchanged drug. A formal evaluation of the amount of unchanged drug secreted in human bile has not been performed. From the data obtained in rats and dogs, substantial amounts of DRM were recovered in the bile. Subsequent profiling of the metabolites showed that only a minor amount of the radioactivity represented intact exemestane. No metabolites of exemestane identified to date have shown significant aromatase inhibition with the exception of the 17-hydroexemestane (FCE 25071), which was 2.6 times less potent than intact exemestane.

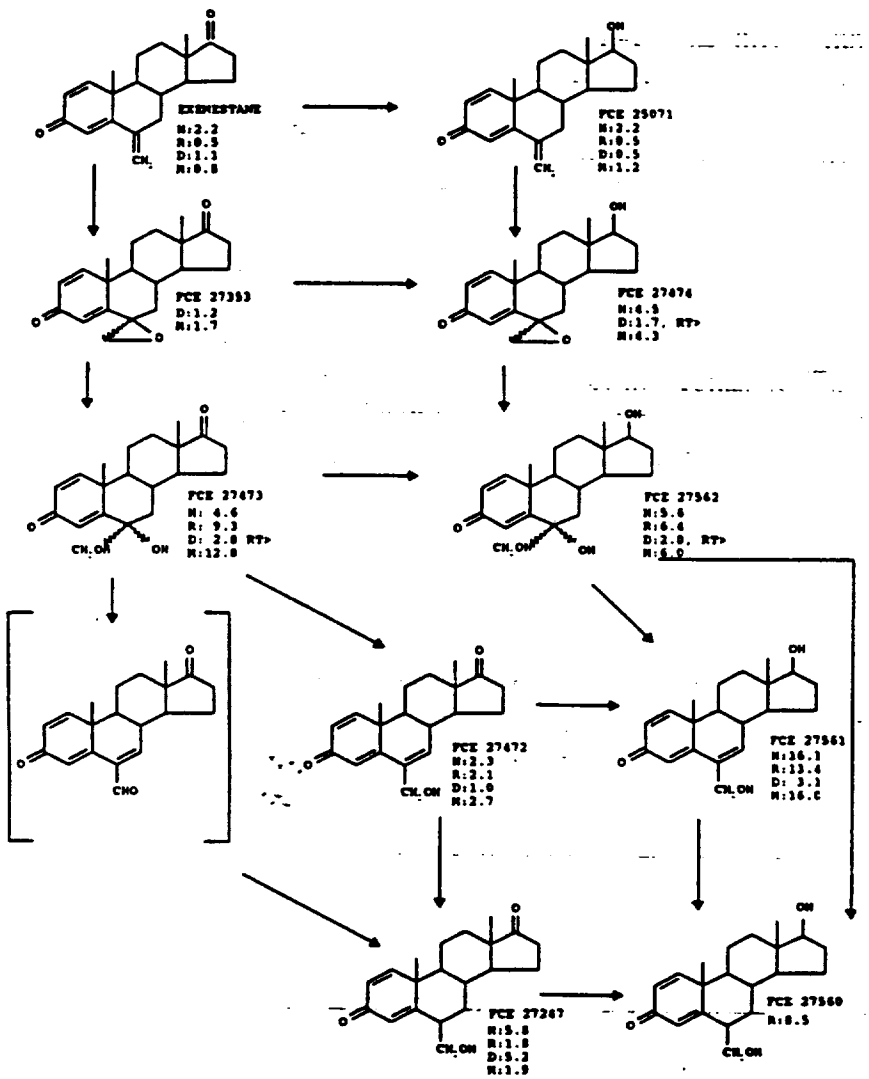
Based on the data obtained in humans as well as in the other animal species, a scheme of the phase I metabolic routes for exemestane has been proposed, as shown in Figure 5 indicating that the pattern of metabolites was similar in all the species (humans, rats, dogs and monkeys). In all species, including man, the initial redox biotransformation reactions involved oxidation of the methylene group at position 6, and/or the reduction of the 17-keto group. Other processes, such as hydrolysis and conjugation reactions, occurred subsequently. The attack at the methylene group of exemestane is an oxidation reaction that produces an epoxy derivative, which is subsequently hydrolyzed. An in vitro study examining the specific Cytochrome(s) P450 (CYP) involved in this biotransformation step suggested that CYP3A4 was the major

isoform involved in this oxidative pathway. Overall, the contribution of other cytochromes sub-families appeared to be minimal.

In general, the shape of the 17-hydroexemestane plasma concentration-time profile was similar to that of exemestane, however, when measured, concentrations of this metabolite were only about 10% of those of the intact drug (Study Study 92-OEXE-008, PKEXEPHKI-011, Study 92-OEXE-023, Study 95-OEXE-024). Thus, its contribution to the overall pharmacological activity of exemestane at therapeutic doses is limited. Formation of 17-hydroexemestane is due to the activity of ubiquitous reductases including those present in blood, responsible for the conversion of androstenedione to testosterone, and might be responsible for the extrahepatic clearance

Additional studies demonstrated that exemestane does not affect the activity of CYP3A4 in humans to any great extent. No significant inhibition of any of the Cytochromes P450 isoenzymes (including CYP3A4) involved in xenobiotic metabolism was observed in human liver preparations. This would suggest that possible drug-drug interactions involving inhibition of Cytochrome P 450 by coadministration with exemestane are unlikely.
Although a slight autoinduction of some metabolic pathways was suggested following repeated administration of exemestane to healthy postmenopausal women (Study 95-OEXE-013), no significant alteration of the ratio of the amount of 6-β-hydroxycortisol/cortisol excreted in urine (a marker of CYP3A activity) was observed, thereby excluding an induction involving CYP 3A. It should be noted, on the other hand, that induction of CYP3A by exemestane was observed in rats. The involvement of this isoenzyme in animal models, but not in humans, could explain the much more pronounced decrease of exemestane plasma levels observed after repeated dosing in animals compared to humans. No significant changes in exemestane pharmacokinetics were observed after coadministration of ketoconazole, a selective inhibitor of CYP3A4. This suggests that the multiplicity of available initial metabolic pathways for exemestane might compensate *in vivo* for the inhibition of this specific biotransformation pathway.

Figure 5. Proposed metabolic routes of exemestane, with metabolite amount, expressed as % of DRM in urine. Legend: H: humans; R: rat; D: dog; M: monkey.



RT> indicates the presence of the only isomer with higher retention time. FCE 27353 was also found in rat plasma. Both isomeric forms of FCE 27473 were found in dog plasma. Both isomeric forms of FCE 27562 were found in dog bile. FCE 27560 was also found in dog bile.

IV. SPECIAL POPULATIONS:

A. Renal Impairment:

Study 95-OEXE-016 evaluated the effect of the renal impairment on exemestane pharmacokinetics. Subjects were classified on the basis of creatinine clearance (healthy

volunteers - $CL_{CR} > 80$ mL/min/1.7 m^2; subjects with moderate renal impairment - 60 mL/min/1.7 m^2 > $CL_{CR} > 30$ mL/min/1.7 m^2; subjects with severe renal impairment - $CL_{CR} < 30$ mL/min/1.7 m^2). The sponsor has submitted the preliminary report (data on three healthy subjects and in seven subjects with severe (or borderline severe) renal impairment) of this study (Table 7) at this time.

In the group of subjects with renal impairment, significant differences were observed in the pharmacokinetic parameters, in comparison with the group of healthy volunteers: AUC increased by a factor of approximately 3 and, in turn, CL/F was significantly decreased and there was also a trend towards an increase in exemestane half-life in these subjects (Table 7). Since renal excretion of intact exemestane represents a minor elimination route (≤ 1% of the dose), it is unlikely that the lower CL_{CR} in subjects with renal impairment could explain the observed differences in the systemic exposure of the drug. Other factors (e.g., decreased hepatic blood flow, decreased intrinsic clearance due to an accumulation of endogenous inhibitors, alterations of plasma or tissue protein binding, etc.) are probably involved in the pharmacokinetic changes observed in the subjects with renal failure.

Table 7. Pharmacokinetic parameters in subjects with renal impairment in comparison with those of healthy volunteers after single dosing (mean ± SD).

Parameter	Subject Group	
	Healthy Subjects (n=3)	Subjects with Renal Impairment (n=7)
C_{max} (ng/mL)	7.1 ± 2.9	16.7 ± 7.2
t_{max} (h)	1.7 ± 0.3	1.6 ± 0.5
AUC (ng·h/mL)	32.4 ± 8.0	92.6 ± 32.1
$t_{1/2,z}$ (h)	27.2 ± 10.0	36.8 ± 16.6
CL/F (L/h)	803 ± 190	313 ± 152
V_z/F (L)	31215 ± 12402	18874 ± 19420

The data from this preliminary report suggests that dose adjustments may be necessary in patients with impaired renal function. Final judgement will be made when the sponsor submits the full study report.

B. Hepatic Impairment:
Study 95-OEXE-015 examined the effects of hepatic impairment on the pharmacokinetics of exemestane. Subjects suffering from liver impairment were classified on the basis of the Child-Pugh score (healthy volunteers, subjects with moderate liver impairment - Child-Pugh B; subjects with severe liver impairment - Child-Pugh C). Ultimately, nine subjects/group will

enter into the study. The preliminay report submitted by the sponsor consisted of data from six healthy subjects, eight subjects with moderate and three subjects with severe liver impairment (Table 8).

In the subjects suffering from severe hepatic impairment, average C_{max} and AUC values were more than 3-times higher than average values observed in healthy volunteers (Table 8). CL/F, in turn, was significantly reduced in subjects with hepatic impairment. The half-lives in the subjects suffering from hepatic impairment were also reduced.

Table 8. Pharmacokinetic parameters in subjects with hepatic impairment in comparison with those of healthy volunteers after single dosing, mean ± SD.

Parameter	Subject Group		
	Healthy Subjects (n=6)	Subjects with Moderate Hepatic Impairment (n=8)	Subjects with Severe Hepatic Impairment (n=3)
C_{max} (ng/mL)	16.3 ± 6.7	38.1 ± 9.6	47.5 ± 31.6
t_{max} (h)	1.7 ±1.2	1.7 ± 1.0	1.5 ± 0.5
AUC (ng·h/mL)	39.3 ± 4.1	114.8 ± 37.7	145.2 ± 19.0
$t_{1/2,z}$ (h)	27.7 ±13.9	12.5 ±7.2	19.4 ± 10.3
CL/F (L/h)	642 ± 74	234 ± 60	174 ± 24
V_z/F (L)	25872 ± 14303	3796 ± 1096	5108 ± 3446

Since the liver is an important metabolic site of exemestane, it is not surprising that a reduced efficiency of the metabolic activity in this organ could give rise to a decrease in CL/F compared to healthy volunteers. The reduction of hepatocellular activity is unlikely to give a significant alteration of CL, since, for an oral drug with high hepatic extraction, such as exemestane, the clearance should be limited by the hepatic blood flow. The reduction of hepatocellular activity, however, could have an impact on the absolute bioavailability, *via* a reduction of the hepatic first pass effect. For high clearance drugs like exemestane, a small reduction in extraction ratio can result in a large increase in absolute bioavailability. The increase in bioavailability in subjects with hepatic impairment is supported by the finding that the C_{max} in these patients was greater than that determined in healthy volunteers. Another observation which is consistent with this interpretation is that the decrease of CL/F was accompanied by a similar decrease in V_z/F. Thus, absolute bioavailability represents the most likely factor to be altered by hepatic impairment. The influence of other factors, such as a decrease in the hepatic blood flow and extrahepatic clearance or alterations of the binding of exemestane to plasma proteins, can not be completely excluded.

The data from this preliminary report suggests that dose adjustments may be necessary in patients with impaired hepatic function. Final judgement will be made when the sponsor submits the full study report.

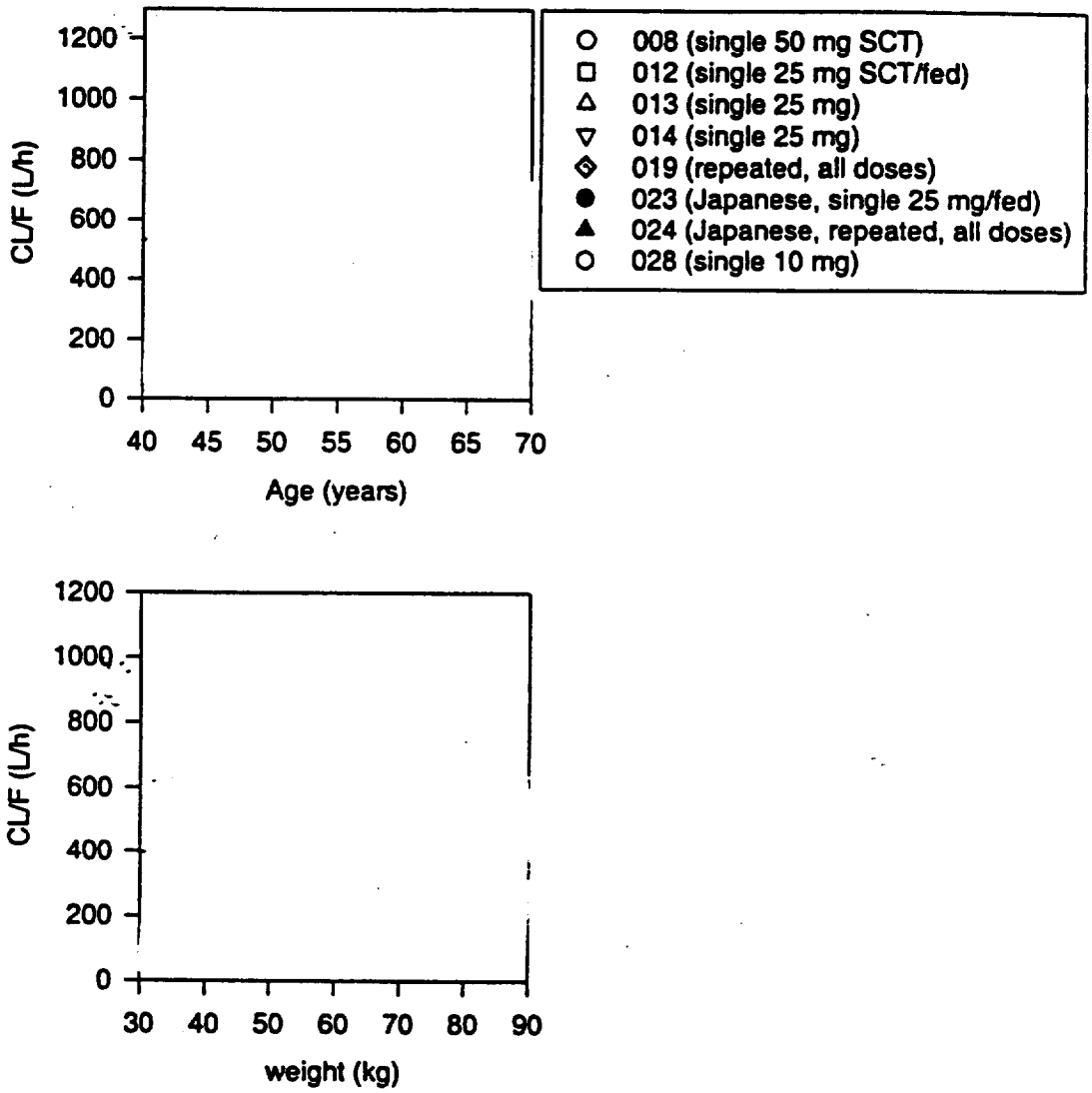
COMMENTS ON RENAL AND HEPATIC IMPAIRMENT STUDIES: From the interim results of the renal impairment study (Study 95-OEXE-016) and the hepatic impairment study (Study 95-OEXE-015), it appears that CL/F and V/F of exemestane were decreased in patients with renal or hepatic impairment compared to healthy volunteers. This observation may be due to decrease in protein binding in this patient population. For a drug that is primarily eliminated by the liver in a restricted manner (i.e. with a low extraction ratio) change in protein binding probably may not alter the free drug concentration (exemestane is 90% bound to plasma protein). However, since the systemic clearance (corrected for bioavailability) is unknown for exemestane it is recommended that free drug concentrations from these two studies should be determined (at least a few samples per subject). Subsequently the data should be analyzed to compare free drug concentrations in healthy volunteers and patients with renal or hepatic impairment.

C. Age and Gender:

The influence of age and weight on exemestane pharmacokinetics was evaluated by plotting oral clearance (CL/F) values versus the age and weight of postmenopausal women who received the recommended 25-mg dose of exemestane (Figure 6.). Only subjects from 45 to 65 years old were enrolled in these trials. Overall, age had no significant influence on the pharmacokinetics of exemestane over this limited age range. Also, exemestane clearance did not show significant dependency on weight.

The effect of gender on exemestane pharmacokinetics was assessed by comparing the systemic exposure obtained in healthy male subjects (mean age 32 years; range 19 to 51 years) who received 25 mg exemestane under fasting conditions (Study 97-OEXE-035) with those obtained in postmenopausal women (mean age 55 years; range 45 to 68 years) who received 25 mg exemestane under fasting conditions (Study 94-OEXE-012). Mean C_{max} and AUC values in healthy males (12.3 ± 5.8 ng/mL and 28.4 ± 17.3 ng·h/mL, respectively) were similar to those in healthy postmenopausal women (11.1 ± 4.4 ng/mL and 29.7 ± 7.8 ng·h/mL, respectively). Thus, the pharmacokinetics of exemestane does not appear to be influenced by gender
The pharmacokinetics of exemestane following administration of a single, 25-mg tablet to fasted healthy males (mean age 32 years; range 19 to 51 years) or to fasted healthy postmenopausal women (mean age 55 years; range 45 to 68 years) have been compared. Mean C_{max} and AUC values in healthy males (12.3 ± 5.8 ng/mL and 28.4 ± 17.3 ng·h/mL, respectively) were similar to those determined in healthy postmenopausal women (11.1 ± 4.4 ng/mL and 29.7 ± 7.8 ng·h/mL, respectively) indicating that the pharmacokinetics of exemestane does not appear to be influenced by gender.

Figure 6. Individual CL/F values obtained in different studies following oral administration of single or repeated dose of exemestane to healthy volunteers. The numbers in the legend refer to the study protocol number. The solid line is the overall regression line (the slopes of both regression lines were not significantly different from zero; r^2 was 0.02 and 0.005 for the regression on age and weight, respectively).



D. Pediatric Population: The pharmacokinetics of exemestane has not been described in the pediatric population.

E. Influence of Race:
The influence of race on the pharmacokinetics of exemestane has not been formally evaluated. Two phase I study were performed in Japanese healthy postmenopausal women following single or repeated dosing (Study 94-OEXE-023, Study 94-OEXE-024). Due to the different experimental conditions adopted (manipulation of blood samples, analytical methods), a formal comparison with the pharmacokinetics of exemestane in Caucasian subjects was not possible. For this reason, the difference observed in the systemic exposure between (Study 94-OEXE-023, Study 94-OEXE-024) and Caucasian ((Study 94-OEXE-013) subjects, especially after repeated administration (Table 9), should be considered with some reservation.

Table 9. Pharmacokinetic parameters of exemestane after single and repeated daily oral doses of 25 mg of the drug as sugar coated tablets after a meal to Japanese and Caucasian (n=8) postmenopausal subjects; mean ± SD [range]

Parameter	Japanese	Caucasian
	Single Administration	
t_{max} (h)	1.4 ± 0.5 [1-2] (n=6)	2.3 ± 1.1 [1.5-4.0]
C_{max} (ng/mL)	14.7 ± 4.7 [7.5-22.1] (n=6)	17.1 ± 12.2 [7.3-42.1]
AUC (ng·h/mL)	93.5 ± 58.2 [34.4-173.7] (n=4)	57.8 ± 26.5 [27.5-102.8]
CL/F (L/h)	368 ± 250 [144-727] (n=4)	517 ± 226 [243-909]
$t_{1/2,z}$ (h)	17.7 ± 6.7 [8.5-23.8] (n=4)	26.6 ± 19.1 [11.3-65.6]
	Repeated Administration	
$t_{max,ss}$ (h)	2.0 ± 0.0 (n=5)	2.9 ± 1.2 [1.5-4.0]
$C_{max,ss}$ (ng/mL)	14.9 ± 3.9 [8.9-18.8] (n=5)	11.4 ± 6.6 [4.8-20.5]
$AUC_{\tau,ss}$ (ng·h/mL)	104.88 ± 30.3 [59.3-137.5] (n=5)	41.4 ± 18.5 [21.5-64.8]
CL/F_{ss} (L/h)	260 ± 96 [182-422] (n=5)	715 ± 296 [386-1165]

F. Patients with Advanced Breast Cancer (ABC):
Pharmacokinetics of exemestane has been studied in patients with ABC following single and repeated doses of 25 mg exemestane (Table 5). After repeated dosing, the average CL/F value in ABC patients were 45% lower than that observed in healthy subjects, with a correspondingly higher systemic exposure (AUC). This could be due to the absence of the slight autoinduction observed in healthy subjects. The influence of the different age range (4 ABC patients had age >65 years) cannot be excluded (See Section II above).

V. DRUG INTERACTIONS:

Drug-drug interactions of exemestane with concomitantly administered medications have not been formally investigated, except for the effect of ketoconazole on exemestane pharmacokinetics (Study 95-OEXE-028).

Exemestane does not inhibit the Cytochromes P450 enzymes commonly involved in the metabolism of xenobiotics (CYP1A2, 2C9, 2D6, 2E1, 3A4). Following repeated administration of 25 mg/day of exemestane, the ratio of the amounts of 6-β-hydroxycortisol/cortisol excreted in urine, a known marker of the activity of the CYP3A, was not significantly altered (Study 95-OEXE-013). Therefore, it is unlikely that exemestane therapy would modify the metabolism of coadministered medications.

Exemestane is metabolized through CYP3A4 and aldoketoreductases, however, no significant influence on the pharmacokinetics of intact exemestane has been observed when 10 mg of exemestane was coadministered with 200 mg of ketoconazole (Table 10). This is probably due to the presence of alternative compensating biotransformation pathways for exemestane and suggests that no substantial alteration of exemestane metabolism would be expected when the drug is given with medications known to inhibit CYP3A4.
Overall, clinically significant pharmacokinetic interactions, mediated by CYPs, appear unlikely, even though a possible decrease of exemestane plasma levels by known inducers of CYP3A4 cannot be excluded.

Table 10:The statistical analysis on non-compartmental pharmacokinetic parameters of exemestane after 10 mg oral administration of exemestane to healthy postmenopausal subjects before and during repeated administrations with ketoconazole is listed in the following table (n=5).

Parameter	mean values		Student's t-test	mean ratio During/before ketoconazole	90% CI of the Mean ratio during/before ketoconazole
	Single dose before ketoconazole	single dose during ketoconazole			
C_{max} (pg/ml)*	4.06 (15262±10271)	3.94 (9158±2767)	NS	0.97	0.33 1.81
AUC (pg·h/ml)*	4.48 (31328±8947)	4.45 (28373±5066)	NS	0.99	0.69 1.26
$t_{1/2,z}$ (h)	26.85	42.48	NS		
CL/F (l/h)	351	360	NS		
V_z/F (l)	12507	22258	NS		

*Statistics based on log-transformed values. The actual values (mean ± SD) are shown below.

VI. Comparison of the Pharmacokinetics in Animal Species and Humans.

The chronic oral doses used in the toxicology assessments were various orders of magnitude higher than the proposed therapeutic doses in humans, thus ensuring an adequate exposure to the drug for assessment of safety margin. Using average AUC as an index of systemic exposure in animals and humans, at least a 3- to 6-fold safety margin was achieved in man at the recommended dose level (Table 11).

Table 11. Comparison of doses and systemic exposure indices after repeated dosing at the no-observed-adverse-effect-level (NOAEL) in the toxicology assessments with those obtained in humans after repeated dosing at the therapeutic dose level.

Species	Dose (mg/kg/d)	Dose ($mg/m^2/d$)	$C_{max,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng·h/mL)
Rat	50	300	61	137
Dog	30(1)	600	158	243
Man (2)	0.4	16	11.4	41

(1) No-observed-effect- level (NOEL)

(2) 2-week repeated dosing; doses calculated assuming 60 kg average weight and 1.60 m^2 average body surface area.

The pattern of metabolites appeared similar between man and animal species, confirming the relevance of the animal species chosen for the toxicity assessment.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP

The sponsor has conducted a number of studies in which estrogen suppression was measured (Study 94-OEXE-024, Study 92-OEXE-019, Study 92-OEXE-008, Study 94-OEXE-012, Study 94-OEXE-023). However, no PK-PD analysis was done by the sponsor.
Plasma estrogen (estradiol – E_2, estrone – E_1, and estrone sulfate – E_1S) suppression was seen starting at a 5-mg daily dose of exemestane, with a maximum suppression achieved at a 25-mg dose. After a single dose of exemestane 25 mg, the maximal suppression of circulating estrogens occurred 2 to 3 days after dosing and persisted for 4 to 5 days.

Study 94-OEXE-024 examined the inhibitory effect of exemestane on serum and urinary estrogens following a 7-day repeated oral dose administration to healthy postmenopausal Japanese volunteers. The results obtained from the study showed that a dose related decrease in serum and urinary estrogens was observed. The estrogen suppression was still present 1 week after discontinuation of therapy and almost disappeared at 2 weeks (Table 12, Figure 7).

Table 12

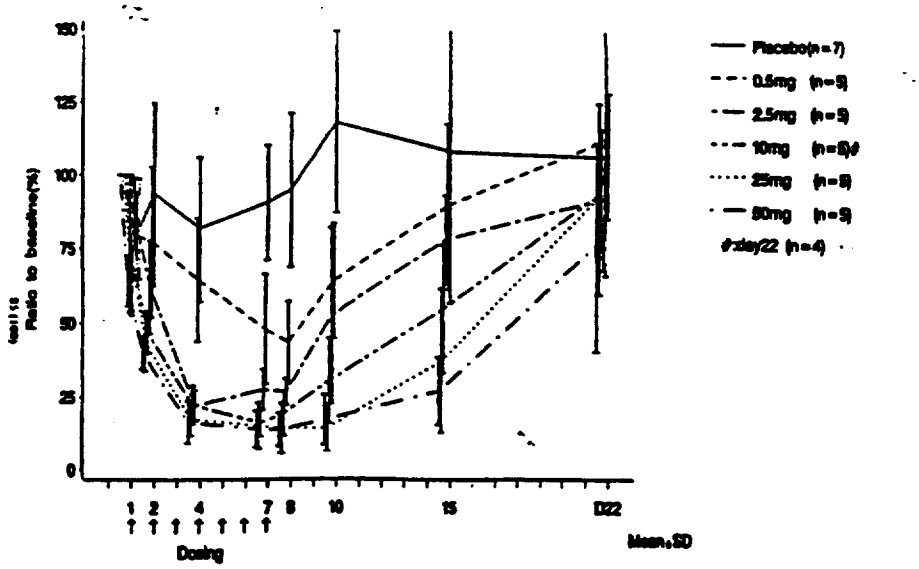
Pharmacodynamics:

In the Table below the serum estrogen levels (n=5) or the urinary estrogen excretion (n=5) were expressed as percentage of baseline values (Mean ± SD)

Parameter	Study day	Dose (mg/day for 7 days)					
		0.5	2.5	10	25	50	placebo
Serum E_2	4	69±24	54±16	33±17	31±10	35±17	95±14
	8[a]	58±14	50±19	31±18	27±13	31±12	101±37
	15[b]	97±26	85±21	49±22	45±14	33±14	111±45
Serum E_1	4	59±13	49±31	33±13	29±10	35±16	86±21
	8	50±17	51±29	36±9	29±17	38±15	100±28
	15	97±31	87±57	54±10	28±6	41±22	105±27
Serum E_1S	4	65±21	22±5	22±7	18±6	17±7	82±25
	8	44±14	27±4	20±8	14±9	14±6	95±26
	15	90±28	78±15	55±22	37±24	27±12	109±52
Urinary E_2	4	81±33	38±19	36±18	25±10	33±15	107±37
	8	86±54	29±9	23±6	17±11	28±14	132±37
	15	134±66	56±24	89±91	25±13	16±5	114±37
Urinary E_1	4	76±35	31±14	30±12	30±15	43±13	87±31
	8	70±44	24±7	25±11	19±4	67±34	127±36
	15	135±84	58±35	51±39	20±12	15±3	101±31

[a] Day 8 = 24 hours after the last dose; [b] Day 15 = 8 days after treatment discontinuation

Figure 7:Changes in Serum Estrone Sulfate Concentration



Study 94-OEXE-019 examined the inhibitory effect of exemestane on serum and urinary estrogens following a 7-day repeated oral dose administration to healthy postmenopausal volunteers. The results obtained from the study showed that a dose related decrease in serum

and urinary estrogens was observed. The estrogen suppression was still present 5 days after discontinuation of therapy (Figures 8-10).

Figure 8

Mean percentage of baseline value of E1 plasma level measured during the treatment at the dose of 1mg (◆), 2.5mg (◆), 5mg (▲), 10mg (■). The standard deviation of the mean is shown as a vertical bar adjacent to each plotted symbol.

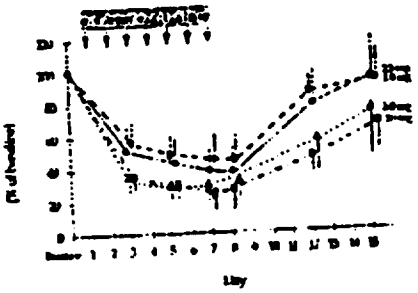


Figure 9

Mean percentage of baseline value of E1S plasma level measured during the treatment at the dose of 1mg (◆), 2.5mg (◆), 5mg (▲), 10mg (■). The standard deviation of the mean is shown as a vertical bar adjacent to each plotted symbol.

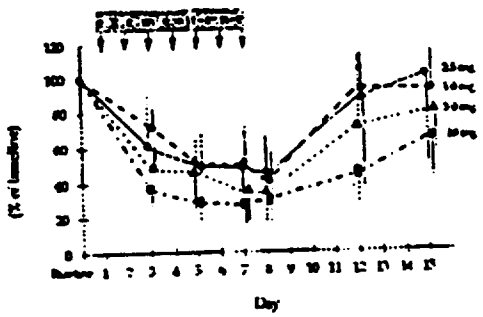
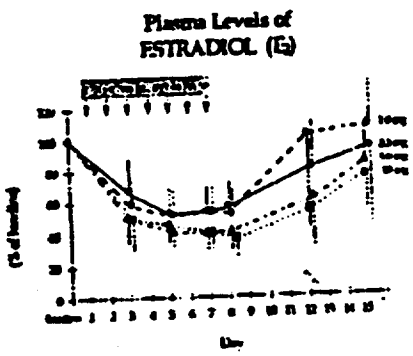


Figure 10

Mean percentage of baseline value of E2 plasma level measured during the treatment at the dose of 1mg (◆), 2.5mg (◆), 5mg (▲), 10mg (■). The standard deviation of the mean is shown as a vertical bar adjacent to each plotted symbol.

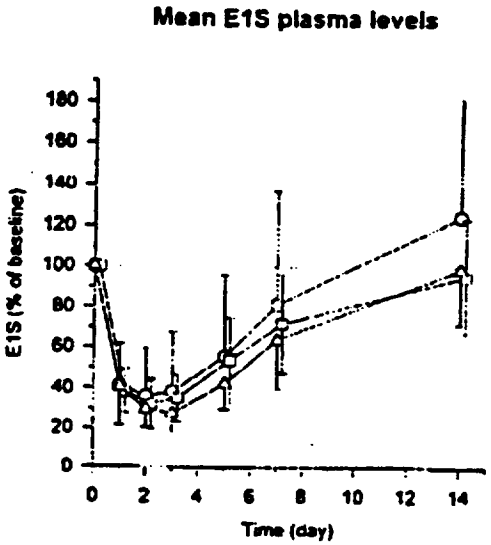


Study 94-OEXE-012 showed that three means of administration of exemestane (tablet/fast, suspension/fast, tablet/fed) caused similar inhibition of E1S (70-76%) which was reached at 2.5-2.7 days post-dosing and a similar inhibition during the 14-day observation period

(AUC_{effect}). A longer duration of the inhibitory effect ($t_{\frac{1}{2},effect}$) was observed when the drug was administered with food which corresponds to the increased systemic exposure to exemestane when given with food (Figure 11).

Figure 11

Effect of a single oral dose of 25 mg exemestane given as sugar-coated tablet either in fasting (treatment A, ○) or fed conditions (treatment C, Δ), and as suspension in fasting conditions (treatment B, □), on plasma estrone sulphate levels (E1S) (mean±SD) in healthy postmenopausal volunteers. Cross-over study in 12 subjects.



Study 94-OEXE-023 examined the inhibitory effect of exemestane on serum and urinary estrogens in healthy postmenopausal Japanese volunteers and showed that the serum estrogen (E_1, E_2, and E_1S) suppression was similar at 25 mg (with and without food) and 50 mg exemestane, reached its maximum (22-39% of baseline) 2 or 3 days after drug administration and almost disappeared at 2 weeks as previously observed (Table 13).

A population PK-PD analysis was conducted on the data from Study 94-OEXE-012. A two compartment model best described the PK data and the analysis showed that bioavailability was influenced by both food and formulation while formulation influenced the absorption rate. The PD (suppression of E_1S) was fitted to an indirect inhibitory model and simulations showed that the PD model predicted the onset and off set of estrogen suppression by exemestane.

Table 13: Suppression of serum estrogen by exemestane in healthy postmenopausal Japanese volunteers

1. Single dose study at 25/50mg

	Study day	E_2 (%)		E_1 (%)		E_1S(%)	
		Mean±SD	value*	Mean±SD	p value	Mean±SD	p value
25mg (n=4)	Baseline	100.00	-	100.00	-	100.00	-
	Hours after dosing	81.57 ± 15.16	N.S	53.41 ± 9.93	0.003	104.25 ± 41.04	N.S
	D2	43.49 ± 9.13	0.001	34.16 ± 13.36	0.002	47.63 ± 14.80	0.006
	D3	27.31 ± 7.34	<0.001	26.68 ± 7.18	<0.001	33.69 ± 9.70	0.001
	D4	27.50 ± 6.80	<0.001	30.09 ± 10.09	0.001	29.88 ± 11.71	0.001
	D8	47.83 ± 11.77	0.003	54.94 ± 6.19	0.001	65.45 ± 14.70	0.018
	D15	96.71 ± 22.79	N.S	93.28 ± 11.81	N.S	133.80 ± 50.07	N.S

	Study day	E_2 (%)		E_1 (%)		E_1S(%)	
		Mean±SD	p value	Mean±SD	p value	Mean±SD	p value
50mg (n=4)	Baseline	100.00	-	100.00	-	100.00	-
	Hours after dosing	89.50 ± 14.57	N.S	66.99 ± 36.70	N.S	75.43 ± 5.95	0.004
	D2	58.62 ± 9.49	0.003	56.50 ± 28.27	N.S	50.61 ± 11.92	0.004
	D3	39.16 ± 8.08	0.001	36.36 ± 10.97	0.001	24.63 ± 4.52	<0.001
	D4	36.77 ± 10.84	0.001	38.27 ± 11.66	0.002	22.41 ± 5.64	<0.001
	D8	38.69 ± 13.43	0.003	46.13 ± 13.73	0.004	26.04 ± 15.66	0.003
	D15	76.74 ± 15.83	N.S	93.99 ± 22.86	N.S	80.82 ± 29.54	N.S

	Study day	E_2 (%)		E_1 (%)		E_1S(%)	
		Mean±SD	p value	Mean±SD	p value	Mean±SD	p value
Placebo (n=4)	Baseline	100.00	-	100.00	-	100.00	-
	Hours after dosing	97.05 ± 9.66	N.S	86.01 ± 15.63	N.S	100.99 ± 17.14	N.S
	D2	111.15 ± 5.61	0.028	101.02 ± 17.61	N.S	105.08 ± 15.54	N.S
	D3	94.84 ± 11.26	N.S	97.23 ± 5.38	N.S	82.08 ± 8.86	0.027
	D4	93.81 ± 9.25	N.S	112.04 ± 20.43	N.S	91.79 ± 9.18	N.S
	D8	94.95 ± 9.19	N.S	94.64 ± 15.05	N.S	116.40 ± 19.71	N.S
	D15	83.09 ± 11.73	N.S	95.05 ± 18.39	N.S	106.51 ± 14.67	N.S

*: One sample t-test , N.S : No Significance(p>0.05)

(Assuming that each baseline is 100%, statistical analysis were performed with percentage changed from baseline.)

VIII. FORMULATION: The quantitative composition of the tablet formulation to be marketed (25 mg) is shown on Table 14.

TABLE 14

The quantitative composition of Exemestane 25 mg sugar-coated tablets is provided in the following table:

Ingredient	Per sugar-coated tablet	Per 1,600,000 sugar-coated tablets
Exemestane (PNU-155971)		
Mannitol, USP		
Hydroxypropyl methylcellulose 2910, USP		
Polysorbate 80, NF		
Crospovidone, NF		
Silicon dioxide, NF		
Microcrystalline cellulose, NF		
Sodium starch glycolate, NF		
Magnesium stearate, NF		
Purified water for granules preparation (removed during processing) USP		
Total		
Sugar-coating:		
Sealing:		
Hydroxypropyl methylcellulose 2910, USP		
Simethicone emulsion, USP		
Polyethyleneglycol 6000, NF		
Sucrose, NF		
Total		
Greasing:		
Magnesium carbonate, USP		
Titanium dioxide, USP		
Methylparaben, NF		
Polyvinyl alcohol, USP		
Sucrose, NF		
Total		
Final sugar-coating:		
Sucrose, NF		
Purified water, USP for the sugar coating steps (removed during processing)	q.s.	q.s.

NOTE : the quantities of active drug substance and mannitol used to prepare the initial wet granulation, can be adjusted according to the active ingredient assay.

VIII. DISSOLUTION

The proposed dissolution method of USP Apparatus I at 100 rpm, 0.5% (w/v) sodium lauryl sulfate aqueous solution at 37°C is appropriate but the specification should be changed from Q of ⌐ ¬% in ⌐ ¬minutes to Q of ⌐ ¬% in ⌐ ¬minutes.

IX. ASSAYS

XI. PLASMA PROTEIN BINDING

The binding of exemestane to plasma proteins in man was evaluated using the radiolabelled drug and equilibrium dialysis. A range of concentrations from . ng/mL was

evaluated. The fraction bound was of the order of 90% of the total concentration. A comparison of the results obtained in plasma of healthy volunteers and animal species is shown in Table 6. In all species, there was no significant dependence of the fraction bound on the total exemestane concentration, suggesting that a nonspecific hydrophobic interaction occurred, rather than a specific binding to globulin which is typical of corticosteroids. The fraction of [^{14}C]-exemestane bound to either albumin or human α_1-acid glycoprotein was demonstrated to be concentration-independent up to 1000 ng/mL. Albumin and α_1-acid glycoprotein contributed equally to the binding (fraction bound 93-95%), again demonstrating the non-specificity of the interaction of exemestane with plasma proteins.

Table 6
Fraction of [^{14}C]-exemestane bound to plasma proteins of various species.

Species	% Bound
Humans	90-91
Mouse	90-91
Rat	88-89
Rabbit	97-98
Dog	91-92

XII. LABELING: The clinical pharmacology section of the labeling is deficient and the firm has been advised to modify it accordingly.

APPENDIX

METABOLIC PROFILING

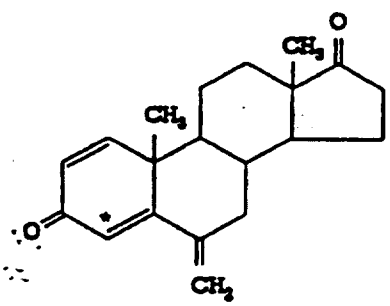
STUDY PK EXEPHKI-011 VOLUME: 1.35 PAGES: 126 - 394

INVESTIGATOR AND LOCATION:

STUDY DATE: May to September 1993.

OBJECTIVES: (i) To evaluate the metabolism, pharmacokinetics and the rates and routes of excretion of a single dose of ^{14}C-FCE 24304 (exemestane) in postmenopausal healthy volunteers, (ii) To record any other effects of the test product during study period. plasma to determine the protein binding of ^{14}C-radioactivity.

FORMULATIONS:
100 mg ^{14}C- FCE 24304 (exemestane) capsules; Batch: RT 10178/72 (specific activity of 0.496 µCi/mg and radiochemical purity >98%).



* Denotes position of radiolabelling

Figure 1. Structural formula of ^{14}C- exemestane (^{14}C- FCE 24304)

STUDY DESIGN:
An open-label, single dose study in four postmenopausal female vounteers. Each subject received a single oral dose of 100 mg ^{14}C-FCE 24304 after a light breakfast. Blood, urine and fecal samples were collected for 7 days (168 hours) and analyzed for total radioactivity. Blood samples (12 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144 and 168 h after oral administration of the capsule formulation. Urine samples were collected blank (pre-dose), 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 120-168 h post-dose. Radiactivity was measured with an

ASSAYS:

IDENTIFICATION OF METABOLITE:

DETERMINATION OF PROTEIN BINDING: By centrifugation method (Centrifree™ micropartition systems).

DATA ANALYSIS: (AUC0-168), the amount of radioactivity excreted in urine and faeces and the total amount of radioactivity excreted, AUC, Cmax, Tmax, $t_{1/2}$, %Dose excreted were calculated.

RESULTS: Tables 1- 4 and Figures 2-5 summarize the data obtained from the study.

Table 1.

The protein binding of radioactivity in selected plasma samples

Results are expressed as % radioactivity bound to protein

Time after dose administration (hours)	Subject number			
	1	2	3	4
4	70	72	75	NA
6	NA	NA	NA	74
12	83	NA	84	80
16	NA	77	NA	NA
24	85	NA	NA	85
48	NA	94	NA	NA
72	NA	NA	100	NA

NA Not analysed

Table 2.

The excretion of radioactivity by postmenopausal female human subjects following the administration of single oral doses of ^{14}C-PCE-24304

Results are expressed as % dose

Subject number	1	2	3	4	Mean ± SD
Urine					
0 - 2*					0.37 ± 0.34
2 - 4					2.66 ± 0.70
4 - 6					2.52 ± 0.74
6 - 8					2.04 ± 0.19
8 - 12					5.21 ± 1.02
12 - 24					8.73 ± 0.87
24 - 48					11.38 ± 1.56
48 - 72					5.63 ± 1.22
72 - 96					2.95 ± 0.61
96 - 120					1.42 ± 0.57
120 - 144					0.85 ± 0.27
144 - 168					0.50 ± 0.18
Urine total					42.20 ± 3.34
Faeces					
0 - 24*					1.43 ± 1.32
24 - 48					13.35 ± 12.57
48 - 72					7.98 ± 5.20
72 - 96					12.76 ± 13.12
96 - 120					3.46 ± 2.72
120 - 144					2.17 ± 1.49
144 - 168					0.99 ± 0.92
Faeces total					42.13 ± 5.83
Total recovery					84.33 ± 5.57

* Times (in hours after dose administration)
SD Standard deviation
NS No faeces voided (taken as zero in the mean calculation)

Table 3.

Pharmacokinetic parameters of total radioactivity in plasma (taken from [1])

Subject No.	C_{max} ngeq/ml	t_{max} h	AUC(0-t_q) ngeq·h/ml	AUC ngeq·h/ml	$t_{1/2}$ h
01	290	24	24929	26877	40
02	293	16	28560	30070	33
03	815	72	78303	91207	46
04	238	24	14073	14478	31
Mean	409	34	36466	40658	38
SD	272	26	28562	34364	7

Figure 2.

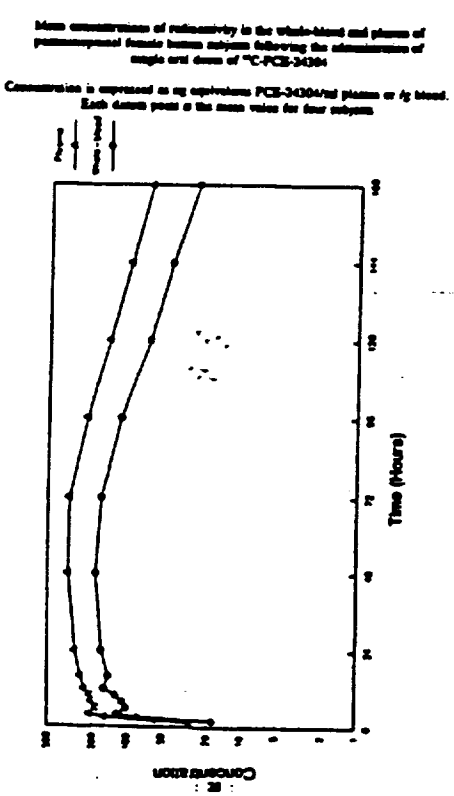
Figure 3.

Table 4

Pharmacokinetic parameters of FCE 24304 after a single oral 100 mg dose of ^{14}C-FCE 24304 in four healthy female volunteers. The parameters were calculated from plasma levels measured by

Subject No.	C_{max} ng/ml	t_{max} h	AUC(0-t_z) ng·h/ml	AUC ng·h/ml	%EXT(t_z-∞)$_{AUC}$	Regression range h	points	$t_{1/2}$ h
01	10.19	4.00	127.43	131.85	3.35	48-96	3	36.50
02	11.77	3.00	105.49	110.17	4.25	24-72	3	19.79
03	21.29	3.00	166.33	168.42	1.24	48-96	3	17.22
04	14.12	4.00	172.32	176.72	2.49	48-144	5	31.40
Mean	14.34	3.50	142.89	146.79	2.83			26.23
SD	4.91	0.58	31.91	31.24	1.28			9.22

Figure 4:



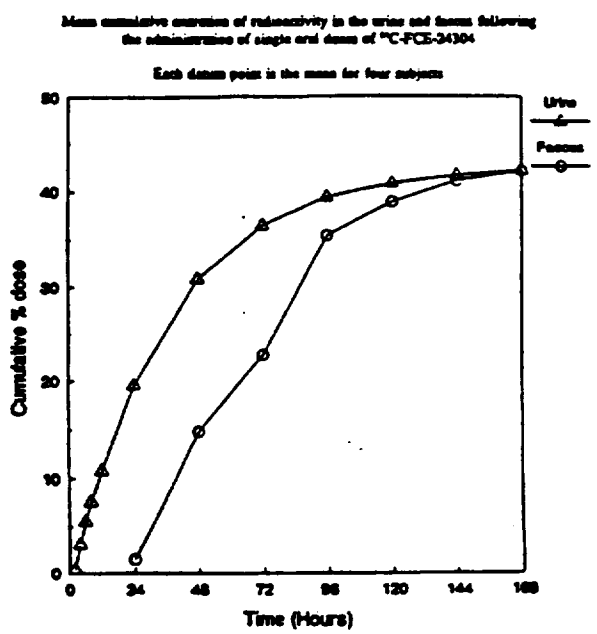


Figure 4.

Mean (± SEM) radioactivity (□) and FCE 24304 (▪) plasma levels after single oral 100 mg ^{14}C-FCE 24304 to the four subjects (log-lin scale).

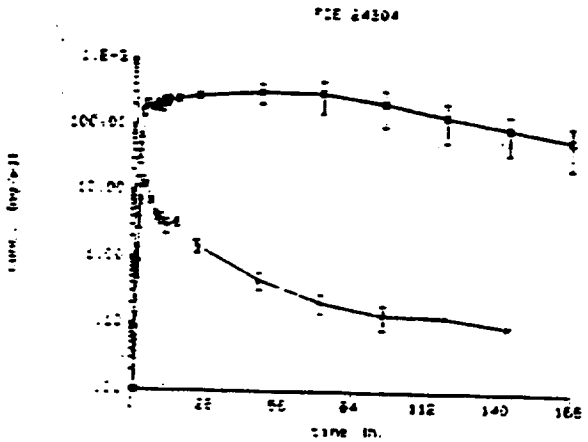
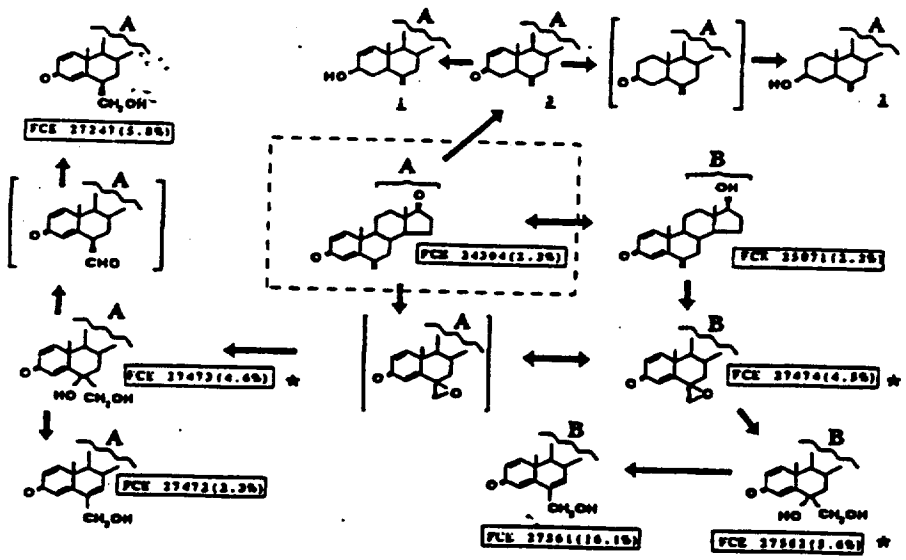


Figure 5:

Proposed metabolic pathway for FCE 24304 in humans; * indicates that both the α and β epimers are present; values in () are given as % of total radioactivity in urine. For metabolites 1, 2, 3 a precise quantification was not possible; the fraction from which these metabolites were the major constituents, together with metabolite 4 (see page 16), amounted to 15.8% of total radioactivity in urine.



CONCLUSIONS: The results obtained from the study show that:

(i) Following oral administration of ^{14}C-FCE 24304, radioactivity is virtually confined to plasma indicating that the uptake of radioactivity into blood cell was generally minimal.

(ii) Plasma pharmacokinetic profiles display 2 concentration maxima and a long $t_{1/2}$ for radioactivity (38±7 hours) indicating possible enterohepatic circulation of ^{14}C-FCE 24304 and/or its metabolites. The $t_{1/2}$ of exemestane is 26±9 hours.

(iii) The recovery of radioactivity at 168 h was on average 84% (range 79 to 91%) with similar amounts recovered in urine (42%) and feces (42%). The mean total excretion in urine indicates that the absorption of orally administered ^{14}C-FCE 24304 was incomplete (on average 42%).

(iv) Exemestane binds to plasma proteins with % radioactivity bound ranging from 70% at 4 hours to 100% at 72 hours post dose.

(v) Exemestane is extensively metabolized to several polar metabolites in plasma and urine (Figure 5). Metabolites identified as FCE 27562, FCE 27473 and FCE 27474 were present as the two isomers and FCE 27561 is main metabolite in urine. Based on the analysis of urine eliminated within the first 48 hours (31% of dose), about 60% of the radioactivity was identified as unchanged exemestane (2.2% of radioactivity) or metabolites. AUC of exemestane accounted for less than 1% of the AUC determined from the radioactivity in plasma (Figure 4) indicating extensive metabolism, possibly both systemically and by first-pass effect. The plasma levels of the 17-dihydro metabilite (FCE 25071) were always below LOQ in this study.

IN VITRO METABOLIC STUDIES

REPORT NUMBERS: FCE 24304/9750052, FCE 24304/9550346 & PNU-155971/9850104
VOL. 1.53 PAGES 336-444

INVESTIGATORS AND LOCATION:

OBJECTIVE: To identify the CYP-450 isozyme primarily responsible for the oxidative metabolism of exemestane; to investigate the inhibitory potential of specific CYP-450 isozymes by exemestane and to evaluate the potential of exemestane for metabolic drug-drug interactions.

PROCEDURES:

The biotransformation of exemestane was investigated using a bank of human liver microsomes (from 26 different donors) , micromes prepared from human hepatocyte culture, and microsomes prepared from a human lymphoblastoid cell line transfected with human CYP cDNAs. Various tests were performed including: (i) correlations between the rate of production of the main metabolites of exemestane and the levels of various CYP forms (CYP1A2, CYP2D6, CYP2E1, and CYP3A4) and various monoxygenase activities (acetanilide hydroxylase for CYP1A2, ethoxyresorufin O-deethylase for CYP1A1 and 1A2, phenacein O-deethylase for CYP1A2, coumarin hydroxylase for CYP2A6, tolbutamide 4-hydroxylase for CYP2C9, debrisoquine 4-hydroxylase for CYP2D6, S-mephenytoin hydroxylase for CYP2C19, chlorzaoxazone 6-hydroxylase for CYP2E1, terfenadine hydroxylase and cyclosporin A oxidase for CYP3A4); (ii) effect of CYP-specific inhibitors or substrates (ketoconazole and cyclosporin A for CYP3A4, furafyllin for CYP1A2, coumarin for CYP2A6, diethyldithiocarbamate for CYP2A6 and CYP2E1, sulfaphenazole for CYP2C9, quinidine for CYP2D6 and S-mephenytoin for CYP2C19); (iii) effect of CYP-specific inducers (rifampin for CYP3A4, TCDD for CYP1A1 and 1A2; in this case the microsomes used were extraxted from human hepatocytes exposed to these inducers); (iv) the use of cDNA-expressed human CYPs including CYP1A1, CYP1A2, CYP2D6, CYP2B6, CYP2D6, CYP2E1, and CYP3A4).

The experiments were performed using exemestane concentrations of 50 μM to 200 μM or up to 50 ng/ml (Cmax after 7 daily doses of 10 mg is 11 ng/ml and plasma protein binding is about 91%). The concentration of exemestane is lower than its Km while the concentrations of the inhibitors or substrates exceeded their respective Ki or Km in order to amplify their putative inhibitory effect.

RESULTS: Tables 1-3 and Figures 1-3 summarise the results obtained from the study.

Table 1. Correlations

	25071	27353	27473	Sum*	1A2	2D6	3A4	Act Hyd	EROD	CSAOx	2E1	Coum	S-MP
25071	-	0,404	0,626		0,336	0,108	0,269	0,508	0,348	0,238	0,278	0,095	-0,030
		0,07	0,0024		0,138	0,646	0,241	0,018	0,124	0,302	0,225	0,685	0,899
27353		-	0,716		0,436	0,262	0,403	0,212	0,245	0,650	0,326	0,039	0,046
			0,0002		0,047	0,255	0,070	0,360	0,288	0,001	0,151	0,867	0,845
27473			-		0,661	0,106	0,538	0,620	0,515	0,625	0,548	0,349	-0,094
					0,001	0,661	0,013	0,003	0,019	0,0025	0,011	0,294	0,697
Sum*				-	0,536		0,459	0,341	0,344	0,682	0,414	0,093	-0,039
					0,014		0,041	0,143	0,140	0,0006	0,069	0,697	0,871
1A2					-			0,707	0,668				
					-			≤0,0001	0,0001				
3A4							-			0,769			
										≤0,0001			
Act Hyd								-	0,709				
									≤0,0001				

* Sum of 27353 and 27473. First line: Fisher's R correlation coefficient; second line: P-value. Act Hyd, acetanilide hydroxylase; EROD, ethoxyresorufin O-deethylase; CSAOx, cyclosporine oxidase; Coum, coumarine hydroxylase; S-MP, mephenytoin hydroxylase.

Table 2. Biotransformations of exemestane by cDNA-expressed human CYPs

CYP forms	FCE25071	FCE27353	FCE27474
control	0.81	0.13	0.39
1A1	1.11	0.26	0.51
1A2	1.21	0.39	0.64
2A6	0.4	0.26	0.64
2B6	1.11	0.39	0.64
2D6	0.81	0.26	0.51
2E1	0.67	0.26	0.77
3A4	0.53	12.31	0.64

Activity in nmol/60min/mg

According to the specific content of CYP3A4 is approximately 50pmol/mg. This allowed us to evaluate the turnover number of 4.1 min^{-1} for the production of FCE27353.

Table 3: Maximum inhibitory effect of exemestane on P450 activities

Activity	Maximum percentage inhibition in liver sample:					
	K2	K5	T6	T8	T9	DA6
Phenacetin O-dethylase	24.3	5.3	14.3	18.3	19.1	27.4
Tolbutamide 4-hydroxylase	5.8	0.0	0.7	11.8	12.9	12.8
Debrisoquine 4-hydroxylase	6.4	0.6	0.0	3.2	6.7	3.3
Chlorzoxazone 6-hydroxylase	1.9	10.4	0.0	10.5	8.6	5.0
Terfenadine hydroxylase	8.3	6.9	1.8	0.0	1.0	2.4

Figure 1. Structure of exemestane (FCE 24304) and its known metabolites

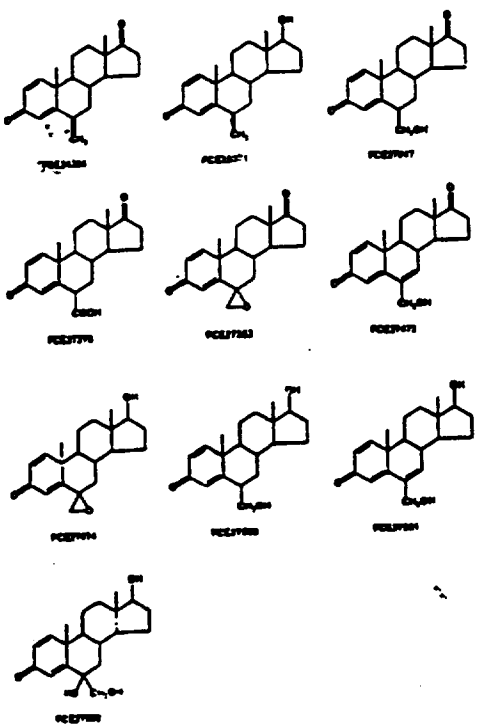


Figure 2. Effect of CYP-specific inhibitors and substrates on the metabolism of exemestane

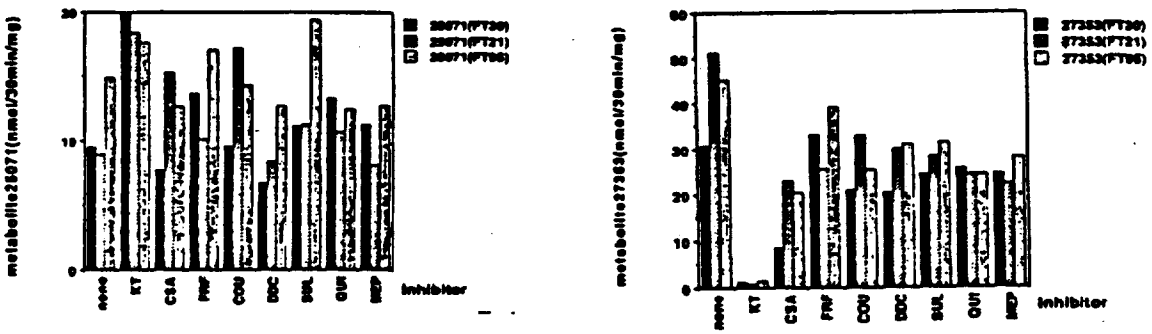
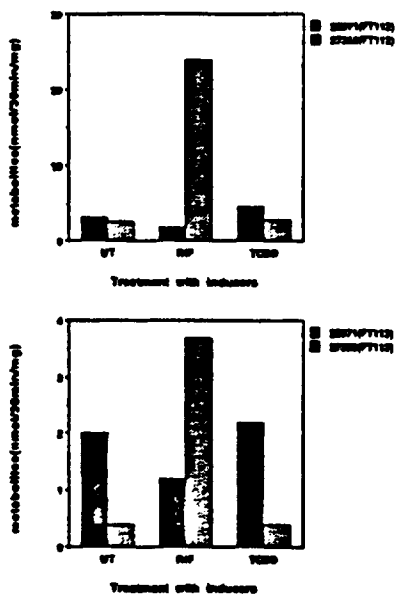


Figure 3. Effect of CYP inducers on the metabolism of exemestane



CONCLUSIONS: The results obtained from the studies showed that:

1. CYP3A4 is the major enzyme involved in the oxidative metaboilism of exemestane (FCE 24304) to FCE 27353, FCE 27473, and possibly to FCE 27562 and FCE 27274. Other CYP forms including CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 appear not to be significantly involved in the biotransformation of FCE 24304. None of the CYP enzymes investigated appear to be involved in the production of FCE 25071. The three main metaboiltes are FCE 25071, FCE 27353 and FCE 27473.
2. Exemestane may therefore be metabolized to a significant extent in the intestinal wall by

CYP3A4 following oral administration.

3. Drug interactions are theoretically expected between exemestane and CYP3A4 inhibitors or inducers (but exemestane has a wide therapeutic window). However, because the Km for exemestane relative to its oxidative metabolism (that is relative to CYP3A4) is in the range of 1 mM and plasma level is not expected to be greater than 0.2 μM (50 ng/ml), it is unlikely that exemestane will interfere to a significant extent with the metabolism of CYP3A4 substrates. In the contrast, it is expected that substrates and inhibitors of CYP3A4 will interfere with FCE 24303 metabolism.
4. Exemetane, at concentrations above therapeutic plasma levels (50 ng/ml), does not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. Based on these results from the in vitro studies and the extensive plasma protein binding of exemestane it could be concluded that clinically relevant drug-drug interactions as a result of metabolic inhibition of other drugs that are substrates of CYP 450 enzymes by therapeutic doses of exemestane are unlikely. In the contrast, it is expected that substrates of CYP3A4 will interfere with FCE 24303 metabolism.

IN VITRO PROTEIN BINDING

PROTOCOL NUMBERS: FCE 24304/810I & PNU 155971/750070
VOL 1.30 PAGES 1-54

INVESTIGATOR AND LOCATION:

PROCEDURES:

Protein Binding: The binding of ^{14}C-exemestane to human plasma proteins was studied in vitro by equilibrium dailysis (Dainorm Equilibrium Dialyse, MSE, UK) at concentrations ranging from 10 to 1000 ng/ml. The samples were dialyzed at 37°C for 2 hours and radioactivity was determined using a scintillation counter.

The binding of ^{14}C-exemestane to human serum albumin (HSA) and α_1-acid glycoprotein (AAG) was studied in vitro by[ ]at concentrations ranging from 10 to 1000 ng/ml. The concentrations of the two proteins used during the experiment of dialysis were 40 and 2 g/l respectively (physiological concentrations). The samples were dialyzed at 37°C for 2 hours and radioactivity was determined using a scintillation counter.

RESULTS: Tables 1-2 summarize the results obtained from the study.

TABLE 1

BINDING OF [^{14}C] FCE 24304 TO HUMAN PLASMA PROTEINS

Drug ng/ml	Dpm Standard	Dpm/ml Plasma	Dpm/ml Buffer	% Bound	Mean	SD
10	1854	1650	149	90.97	91.14	0.44
		1698	156	90.81		
		1698	142	91.64		
50	4724	4038	402	90.04	90.08	1.28
		4210	363	91.38		
		4219	472	88.81		
200	4753	4042	368	90.90	91.20	0.34
		4300	363	91.56		
		4321	383	91.14		
500	4741	4118	361	91.23	91.33	0.22
		4193	370	91.18		
		4339	365	91.59		
1000	4851	4199	385	90.83	91.23	0.38
		4289	378	91.39		
		4274	373	91.47		

Table 2:

Binding of ^{14}C-exemestane to selected fractions of human plasma proteins. Results are reported as mean %±SD (n=3).

Initial concentration (ng/ml)	plasma protein	
	HSA	AAG
10	93.4±0.33	94.5±0.41
50	93.9±0.12	94.8±0.09
200	93.6±0.11	94.2±0.06
500	93.5±0.05	94.1±0.12
1000	93.6±0.10	93.8±0.17

CONCLUSIONS: The data obtained from the study show that;

(i) Exemestane is highly bound to plasma protein (93-95%) and the plasma protein binding remains unchanged over 10-1000 ng/ml concentration range.

(ii) At clinically relevant and higher concentrations exemestane is bound to HSA and AAG to the same extent (fraction bound 93-95%) and the binding to both proteins remains unchanged over 10-1000 ng/ml concentration range suggesting the exemestane binds to plasma protein via a non-specific hydrophobic interaction.

SINGLE DOSE PHARMACOKINETICS

STUDY 95-OEXE-014 VOLUMES: 1.45 - 1.46

INVESTIGATOR AND LOCATION:

STUDY DATE: October 1996 - October 1997.

OBJECTIVES: To evaluate the linearity of pharmacokinetic parameters of exemestane after single oral doses of 25, 100 and 200 mg in postmenopausal volunteers.

FORMULATIONS:
25 mg Exemestane tablet, Batch No. C12F09
50 mg Exemestane tablet, Batch No. C12F18

STUDY DESIGN: An open, randomized, latin square design study in 9 healthy postmenopausal volunteers and a washout period of 3 weeks. Each volunnteer received single oral doses of 25, 100 (2x50) and 200 (4x50) mg exemestane tablet after a standard breakfast. Blood samples (5 ml) were collected from all volunteers pre-dose and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 120 and 168 h after dosing. Plasma samples were stored at -20°C until assayed for exemestane.

ASSAYS:

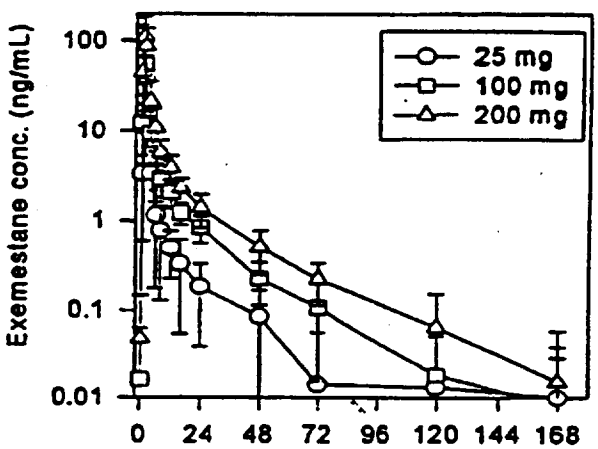
DATA ANALYSIS: AUC, Cmax, Tmax, $t_{1/2}$, t_{lag}, Vz/F, MRTand CL/F were calculated.

RESULTS: Table 1 and Figure 1 summarize the pharmacokinetic data obtained from the study.

Table 1. Pharmacokinetic parameters of exemestane after oral administration of single doses of 25, 100 and 200 mg to postmenopausal subjects; mean ± SD (n=9).

		Dose (mg)		
Parameter		25	100	200
t_{lag}	(h) (median)	0.25	0.25	0.5
t_{max}	(h) (median)	1.5	1	1
C_{max}	(ng/mL)	19.55 ± 8.81	79.54 ± 30.57	158.19 ± 91.40
AUC(0-t_z)	(ng·h/mL)	47.54 ± 27.08	191.86 ± 85.60	390.09 ± 158.29
AUC	(ng·h/mL)	53.38 ± 29.44	197.04 ± 85.37	398.40 ± 159.03
$t_{1/2,z}$	(h)	29.6 ± 26.0	24.5 ± 18.6	32.2±17.9
MRT	(h)	18.8 ± 15.8	9.94 ± 3.82	10.9±3.8
CL/F	(L/h)	574 ± 244	574 ± 176	568±196
V_z/F	(L)	19023 ± 13106	16960 ± 7582	23855±10585

Fig. 1 Average (±SD) Exemestane plasma levels (ng/mL) obtained following single oral administration of exemestane sugar-coated tablets at three different doses (25 mg: one 25-mg sugar-coated tablet, 100 mg: 2x50 mg sugar-coated tablets, 200 mg: 4x50mg sugar-coated tablets) to healthy postmenopausal subjects.



CONCLUSIONS: The results obtained from the study show that the pharmacokinetics of exemestane are linear up to 200 mg single oral dose.

SINGLE DOSE PHARMACOKINETICS

STUDY 89-OEXE-001 (MI MAD DRFI 001) VOLUMES: 1.34 PAGES: 1-19

INVESTIGATOR AND LOCATION: [redacted]

OBJECTIVES: To determine exemestane plasma levels in healthy postmenopausal female volunteers during a tolerability study.

FORMULATIONS:
25 mg Exemestane tablet, Batch No. SF 1042
200 mg Exemestane tablet, Batch No. SF 1043

STUDY DESIGN: An open-label study in healthy postmenopausal volunteers (3 subjects/group/dose) received single oral doses of 25, 100, 200, 400 and 800 mg exemestane tablet after a jigh lipid breakfast. Blood samples (5 ml) were collected from all volunteers pre-dose and at 0.5, 1, 1.5, 2, 4, 8, 12 and 48 h after dosing. Plasma samples were stored at -20°C until assayed for exemestane.

ASSAYS: [redacted]

DATA ANALYSIS: AUC, Cmax and Tmax were calculated.

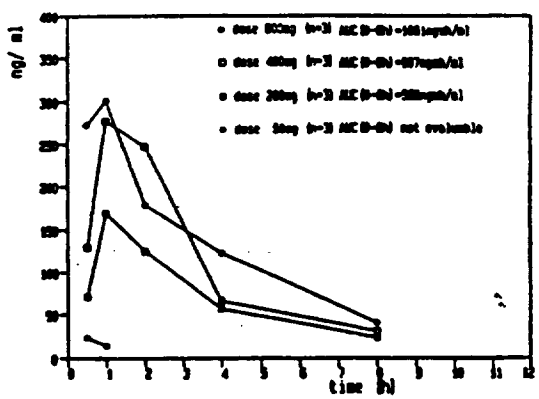
RESULTS: Table 1 and Figure 1 summarize the pharmacokinetic data obtained from the study.

Table 1. Pharmacokinetic parameters of exemestane after oral administration of single doses of 50, 200, 400 and 800 mg to postmenopausal subjects

Subject No.	Dose (mg)	Cmax (ng/ml)	Tmax (h)	AUC(0-8h) ng x h/ml
4	50	24	0.5	n.e.
5	50	38	0.5	n.e.
6	50	19	1	n.e.
Mean value±S.E.M.		27±6	0.7±0.2	n.e.
7	200	162	1	618
8	200	276	1	365
9	200	225	2	716
Mean value±S.E.M.		221±33	1.3±0.3	566±104
10	400	250	1	634
11	400	507	2	1346
12	400	270	1	735
Mean value±S.E.M.		343±83	1.3±0.3	907±222
13	800	527	0.5	1043
14	800	267	2	1280
15	800	448	1	922
Mean value±S.E.M.		414±77	1.2±0.4	1081±105

n.e.. not evaluable

Figure 1. Mean exemestane plasma levels in healthy female volunteers after single oral dose



CONCLUSION: The data from this study showed that the pharmacokinetics of exemestane are non-linear up to 800 mg single oral dose (there are obvious assay problems associated with the study).

SINGLE AND MULTIPLE DOSE PK AND PD

STUDY 94-OEXE-024 VOLUMES: 1.44

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: April to August 1994.

OBJECTIVES: To determine the safety, inhibitory effect on serum and urinary estrogens, the plasma pharmacokinetics and urinary excretion of exemestane, following a 7-day repeated oral dose of exemestane to healthy postmenopausal Japanese volunteers.

FORMULATIONS:
0.5 mg Exemestane tablet, Batch No. SA1325
2.5 mg Exemestane tablet, Batch No. SF1351
5 mg Exemestane tablet, Batch No. SF1347
25 mg Exemestane tablet, Batch No. A12F06
Placebo tablets, Batch No. A12F04

STUDY DESIGN: Single-blind, placebo-controlled design study in 32 Japanese healthy postmenopausal women. The study was divided into three sequential phases: (1) 18 subjects received orally for a 7-day period exemestane at doses of 0.5, 2.5, 10 mg/day (5 subjects/dose level) or placebo (3 subjects) after a standard breakfast; (2) after a suitable period of observation (> 3 weeks), 7 subjects received orally for a 7-day period exemestane at a 25 mg/day (5 subjects) or placebo (2 subjects) after a standard breakfast, (3) after a suitable period of observation (> 3 weeks), 7 subjects received orally for a 7-day period exemestane at a 50 mg/day (5 subjects) or placebo (2 subjects) after a standard breakfast. Blood samples for the determination of serum levels of estrone (E_1), estradiol (E_2) and estrone sulfate (E_1S) were collected before and 8 hour after the first dose (day 1) and in the morning of days 2, 4, 7, 8, 10, 15 and 22. Twenty-four hour urine collection for the determination of total E_1 and E_2 was performed on day -1 (baseline) and days 1 to 8, and on days 10, 12, 15 and 22. E_1, E_2 and E_1S were measured by RIA and celite chromatography. Blood samples for the determination of exestane and its metabolite were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours on days 1 ans 7 after dosing. Urine samples were collected before and then daily from day 1 to 8.

ASSAYS: [redacted]

DATA ANALYSIS: AUC, Cmax, Tmax, and Ae (amount excreted in urine) were calculated. Serum E_1, E_2 and E_1S and urinary E_1 and E_2 levels were calculated.

RESULTS: Tables 1 and 2 and Figures 1-9 summarize the pharmacokinetic pharmacodynamic data obtained from the study.

Table 1:

Pharmacodynamics:

In the Table below the serum estrogen levels (n=5) or the urinary estrogen excretion (n=5) were expressed as percentage of baseline values (Mean ± SD)

Parameter	Study day	Dose (mg/day for 7 days)					
		0.5	2.5	10	25	50	placebo
Serum E_1	4	69±24	54±16	33±17	31±10	35±17	95±14
	8*	58±14	50±19	31±18	27±13	31±12	101±37
	15*	97±26	85±21	49±22	45±14	33±14	111±45
Serum E_2	4	59±13	49±31	33±13	29±10	35±16	86±21
	8	50±17	51±29	36±9	29±17	38±15	100±28
	15	97±31	87±57	54±10	28±6	41±22	105±27
Serum E_1S	4	65±21	22±5	22±7	18±6	17±7	82±25
	8	44±14	27±4	20±8	14±9	14±6	95±26
	15	90±28	78±15	55±22	37±24	27±12	109±52
Urinary E_2	4	81±33	38±19	36±18	25±10	33±15	107±37
	8	86±54	29±9	23±6	17±11	28±14	132±37
	15	134±66	56±24	89±91	25±13	16±5	114±37
Urinary E_1	4	76±35	31±14	30±12	30±15	43±13	87±31
	8	70±44	24±7	25±11	19±4	67±34	127±36
	15	135±84	58±35	51±[illegible]	20±12	15±3	101±31

*Day 8 = 24 hours after the last dose; *Day 15 = 8 days after treatment discontinuation

Table 2:

Pharmacokinetics:

Day 1: Exemestane pharmacokinetic parameters (Mean±SD)

	Dose (mg/day)				
Parameter	**0.5**	**2.5**	**10**	**25**	**50**
C_{max} (ng/ml)	n.a.	2.00±0.97	4.75±2.16	13.14±4.33	23.12±5.54
t_{max} (h)	n.a.	0.9±0.4	2.6±1.1	1.6±0.4	2.1±1.1
AUC(0-24 h) (ng-h/ml)	n.a.	5.00±2.96	22.23±10.91	53.24±14.22	116.55±32.55

Day 7: Exemestane pharmacokinetic parameters (Mean±SD)

	Dose (mg/day)				
Parameter	**0.5**	**2.5**	**10**	**25**	**50**
C_{max} (ng/ml)	0.55±0.01	2.75±2.23	7.63±3.52	14.89±3.93	27.13±6.05
t_{max} (h)	1.3±1.4	1.3±1.2	2.0±1.0	2.0±0.0	2.2±1.2
AUC(0-24 h) (ng-h/ml)	0.95±0.22	10.57±6.58	35.78±16.69	104.88±30.29	206.83±37.29
Ae(day1-day7) (μg)	1.9±1.3	21.2±9.1	51.9±22.4	105.0±50.0	277.0±164.0

Day 1: 17-hydroexemestane pharmacokinetic parameters (Mean±SD)

	Dose (mg/day)				
Parameter	**0.5**	**2.5**	**10**	**25**	**50**
C_{max} (ng/ml)	n.a.	n.a.	0.47±0.20	1.13±0.48	1.81±0.60
t_{max} (h)	n.a.	n.a.	2.3±0.6	2.0±0.7	2.6±1.3
AUC(0-24 h) (ng-h/ml)	n.a.	n.a.	1.23±1.02	3.93±2.30	13.98±2.43

Day 7: 17-hydroexemestane pharmacokinetic parameters (Mean±SD)

	Dose (mg/day)				
Parameter	**0.5**	**2.5**	**10**	**25**	**50**
C_{max} (ng/ml)	n.a.	n.a.	0.62±0.19	1.25±0.31	2.71±0.70
t_{max} (h)	n.a.	n.a.	2.2±0.8	2.4±0.5	2.6±0.9
AUC(0-24) (ng-h/ml)	n.a.	n.a.	3.20±1.85	13.32±3.65	30.98±5.66
Ae(day1-day7) (μg)	n.a.	0.2±0.5	0.6±0.6	1.4±0.9	8.3±6.6

n.a.: not analyzed

Figure 1: Change in Serum Estradiol Concentration

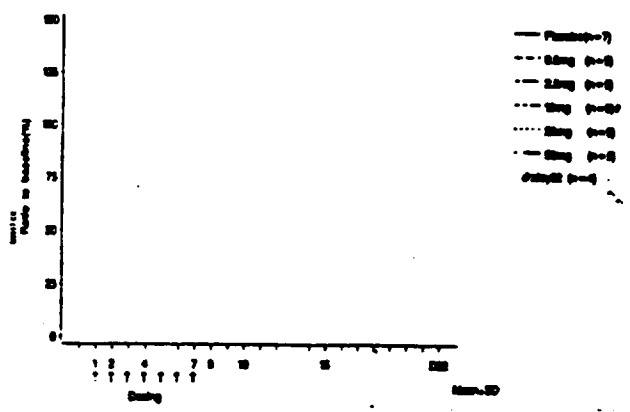


Figure 2:Changes in Serum Estrone Concentration

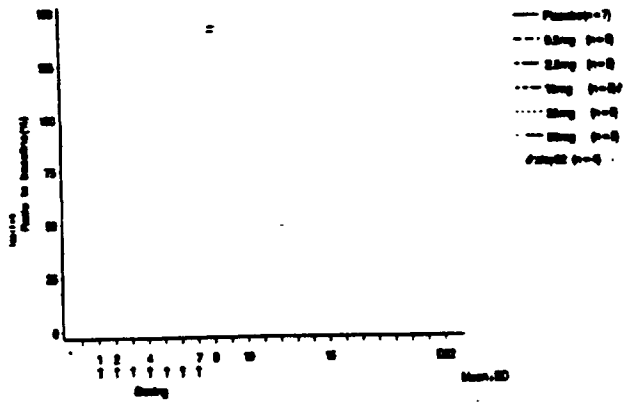


Figure 3:Changes in Serum Estrone Sulfate Concentration

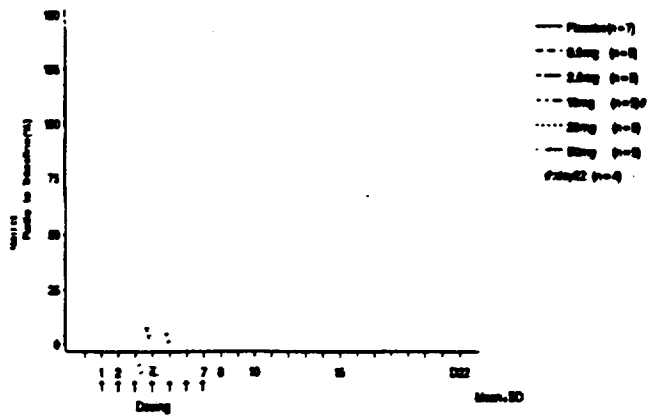


Figure 4: Changes in Urinary Excretion of Estradiol

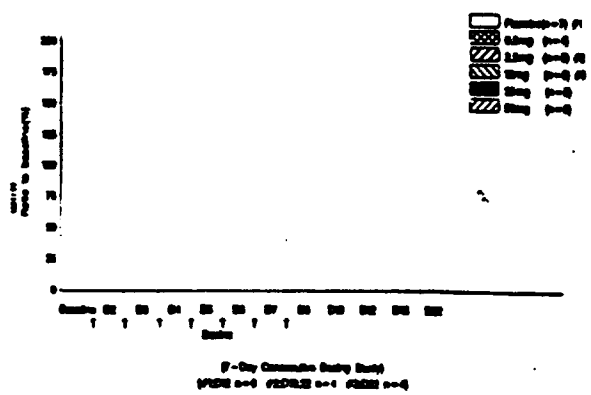


Figure 5: Changes in Urinary Excretion of Estrone

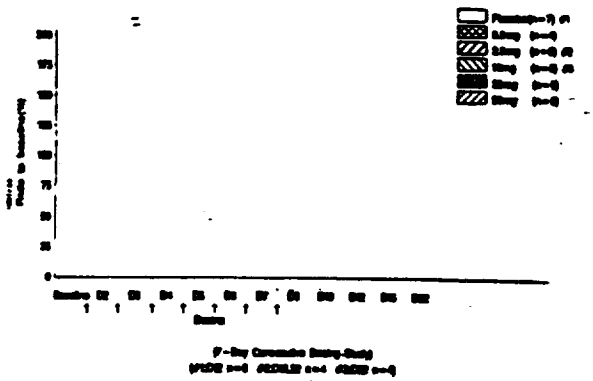


Figure 6: Mean Plasma Profiles of Exemestane

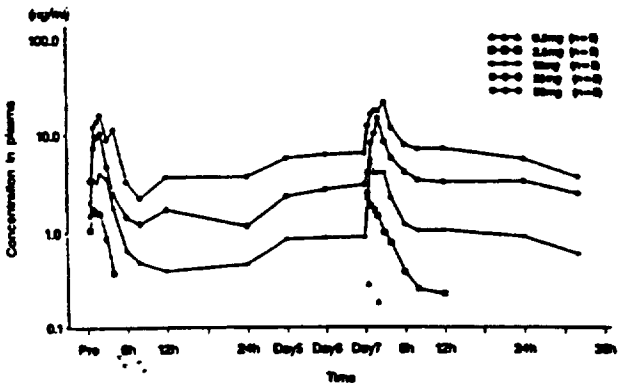


Figure 7: Mean Plasma Profiles of 17-hydroexemestane