Figure 8: Cummulative Urinary Excretion of Exemestane

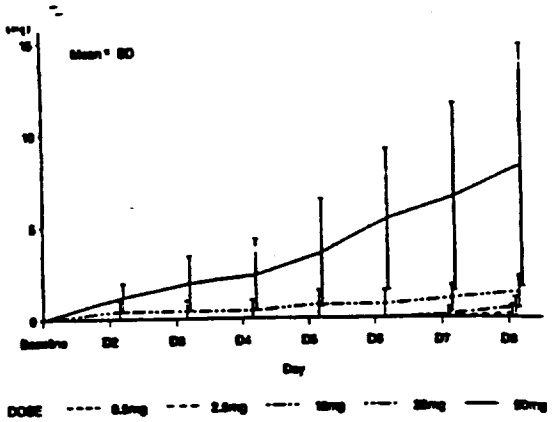
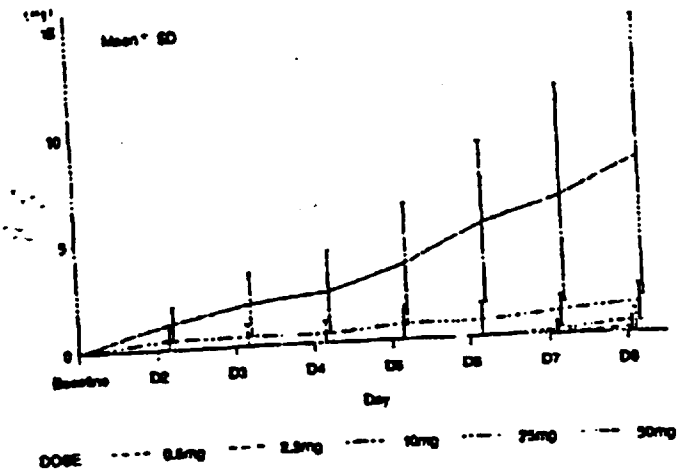


Figure 9: Cummulative Urinary Excretion of hydroexemestane



CONCLUSIONS: The results obtained from the study show that:

1. The pharmacokinetics of exemestane are linear up to 50 mg single or multiple oral doses
2. Upon multiple dose adminstration, plasma levels levels of both exemestane and 17-hydroxyexemestane increase with an accumulation factor of about 2.
3. Negligible amounts of exemestane and hydroxyexemestane were excreted in urine
4. Steady state conditions are achieved after 5 days of daily administration of exemestane.
5. A dose related decrease in serum and urinary estrogens were observed. The estrogen supression was still present 1 week after discontinuation of therapy and almost disappeared at 2 weeks.

SINGLE AND MULTIPLE DOSE PHARMACOKINETICS

STUDY 92-OEXE-019 (MIEXEPHDY019) VOLUME: 1.39

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: April to December 1993.

OBJECTIVES: (1) To evaluate the pharmacodynamics, in terms of decrease of plasma estrogen levels, of low doses of exemestane administered daily for 7 days to postmenopausal healthy volunteers; (2) to evaluate the plasma pharmacokinetics at the same doses; and (3) to assess the tolerability of exemestane at these dose levels in the subject population.

FORMULATIONS:
0.5 mg Exemestane tablet, Batch No. SF 1350
2.5 mg Exemestane tablet, Batch No. SF 1348
5 mg Exemestane tablet, Batch No. SF 1346
Placebo tablets, Batch No. SF 1349

STUDY DESIGN: Double-blind, randomized design study in four groups of 8 healthy postmenopausal women treated for 7 days with one of the following oral doses of exemestane: 1, 2.5, 5 and 10 mg. Blood samples for the determination of serum levels of estrone (E_1), estradiol (E_2) and estrone sulphate (E_1S) were collected at baseline (days -7 to 0), before the first dose (day 1), during treatment on days 3, 5 and 7 and after treatment at days 8 12 and 15. Blood samples for the determination of exestane were collected pre-dose on days 1, 5, 6, and 7 and the following time: 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours after dosing on day 7. Urine samples were collected before and then daily from day 1 to 8.

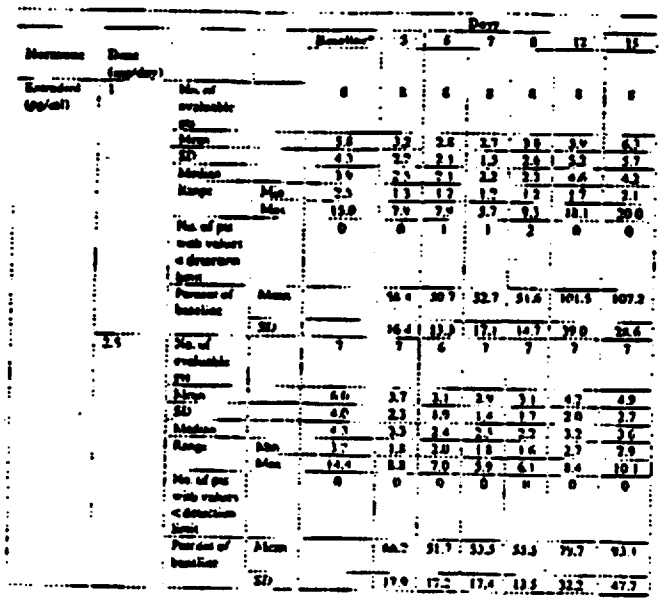
ASSAYS: [redacted]

DATA ANALYSIS: AUC, Cmax, C_{24}, and Tmax were calculated.
Plasma E_1, E_2 and E_1S levels were calculated.

RESULTS: Tables 1-5 and Figures 1-7 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1:

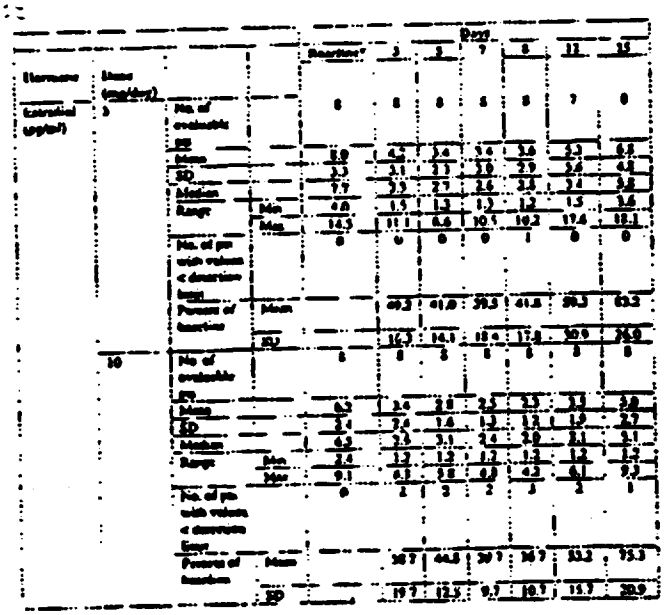
Plasma levels of estradiol (T_{E2}) at different time intervals in healthy post-menopausal women treated for 7 days with different doses of estrogens



* The baseline value is the mean of values measured in the preliminary and in the baseline assessments

Table 2:

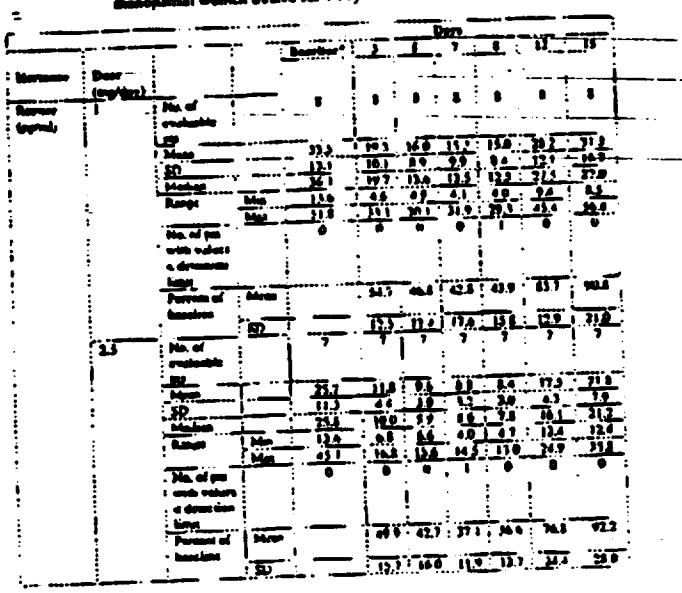
Plasma levels of estradiol (E_2) at different time intervals in healthy post-menopausal women treated for 7 days with different doses of estrogens



* The baseline value is the mean of values measured in the preliminary and in the baseline assessments

Table 3:

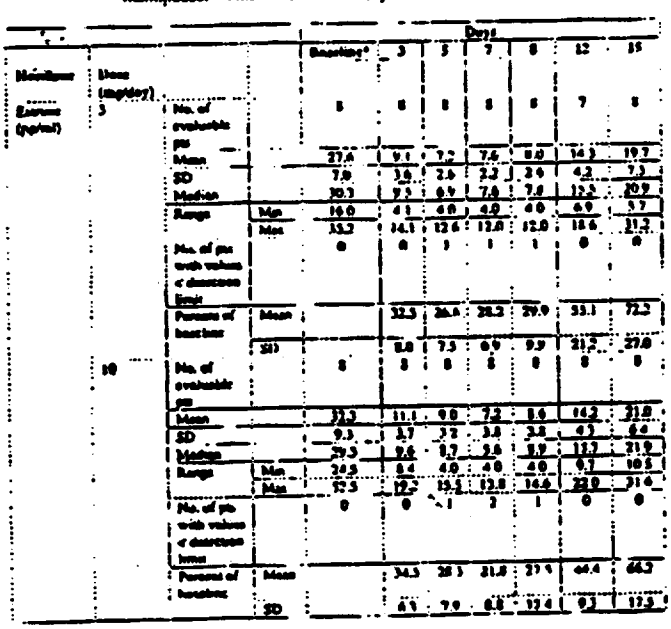
Plasma levels of estrone (E_1) at different time intervals in healthy post-menopausal women treated for 7 days with different doses of estrogens



* The baseline value is the mean of values measured on the preliminary and in the baseline assessments

Table 4:

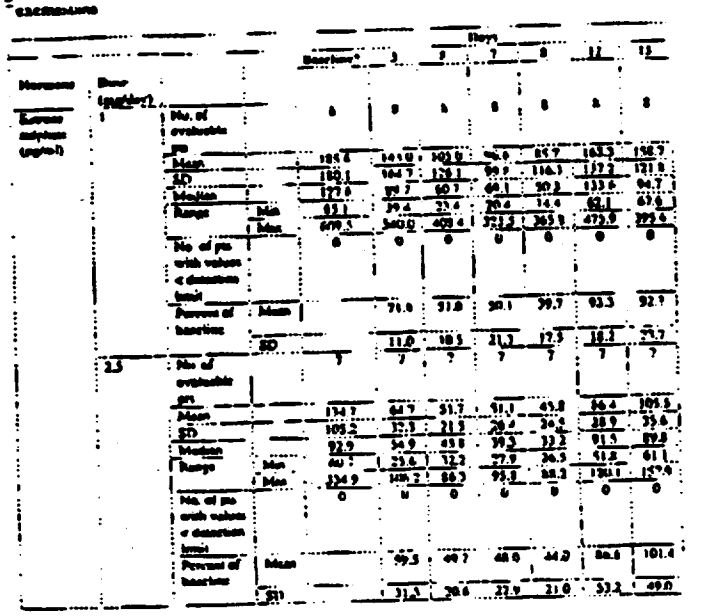
Plasma levels of estradiol (E_2) at different time intervals in healthy post-menopausal women treated for 7 days with different doses of estrogens



* The baseline value is the mean of values measured on the preliminary and in the baseline assessments

Table 5:

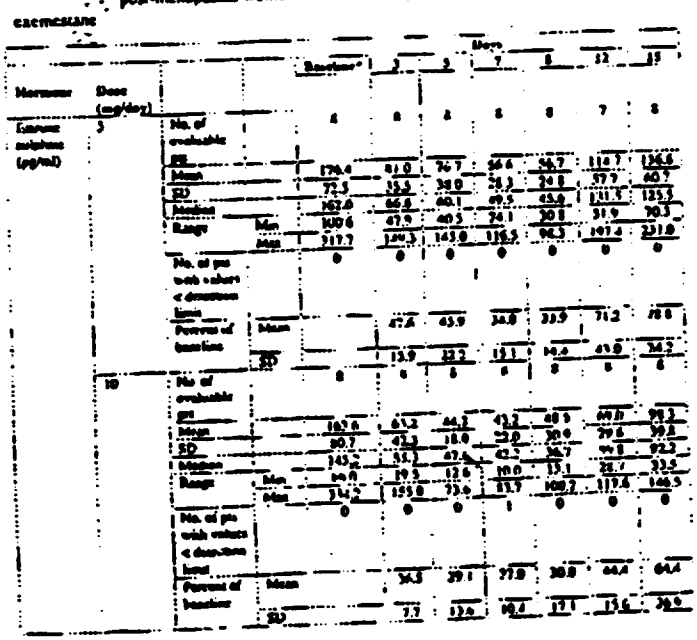
Plasma levels of exemestane sulphate (Ex.S) at different time intervals in healthy post-menopausal women treated for 7 days with different doses of exemestane



* The baseline value is the mean of values measured on the preliminary and on the baseline assessment

Table 6:

Plasma levels of exemestane sulphate (Ex.S) at different time intervals in healthy post-menopausal women treated for 7 days with different doses of exemestane



* The baseline value is the mean of values measured on the preliminary and on the baseline assessment

Table 7:

Average values of AUC(0-24 h)$_{day\ 7}$, $C_{max,day\ 7}$, $t_{max,day\ 7}$, and C(24 h) values calculated for the volunteers enrolled in the study receiving daily administration of exemestane at the doses of 1, 2.5, 5, and 10 mg. Values are expressed as mean±SD (n=8 for each dose), except for t_{max} for which median and range are reported. For AUC (0-24h), C_{max} and C(24h), values normalized to the dose of 1 mg are shown within parentheses.

	1 mg/day	2.5 mg/day	5 mg/day	10 mg/day
AUC(0-24 h)$_{day\ 7}$ (ng.h/ml)	2.297±0.521 (2.297±0.521)	6.016±1.935 (2.406±0.774)	15.238±6.883 (3.048±1.377)	29.980±8.695 (2.998±0.869)
$C_{max,day\ 7}$ (ng/ml)	0.833±0.255 (0.833±0.521)	2.183±1.044 (0.873±0.418)	7.286±8.072 (1.457±1.614)	11.044±3.705 (1.104±0.370)
$t_{max,day\ 7}$ (h)	1 1-1.5	1 0.5-2	1 0.5-1.5	1 1-1.5
C(24h)$_{day4}$ (ng/ml)	0.022±0.011 (0.022±0.011)	0.050±0.015 (0.020±0.006)	0.141±0.063 (0.028±0.013)	0.313±0.129 (0.031±0.013)
C(24h)$_{day5}$ (ng/ml)	0.026±0.011 (0.026±0.011)	0.055±0.018* (0.022±0.007)	0.152±0.056 (0.030±0.011)	0.314±0.128 (0.031±0.013)
C(24h)$_{day6}$ (ng/ml)	0.027±0.014 (0.027±0.014)	0.057±0.018 (0.023±0.007)	0.168±0.052 (0.034±0.010)	0.393±0.190 (0.039±0.019)
C(24h)$_{day7}$ (ng/ml)	0.028±0.011 (0.028±0.011)	0.057±0.021* (0.023±0.009)	0.142±0.050 (0.028±0.010)	0.302±0.074 (0.030±0.007)

* n=7

Figure 1:

Mean pharmacokinetic values of E2 plasma level measured during the treatment at the dose of 1mg (♦), 2.5mg (◆), 5mg (Δ), 10mg (■). The standard deviation of the means is shown as a vertical bar adjacent to each plotted symbol.

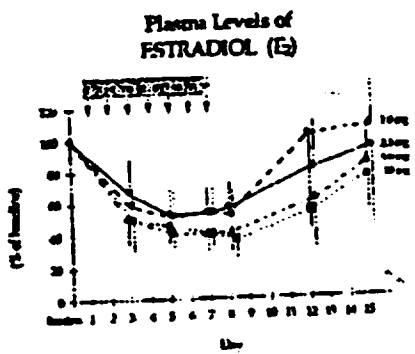


Figure 2:

Mean percentage of baseline value of F1 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.

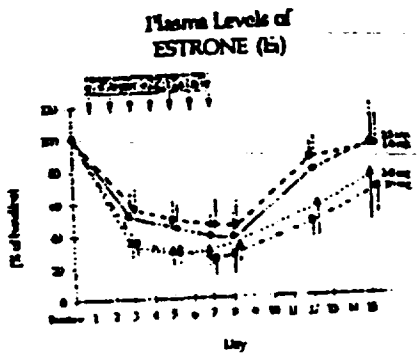


Figure 3:

Mean percentage of baseline value of E_1S 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.

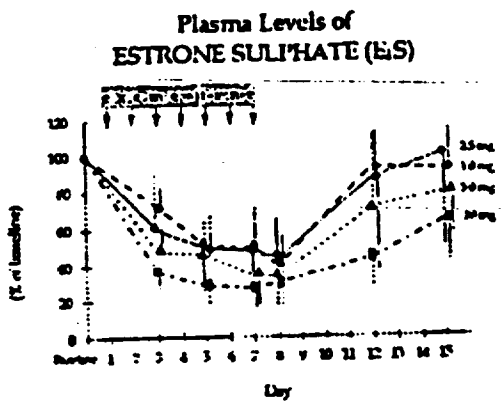
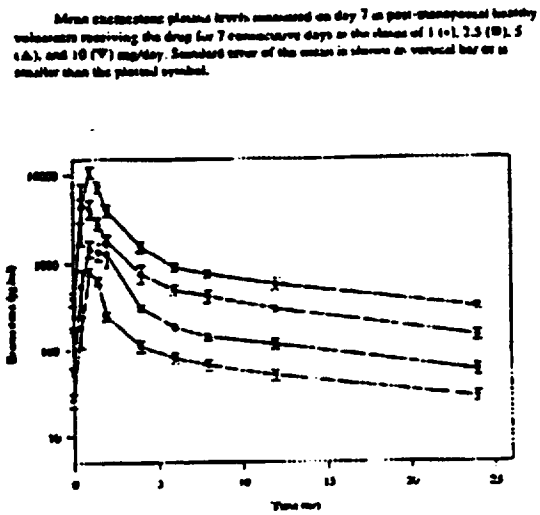


Figure 4:



CONCLUSIONS: The results obtained from the study show that:

1. The pharmacokinetics of exemestane are linear up to 10 mg multiple oral doses
2. Steady state conditions are achieved after 5 days of daily administration of exemestane.
3. A dose related decrease in plasma estrogens were observed. The estrogen suppression was still present 5 days after discontinuation of 10 mg dose.

APPEARS THIS WAY
ON ORIGINAL

MULTIPLE DOSE PHARMACOKINETICS

STUDY 92-OEXE-003 (MI MAD DRFI 003) VOLUME: 1.34

INVESTIGATOR AND LOCATION: [ ]

OBJECTIVES: (1) To determine the minimal dose achieving the maximal endocrine effects as measured by a decrease of plasma and urine estrogens in postmenopausal patients with advanced breast cancer; (2) to asses the pharmacokinetics of exemestane after repeated oral administration; and (3) to assess the tolerability of exemestane in the subject population.

FORMULATIONS:
100 mg Exemestane capsule, Batch Nos. SF 1188, SF 1256, SF 1324
200 mg Exemestane capsule, Batch Nos. SF 1189, SF 1257, A12G03

STUDY DESIGN: Open, uncontrolled, dose escalation study in 12 postmenopausal breast cancer patients. Patients started exemestane treatment at 5 mg daily dose; the dose was escalated every 2 weeks to 10, 25, 50, 100 and 200 mg/day administered in the morning after a light meal. Pharmacokinetics were evaluated on day 14 of therapy with 100 and 200 mg/day. Pharmacokinetics of exemestane and its metabolite were further evaluated in 5 subjects (3 received 200 mg/day and 2 received 100 mg/day due to reduction in daily dose as a result of poor tolerability) who continued the therapy for more than one year. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post dose.

ASSAYS: [ ]

DATA ANALYSIS: AUC, Cmax, and Tmax were calculated.

RESULTS: Table 1 and Figures 1-2 summarize the pharmacokinetics data obtained from the study.

Table 1. Pharmacokinetic parameters of exemestane after oral administration of 100 and 200 mg to postmenopausal cancer patients; mean ± SD).

Parameter	Dose (mg) /time			
	100 /Day 14	200 / Day 14	100 / 1 year	200 / 1 year
Tmax (h)	2.5 ±2.1	2.0 ±1.3	0.5 (n=2)	2.2 ±0.8 (n=3)
Cmax (ng/ml)	169 ±185	300 ±233	141 (n=2)	217 ±89 (n=3)
AUCτ (ng.h/ml)	1149 ±666	1854 ±678	1365 (n=2)	919 ±196 (n=3)

17-hydroexemestane (200 mg / day 14 only) mean ± SEM (n=9):
Tmax = 2 h
Cmax = 28±9 ng/ml
AUCτ = 92±49 ng.h/ml (n=7)

Figure 1: Comparison of the mean plasma levels of exemestane after day-14 oral administration of 100 and 200 mg/day to postmenopausal cancer patients.

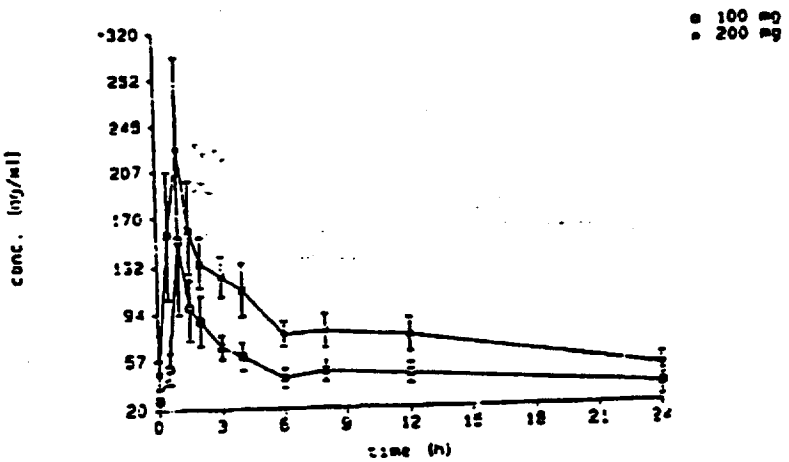
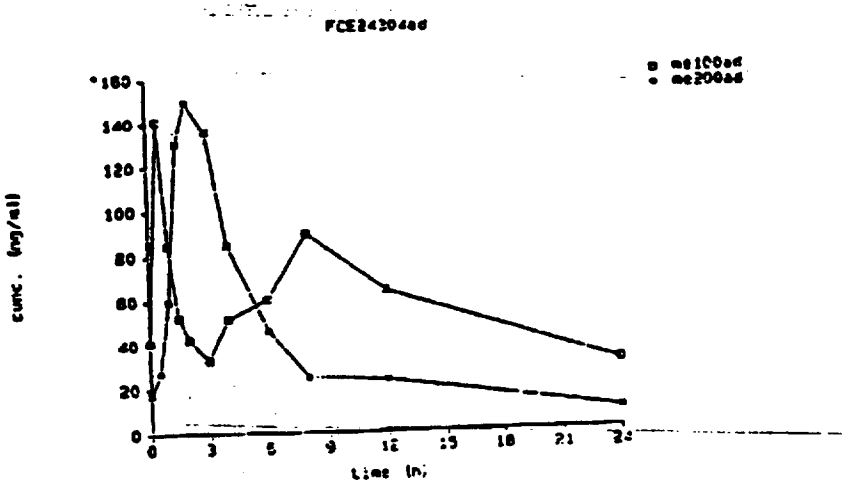


Figure 2: Comparison of the mean plasma levels of exemestane after 1 year oral administration of 100 and 200 mg/day to postmenopausal cancer patients



CONCLUSIONS: The results obtained from the study show that:

1. The pharmacokinetics of exemestane are linear in the dose range investigated (100-200 mg).
2. Plasma levels of 17-hydroxyexemestane accounted for approximately 5% of those of the unchanged drug (AUCτ at 200 mg dose).
3. Repeated treatment with exemestane for more than 1 year did not appreciably modify the pharmacokinetics of exemestane.

BIOAVAILABILITY / BIOEQUIVALENCY STUDY

STUDY 92-OEXE-008 (MI MAD BAVA 008) **VOLUME: 1.34**

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: May to August 1992.

OBJECTIVES: (1) To evaluate the relative bioavailability of two different formulations of exemestane in healthy postmenopausal subjects; (2) to determine the pharmacodynamics and tolerability of these two formulations in the study population.

FORMULATIONS:
Reference: 50 (2 x 25) mg hard gelatin capsules of exemestane, formulation B, Batch No. SF 1255.
Test: 50 (2 x 25) mg sugar-coated tablets of exemestane, formulation A, Batch No. SF 1294.

STUDY DESIGN: Open, randomized, two-period, crossover study in 12 healthy postmenopausal volunteers and a washout period of 3 weeks. Each subject received two single oral administrations (formulation A: reference; formulation B: test) of 50 mg exemestane after a light breakfast. Blood samples (6 ml) for the determination of exemestane were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32 and 48 h post dose on days 1 and 22. Blood samples (7 ml) for the determination of estrone sulfate were collected at pre-study screens, pre-dose and at 2, 8, 24, 48, 72 and 96 h post dose on days 1 and 22. Plasma E_1S were measured by RIA.

ASSAYS:

[redacted]

DATA ANALYSIS: AUC, Cmax, $t_{1/2}$, $t_{1/2}$ and Tmax were calculated. E_1S levels were reported.

RESULTS: Tables 1-2 and Figures 1-7 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1: Pharmacokinetic Parameters of exemestane after administration of two different formulations to healthy volunteers (mean±SD)

Parameter	Formulation A (Reference)	Formulation B (Test)	90% Confidence Interval
t_{lag} (h)	0.3±0.2	0.8±0.5	-
$t_{1/2}$ (h)	10.7±7.6	10.7±6.8	-
Tmax (h)	2.3±0.7	3.1±1.1	-
Cmax (ng/ml)	25.9±8.2	23.4±9.7	76.2 - 101.2
AUC_{0-t} (ng.h/ml)	99.2±28.9	91.5±22.7	86.0 - 100.2
$AUC_{0-\infty}$ (ng.h/ml)	121.0±30.2	113.3±27.4	88.3 - 99.5

Table 2:

Effect of a single oral dose of 50 mg exemestane, given as either 2 x 25 mg gelatine capsules (Formulation A) or 2 x 25 mg sugar-coated tablets (Formulation B), on plasma estrone sulphate levels in healthy postmenopausal volunteers. Cross-over study in 12 subjects.

Unit	Formulation	Plasma estrone sulphate levels at post-treatment time									
		Hours				Days					
		0	2	8	24	2	3	4	7	14	21[c]
pg/ml[a]	Capsules	152[c] 57[d]	122 41	107 36	70 28	48 14	30 14	30 14	51 32	138 68	141[c] 47
	Tablets	159 59	133 55	121 62	69 36	39 17	30 11	31 14	58 51	113 54	153[c] 69
Percentage of baseline[b]	Capsules	100 -	81 6	72 13	47 9	28 10	21 11	21 10	38 21	95 53	94 21
	Tablets	100 -	84 15	75 15	43 10	25 5	20 9	21 11	37 26	73 27	87 12

[a] Expressed as pg of free estrone/ml; [b] Percentage of the 0 h value (baseline);
[c,d] Mean and standard deviation; [e] Six subjects.

Figure 1: Mean exemestane concentration-time profiles after the administration of formulations A and B

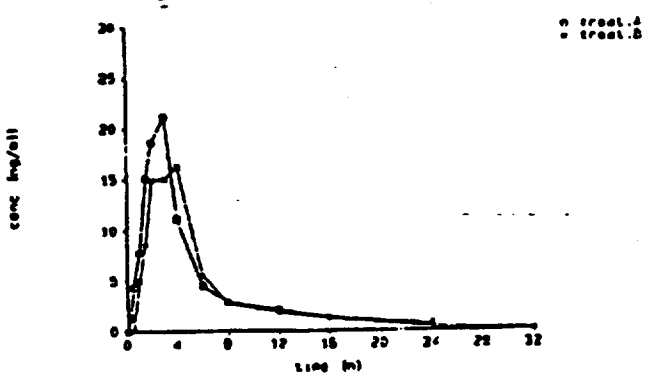
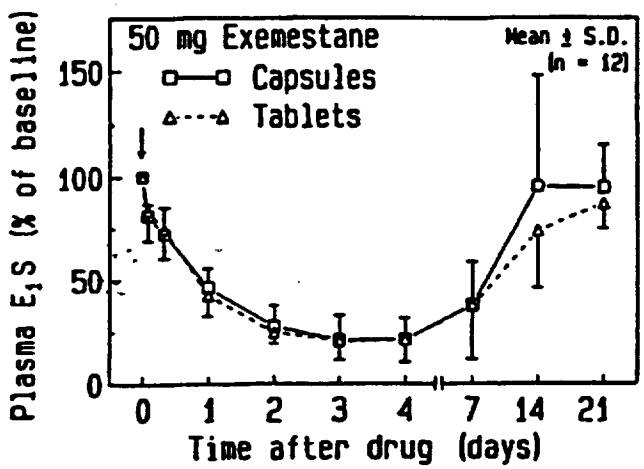


Figure 2: Effect of single oral dose of 50 mg of exemestane, given as either gelatine capsules (Formulation A) or sugar-coated tablets (Formulation B), on plasma estrone sulfate levels in healthy postmenopausal volunteers



CONCLUSIONS: The data obtained from the study showed that:

1. The two formulations are bioequivalent with respect to AUC but bioinequivalent with respect to Cmax of exemestane.
2. The two formulations have similar effect in decreasing plasma E_1S levels.

BIOAVAILABILITY / BIOEQUIVALENCY STUDY

STUDY 97-OEXE-035 **VOLUME**: 1.46 -1.48

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: January to April 1998.

OBJECTIVES: (1) To assess the bioequivalence in healthy male volunteers after single oral administration of 25 mg sugar-coated exemestane tablet formulations used for the clinical trails and the to-be marketed formulation.

FORMULATIONS/TREATMENTS:
Treatment A (Reference): 25 mg sugar-coated tablets of exemestane (Process A2), Batch No. E12F01.
Treatment B (Test): 25 mg sugar-coated tablets of exemestane (Process A3), Batch No. D12F07.
Treament C (Test): 25 mg sugar-coated tablets of exemestane (Process A4), Batch No. D12F06.

STUDY DESIGN: Open, randomized, latin square, crossover study in 36 healthy male volunteers and a washout period of 2 weeks. Each subject received a single oral dose of 25 mg exemestane after an overnight fast administered as Treatments A, B and C above. Blood samples (8 ml) for the determination of exemestane were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 120 and 168 h post dose.

ASSAYS:

[redacted]

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

RESULTS: Tables 1-2 and Figures 1-2 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1: 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
t_{lag} (h)	0.12±0.13	0.13±0.13	0.13±0.13	-	-
$t_{1/2}$ (h)	10.2±12.0	8.4±3.7	9.6±5.2	-	-
Tmax (h)	0.95±0.3	1.1±0.6	0.97±0.3	-	-
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
MRT (h)	8.2±16.8	5.4±2.5	6.0±2.8	-	-
CL/F (L/h)	1109±524	9870±399	1052±360	-	-
Vz/F (L)	14019±10203	12224±8431	14438±8887	-	-

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)

Formulations A2, A3 and A4 have the same composition and similar in vitro dissolution profiles.

Fig. 1 Average (±SD) exemestane plasma levels (ng/mL) obtained following single oral administration of three different treatments of exemestane 25 mg sugar-coated tablets (treatment A: A2 process, treatment B: A3 process, treatment C: A4 process) to healthy male subjects.

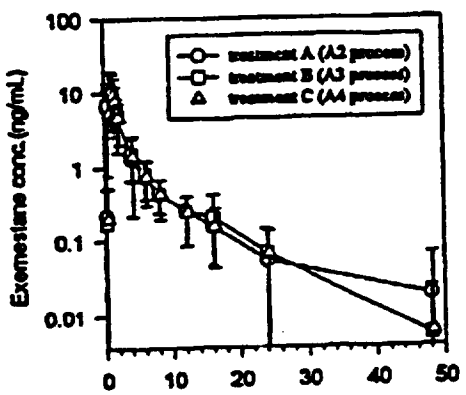
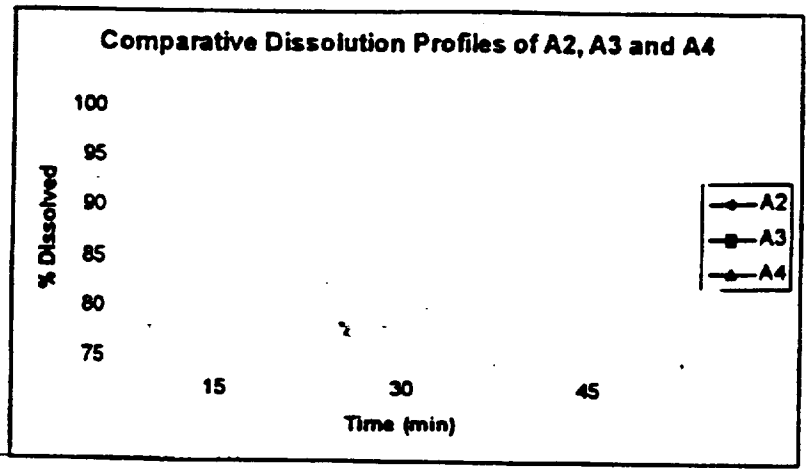


Figure 2: Comparative Dissolution Profiles of Formulations A2, A3 and A4.



CONCLUSIONS: The data obtained from the study showed that:

1. Formulation A4 (to be marketed) is bioequivalent to the clinical formulation A2.
2. Formulations A2 and A3 are 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.

COMMENTS: 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 see Table 2 below). Therefore, these formulations should be considered bioequivalent. Formulation A2 has been linked to the hard gelatin capsules through Study 92-OEXE-008.

Table 2: Similarity Factors for comparison of the Formulations

	A2/A4	A2/A3	A3/A4
f2 (%)	82	93	75

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 28, 1999

FROM: Sriram Subramaniam, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-345)

THROUGH: C.T. Viswanathan, Ph.D. CTV 5/3/99
Associate Director
Division of Scientific Investigations (HFD-345)

SUBJECT: Review of EIR Covering NDA 20-753
Aromasin® (Exemestane) Tablets, 25 mg
Sponsored by Pharmacia and Upjohn Co., Kalamazoo, MI

TO: Robert Justice, M.D.
Acting Director
Division of Oncologic Drug Products (HFD-150)

At the request of HFD-150, the Division of Scientific Investigations conducted an audit of the following study:

> Protocol 97-OEXE-035: Bioequivalence Study of Three Different Batches of Exemestane Administered as a Single Dose (25 mg) to Healthy Male Volunteers.

The clinical and analytical portions of this study was conducted at Pharmacia and Upjohn at Kalamazoo, MI and at Nerviano-Milan, Italy, respectively.

This memorandum reports the findings of the analytical portion of the audit performed at Pharmacia and Upjohn in Nerviano-Milan, Italy. Following the inspection a Form 483 was issued (see attached). The significant findings and our evaluation of these findings follows:

Analytical Site: Pharmacia & Upjohn, Nerviano-Milan, Italy

1. The Assay Method was NOT Validated at the Lower Range

Our review of the chromatograms revealed significant background noise at the low concentration range, between [redacted] of the analytical runs (Exhibit 1). The chromatograms in remaining runs showed a higher background noise affecting concentrations between [redacted] (Exhibit 2). Consequently, the analyte signal at these concentrations was not resolved. We also found that: 1) peak integration at the low concentrations were inconsistent due to the low signal to noise ratio and the lack of established chromatography acceptance criteria; 2) analyte signal at the low concentrations often had multiple peaks; and 3) standard blanks immediately following the high calibration standard often exhibited significant interference, suggesting a carry-over effect. In our opinion, the lower limit of quantitation [redacted]

Review of the subject data shows that about [redacted] there would be insufficient data to accurately calculate the pharmacokinetic parameters (e.g. AUC, C_L and Kel).

The firm in their response (dated 4/22/99: Exhibit 3) agreed that the peak integration was not consistent. In an attempt to address the Form 483 findings, the firm claimed that they used a smoothing function to improve assessment of peaks and reintegrated all the chromatograms based on a newly issued SOP. Following the reevaluation, the firm maintains that the [redacted] Moreover, the firm claimed that statistical reanalysis using the modified data set did not affect the results of the study. However, the firm did not submit the reanalyzed chromatograms or the results of the reanalysis for our evaluation, but promised to submit them soon.

Conclusion:

Based on the data presented during the inspection, the assay was NOT validated below [redacted] As the majority of subject data are below [redacted] the pharmacokinetic parameters reported in Study 97-OEXE-035 are not accurate and cannot be reliably estimated. We recommend that the subject data from the study be NOT acceptable for Agency review.

In the event the firm submits their modified data set, we would, upon evaluation of the data set, inform HFD-150 only if the data set warrants changes to our current recommendations.

In light of the significant deficiencies found at the analytical site, the audit of the clinical portion of the study was determined to be unnecessary and is scheduled to be cancelled, unless HFD-150 finds otherwise and informs DSI.

After you have reviewed this memo, please append it to the original NDA submission.

/S/

Sriram Subramaniam, Ph.D.

Attachments*

cc: Orig NDA 20-753 / HFD-150 Div File
HFD-340/Lepay
HFD-345/Fujiwara/Subramaniam(2)/Yau/cf
HFD-860/Rahman/Fadiran
HFD-150/Guinn
HFR-MW2545/Austin
Class:OAI - Pharmacia & Upjohn, Milan, Italy
Draft:SS 4/23/99
Edit:MKY MKY 5/3/99
Final:CTV
File:5246;O:\BE\EIRCOVER\20753pha.exe

* Due to the number of chromatograms involved, Exhibits are provided to the OCPB reviewer only. Exhibits will be available on request for others on the distribution list.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FOOD & DRUG ADMINISTRATION HFC-150/HFC-150/ROUTE 13-45 5600 FISHERS LANE ROCKVILLE MD 20857 (301)827-5647	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: ROBERT M. J. INGS PhD	PERIOD OF INSPECTION 3-24/26-99	C. F. NUMBER 9614876
TITLE OF INDIVIDUAL DIRECTOR DMR - ITALY	TYPE ESTABLISHMENT INSPECTED BIOANALYTICAL LABORATORY	
FIRM NAME PHARMACIA & UPJOHN S.p.A.	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
STREET ADDRESS VIALE PASTEUR, 10	STREET ADDRESS OF PREMISES INSPECTED SAME	
CITY AND STATE (Zip Code) 20014 NERVIANO (MILAN) ITALY	CITY AND STATE (Zip Code) SAME	

DURING AN INSPECTION OF YOUR FIRM I (WE) OBSERVED:

The following observations pertain to the analytical portion of the Exemestane (970exe035) study:

1) The signal to noise ratio in the bulk of the chromatograms was poor and undesirable, especially for lower concentrations.

2) Peak interference was observed in many chromatograms.

3) Both automatic and manual integration were carried out in the same run without an established criteria.

4) No established criteria was used for manual integration and inconsistent baselines were drawn in many chromatograms.

5) In peak area calculations multiple peaks were integrated.

6) The acceptance criteria for QC in the SOP was broad in that a % window was allowed for the middle and high concentrations.

7) Freeze Thaw stability determination of 4 of the nominal concentration.

8) No established criteria for repeat analysis of plasma samples or the reported value following the repeat.

9) In the PK analysis of subject 28 the predose sample was set as zero even though the original and repeated assays registered finite value.

10)No recording devices for freezer temperature or log maintenance for the plasma samples stored in the freezer.

11)Table 4 of the stablity document (9550136) of 17-OH metabolite human plasma data included rat plasma data.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	NAME(S) (Type or Print) AND TITLE(S) CT. VISWANATHAN, PhD, ASSOC. DIR., DS LARRY K. AUSTIN, INVESTIGATOR	DATE ISSUED 3-26-99

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED INSPECTIONAL OBSERVATIONS PAGE OF PAGES

BIOAVAILABILITY / FOOD-EFFECT STUDY

STUDY 94-OEXE-012 **VOLUME: 1.36**

INVESTIGATOR AND LOCATION: [ ]

STUDY DATE: October 1995 to August 1996.

OBJECTIVES: (1) To determine the relative bioavailability of the formulation used in clinical studies (sugar-coated tablet) in comparison with a suspension of exemestane (reference formulation) under fasting conditions, evaluating the plasma pharmacokinetics of exemestane and the inhibitory effect of exemestane on plasma estrone sulfate (E_1S) levels; (2) To evaluate the influence of food on the (a) pharmacokinetics of exemestane sugar-coated tablets, by comparing exemestane plasma levels after administration under fasting conditions and after a standard breakfast, (b) inhibitory effect of exemestane on plasma E_1S levels.

FORMULATIONS/TREATMENTS:
Treatment A (Test): 25 mg sugar-coated tablet of exemestane, Batch No. B12F10. Fasted conditions.
Treatment B (Reference): 25 mg suspension of exemestane, Batch No. B12R12 (powder) and B12R13 (liquid vehicle), Fasted conditions.
Treament C (Test): 25 mg sugar-coated tablet of exemestane, Batch No. B12F10. Fed conditions.

STUDY DESIGN: Open, randomized, 3x3 latin square, crossover study in 12 healthy postmenopausal volunteers and a washout period of 4 or 5 weeks. Each subject received a single oral dose of 25 mg exemestane after an overnight fast administered as Treatments A, B and C above. Treatment C was administered (15 minutes after completion of breakfast) after a standard breakfast consisting of 2 scrambled eggs, 2 strips of bacon, 200 ml of whole milk, 2 slices of buttered toast, 1 tablespoonful of jam/jelly, and coffee or tea ad libitum. Blood samples (5 ml) for the determination of exemestane were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 120 and 168 h post dose. Plasma E_1S levels were determined at baseline (immediately before dosing) and at 24, 48, 72, 120, 168 and 336 h post dose using [ ]

ASSAYS:
[ ]

DATA ANALYSIS: AUC, Cmax, t_{lag}, $t_{1/2}$, MRT, CL/F, Vz/F and Tmax were calculated for exemestane. I_{max} (maximal % inhibition), $t_{max.effect}$ (time to maximal % inhibition of E1S), $t_{z.effect}$ (time (interpolated) at E1S inhibition matches the baseline level) and AUC_{effect} were calculated for the inhibitory effect of exemestane on plasma E1S.

RESULTS: Tables 1-2 and Figures 1-2 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1: Pharmacokinetic parameters of exemestane after administration of three treatments to healthy volunteers (mean±SEM)

Parameter	Treatment A (tablet, fast)	Treatment B (suspension, fast)	Treatment C (tablet, fed)
t_{lag} (h)	0.08 ± 0.04	0	0.10 ± 0.04
C_{max} (pg/ml)	11127 ± 1263	15363 ± 2343	17668 ± 4489
t_{max} (h)	0.97 ± 0.11	0.71 ± 0.07	1.88 ± 0.47
AUC (pg.h/ml)	29703 ± 2248	34525 ± 3271	41347 ± 3418
$t_{1/2}$ (h)	24.04 ± 2.76	21.90 ± 3.66	21.45 ± 3.15
CL/F (l/h)	902 ± 74	798 ± 76	645 ± 46
V_z/F (l)	29566 ± 2642	23347 ± 3705	19432 ± 2687
AUMC/AUC (h)	13.71 ± 1.33	11.84 ± 1.64	12.98 ± 1.60
Statistical comparison:			

90% confidence interval	Treatment A vs. B		Treatment C vs. A	
AUC (ratio)	0.76 - 1.01	NS	1.21 - 1.60	p<0.05
C_{max} (ratio)	0.49 - 1.14	NS	0.83 - 1.90	NS
t_{max} (difference)	0 - 0.5	NS	0 - 1.75	NS

Table 2: Pharmacodynamic parameters for inhibitory effect of exemestane on E1S plasma levels after administration of three treatments to healthy volunteers (mean±SD)

Parameter	Treatment A (tablet, fast)	Treatment B (suspension, fast)	Treatment C (tablet, fed)
I_{max} (% inhibition)	69.5 ± 4.8	71.3 ± 2.5	75.6 ± 1.9
$t_{max.effect}$ (d)	2.6 ± 0.4	2.5 ± 0.3	2.7 ± 0.4
AUC_{effect} (% inhibition d)	487.7 ± 78.2	491.3 ± 57.1	538.2 ± 47.9
$t_{z.effect}$ (d)	10.2 ± 1.2	11.8 ± 0.9	12.2 ± 0.7
Statistical comparison 90% confidence interval:		Treatment A vs. B	Treatment C vs. A
I_{max} (ratio)	0.87 - 1.09	NS	0.97 - 1.20	NS
AUC_{effect} (ratio)	0.80 - 1.19	NS	0.91 - 1.30	NS
$t_{max.effect}$ (difference)	-0.50 - 1.00	NS	-1.00 - 0.50	NS
$t_{z.effect}$ (difference)	-4.22 - 0.46	NS	0.38 - 3.48	p<0.05

Figure 1:

Mean arithmetic (±SD), n=12) plasma levels (pg/mL) after administration of 25 mg as sugar-coated tablet on fasting condition (treatment A), suspension in fasting condition (treatment B), and sugar-coated tablet after a meal (treatment C)

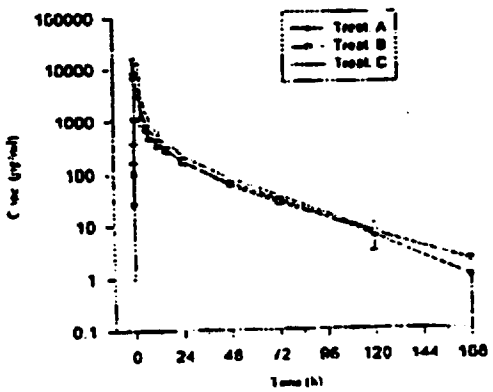
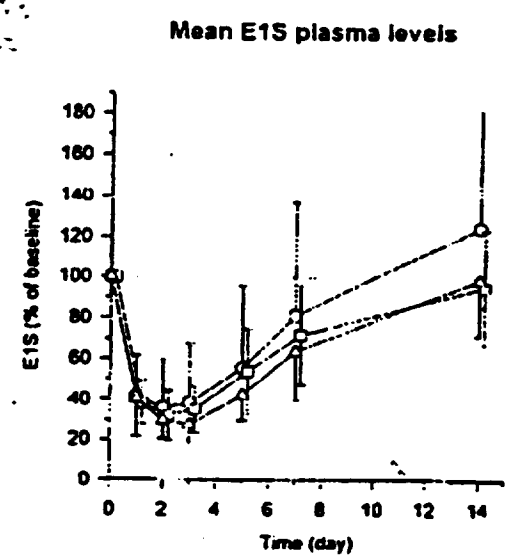


Figure 2:

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, ◐), 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.



CONCLUSIONS: The results obtained from the study showed that:

1. The average bioavailability of the exemestane sugar-coated tablet compared to the suspension formulation is 86%.
2. Co-administration of exemestane with food increased the Cmax by 59% and the AUC by 39% but caused a delay in the tmax of about 1 hour.
3. The three means of administration of exemestane (tablet/fast, suspension/fast, tablet/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 ($t_{z,effect}$) was observed when the drug was administered with food which corresponds to the increased systemic exposure to exemestane when given with food.
4. Exemestane is rapidly absorbed with tmax of 1-2 hours followed by a multiexponential decay with terminal half-life of about 22 hours.
5. Due to the high lipophilicity of exemestane, it has a high volume of distribution (V_z/F) about 600-fold higher than the total body water in humans) which indicates that it undergoes extensive distribution into tissues.
6. The apparent clearance (CL/F) is high (about 10-fold higher than human hepatic blood flow) indicating that exemestane is rapidly eliminated from the systemic circulation by metabolism and/or biliary excretion.

MULTIPLE DOSE PHARMACOKINETIC STUDY

STUDY 95-OEXE-013 VOLUME: 1.38

INVESTIGATOR AND LOCATION:

STUDY DATE: January to July 1996.

OBJECTIVES: (1) To evaluate the autoinduction/autoinhibition of exemestane on its own metabolism after repeated administration to healthy postmenopausal volunteers; (2) To evaluate the possible alteration (induction/inhibition) of the hepatic cytochrome P-450 3A activity.

FORMULATIONS/TREATMENTS:
25 mg sugar-coated tablet of exemestane, Batch No. C12F09

STUDY DESIGN: Open, non-randomized, single vs repeated dose study in 8 healthy postmenopausal volunteers and a washout period of 4 or 5 weeks. Each subject received a single oral dose of 25 mg exemestane on Day 1 and 25 mg daily on Days 8-22 of the study. Blood samples (5 ml) for the determination of exemestane were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 120 and 168 h post dose on Days 1 and 22 and pre-dose on Days 11, 15 and 18 of the study. Total voided urine for the evaluation of cortisol and 6-β-hydoxycortisol was collected over 28 h (0-24 and 24-48 h) on Days -2 and -1 prior to the and Days 21 and 22 of the study.

ASSAYS:

DATA ANALYSIS: AUC, Cmax, $t_{1/2}$, $t_{1/2}$, R_A (accumulation ratio), CL/F, Vz/F and Tmax were calculated for exemestane. Amounts of cortisol and 6-β-hydoxycortisol excreted in urine were reported.

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

Table 1: Pharmacokinetic parameters of exemestane after administration of single and multiple doses to healthy postmenopausal volunteers (mean±SD)

Parameter	Single Dose	Repeated Dose
C_{max} (pg/ml)	17101±12201	11364±6602
t_{max} (h)	2.31±1.87	2.88±1.22
C(24 h) (pg/ml)	235±86	294±162
AUC(0-24 h) (pg.h/ml)	49951±26103	41439±18382
$t_{1/2\alpha}$ (h)	26.63±19.10	35.51±14.03 (n=7)
AUC (pg.h/ml)	57826±26538	
CL/F (l/h)	517±226	715±296
V_z/F (l)	20327±18457	39768±30069
$R_{A,Cmax}$		0.73±0.27
$R_{A,AUC(0-\tau)}$		0.87±0.21
$R_{A,C(24 h)}$		1.22±0.41

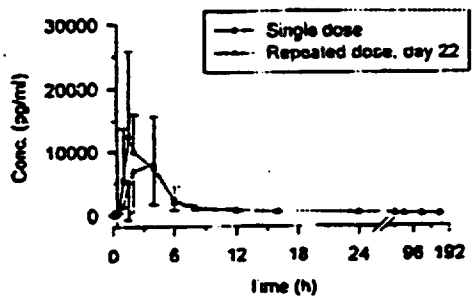
Amount excreted in urine (µg/24 h):	day-2	day-1	average (day -2, -1)	day 21	day 22	average (day 21, 22)
cortisol	44±14	38±13	41±10	59±11	51±16	43±9
6-β-OH-cortisol	225±84	255±83	240±35	187±99	247±62*	223±68*
Ratio	5.16±1.23	7.14±2.52	6.11±1.74	3.38±1.77	4.80±1.30*	5.02±1.44*

Statistical analysis			
Parameter	Day 1	Day 22	Statistics
t_{max} (h)	2.31	2.88	NS
AUC vs AUC, (pg.h/ml)	57826	41439	p<0.05
$t_{1/2\alpha}$ (h)	26.63	35.51	NS
At 6-β-OH-cortisol/cortisol	5.67**	5.02*	NS

* n=6; *average (day -2, -1); *average (day 21, 22)

Day:	11	15	18	21	22	Effect of day
C(24 h) (pg/ml)	310	333	349	300	294	NS

Fig. 1.
Mean (+/-SD) plasma profile of exemestane in the subjects after single and repeated 25 mg dosing regimen of the drug



CONCLUSIONS: The results obtained from the study showed that:

1. 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 induction/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 decrease in biovailability (highly

extracted drug administered orally undergoing prehepatic metabolism) or an increased 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).

2. The accumulation ratios (0.73 and 0.87 by Cmax and AUCτ respectively) were low and also reflect time-dependent pharmacokinetics.
3. The terminal half-life is prolonged after repeated dosing (from 27 to 36 hours), Vz/F is increased by about 96%.

BIOAVAILABILITY / FOOD-EFFECT STUDY

STUDY 94-OEXE-023 **VOLUME: 1.43**

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: December 1993 - March 94.

OBJECTIVES: (1) To determine the safety, the inhibitory effect on serum and urinary estrogens, the plasma pharmacokinetics and urinary excretion of exemestane, following a single oral dose of exemestane to healthy postmenopausal Japanese volunteers; (2) To evaluate the influence of food on the pharmacokinetics of exemestane and its pharmacodynamic effect.

FORMULATIONS/TREATMENTS:
25 mg sugar-coated tablet of exemestane, Batch No. A12F06
Placebo tablet, Batch No. A12F04.

STUDY DESIGN: The study was divided into two sequential phases:

(1) Single-blind, placebo-controlled study, in which 6 healthy postmenopausal volunteers received a dose of 25 mg exemestane (4 subjects) or placebo (2 subjects). After three weeks of observation, the dose was escalated to 50 mg in a different cohort of volunteers.

(2) Single-blind, two-period crossover study in which 8 subjects received orally a 25 mg dose of exemestane (6 subjects) or placebo (2 subjects) under fed and fasting conditions and a washout period of 4 weeks. Treatment under fed conditions was administered (0.5-1 hour after completion of breakfast) after a standard breakfast consisting of 60 g of English bread, 8 g of margarine, 100 g of vegetable salad, 180 ml of orange juice, 50 g of boiled egg (Total enegy= 422 Kcal). Blood samples (5 ml) for the determination of exemestane and metabolite were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32 and 48 h post dose. Plasma E_1, E_2 and E_1S levels were determined at baseline (immmediately before dosing) and at 8 and 24 h post dose and in the mornings of Days 3, 4, 8 and 15 of the study using [redacted]
Twenty-four h urine E_1 and E_2 levels were determined at baseline (Day 1) and on Days 2, 3, 4, 8 and 15 of the study using [redacted]

ASSAYS:

[redacted]

DATA ANALYSIS: AUC, Cmax, $t_{1/2}$, and Tmax were calculated for exemestane and hydroexemestane. Inhibitory effect of exemestane on serum E1, E2 and E_1S levels and urinary E1 and E2 excretion were reported.

RESULTS: Tables 1-3 and Figures 1-5 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1: Pharmacokinetic parameters of exemestane and its metabolite after administration of four treatments to healthy volunteers (mean±SD)

Single dose-response study (n=4)

	Exemestane		17-Hydroexemestane	
Exemestane dose	25 mg/fasting	50 mg/fasting	25 mg/fasting	50 mg/fasting
C_{max} (ng/ml)	14.76±8.15	30.82±16.37	1.44±0.62	1.98±0.55
t_{max} (h)	0.9±0.3	1.0±0.4	1.0±0.0	1.1±0.3
AUC(0-t_n) (ng·h/ml)	49.10±5.26	154.01±22.39	3.10±1.35	10.75±2.80
AUC(0-∞) (ng·h/ml)	59.67±4.60 (n=3)	191.64±51.77	n.a.	n.a.
$t_{1/2}$ (h)	22.5±9.3 (n=3)	20.8±9.0	n.a.	n.a.
Ae(0-48 h) (μg)	31.9±21.6	33.8±9.8	1.1±0.9	1.0±0.8

Crossover study (n=5 for 25 mg/fasting; n=6 for 25 mg/fed)

	Exemestane		17-Hydroexemestane	
Exemestane dose	25 mg/fasting	25 mg/fed	25 mg/fasting	25 mg/fed
C_{max} (ng/ml)	9.66±2.72	14.72±4.69	0.79±0.28	1.12±0.13
t_{max} (h)	1.1±0.2	1.4±0.5	1.4±0.4	1.8±0.7
AUC(0-t_n) (ng·h/ml)	68.90±45.31	88.78±64.39	3.20±2.40	7.52±8.75
AUC(0-∞) (ng·h/ml)	63.85±44.14[1] (n=4)	93.49±58.23 (n=4)	n.a.	n.a.
$t_{1/2}$ (h)	21.3±6.3 (n=4)	17.7±6.7 (n=4)	n.a.	n.a.
Ae(0-48 h) (μg)	25.6±17.2	19.1±8.6	1.1±0.8	0.6±0.3

n.a.: not analyzed

[1] AUC(0-∞) was lower than AUC(0-t_n), as extrapolation could not be obtained in the subject with highest AUC(0-t_n)

Table 2: Serum Estrogen Concnetrations Expressed as Percentage Baseline Values (mean±SD)

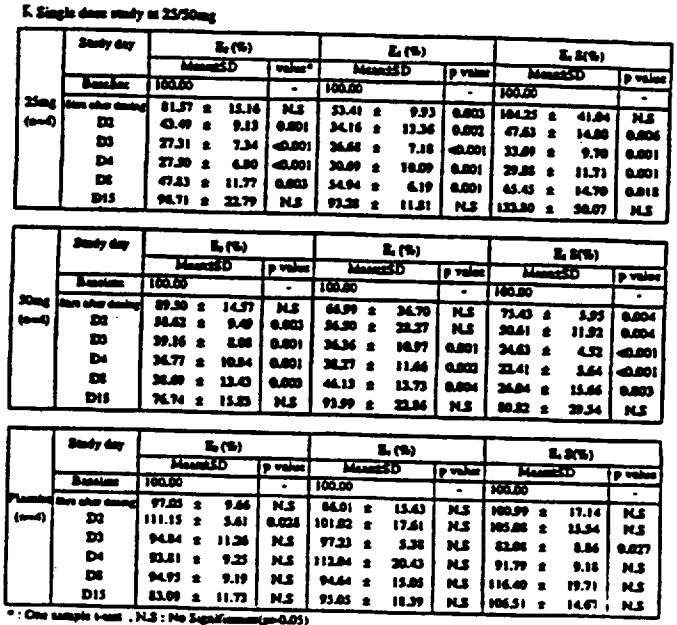


Table 3: Urinary Excretion of Estrogen Expressed as Percentage Baseline Values (mean±SD)

1. Single dose study at 25/50mg

	Study day	E_2 (%) Mean±SD		p value*	E_1 (%) Mean±SD		p value
25mg (n=4)	Baseline	100.00		-	100.00		-
	D2	144.46 ±	32.50	N.S	209.95 ±	88.66	N.S
	D3	64.78 ±	30.40	N.S	77.62 ±	38.71	N.S
	D4	52.69 ±	16.21	0.010	62.61 ±	29.10	N.S
	D8	50.39 ±	24.12	0.026	47.24 ±	22.32	0.018
	D15	159.23 ±	101.50	N.S	131.92 ±	63.98	N.S
50mg (n=4)	Baseline	100.00		-	100.00		-
	D2	119.42 ±	35.37	N.S	125.78 ±	20.56	N.S
	D3	65.89 ±	8.97	0.005	76.05 ±	23.26	N.S
	D4	36.16 ±	20.20	0.008	36.57 ±	19.60	0.007
	D8	35.38 ±	22.26	0.010	36.43 ±	26.99	0.018
	D15	65.86 ±	24.24	N.S	64.71 ±	16.54	0.024
Placebo (n=4)	Baseline	100.00		-	100.00		-
	D2	110.50 ±	18.80	N.S	102.04 ±	27.34	N.S
	D3	102.41 ±	40.34	N.S	95.89 ±	25.74	N.S
	D4	115.99 ±	55.20	N.S	101.93 ±	59.99	N.S
	D8	82.45 ±	27.31	N.S	73.87 ±	19.75	N.S
	D15	116.28 ±	62.87	N.S	93.06 ±	48.31	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.)

2. Crossover study

Fasting

	Study day	E_2 (%) Mean±SD		p value*	E_1 (%) Mean±SD		p value
25mg (n=5)	Baseline	100.00		-	100.00		-
	D2	112.80 ±	59.61	N.S	113.99 ±	51.20	N.S
	D3	47.24 ±	17.62	0.003	49.36 ±	24.41	0.010
	D4	30.42 ±	5.83	<0.001	26.03 ±	8.17	<0.001
	D8	41.41 ±	23.40	0.005	38.74 ±	26.65	0.007
	D15	104.20 ±	49.85	N.S	91.50 ±	50.80	N.S

Fed

	Study day	E_2 (%) Mean±SD		p value	E_1 (%) Mean±SD		p value
25mg (n=5)	Baseline	100.00		-	100.00		-
	D2	84.54 ±	47.41	N.S	94.39 ±	59.75	N.S
	D3	61.07 ±	51.76	N.S	54.36 ±	29.18	0.025
	D4	22.76 ±	5.42	<0.001	22.60 ±	8.41	<0.001
	D8[a]	34.03 ±	13.95	0.003	29.45 ±	18.05	0.004
	D15	61.27 ±	18.99	0.010	64.78 ±	31.18	N.S
Placebo (n=4)	Baseline	100.00		-	100.00		-
	D2	146.44 ±	25.30	0.015	133.22 ±	24.11	N.S
	D3	126.74 ±	47.96	N.S	134.09 ±	63.67	N.S
	D4	136.10 ±	66.95	N.S	127.48 ±	50.43	N.S
	D8	133.93 ±	72.18	N.S	131.16 ±	75.92	N.S
	D15	98.84 ±	48.39	N.S	81.42 ±	33.50	N.S

*: One sample t-test , N.S : No Significance (p>0.05). [a] n=4

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

Figure 1: Changes in serum (a) estradiol and (b) estrone

(a) (b)

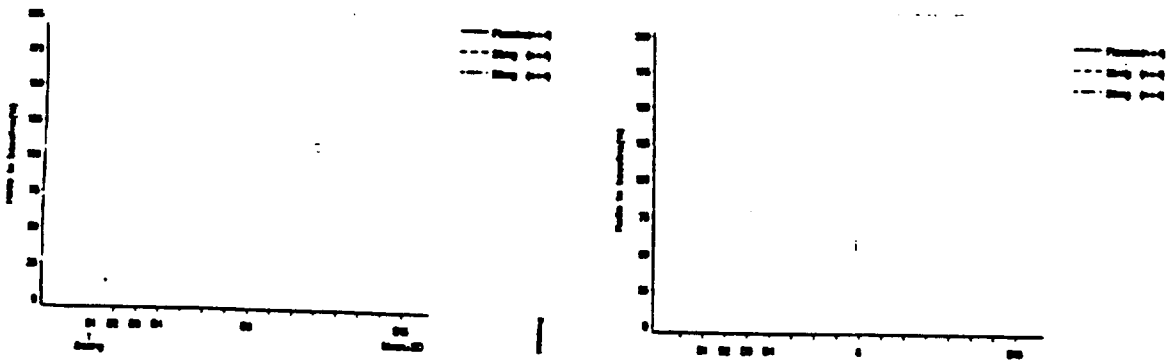


Figure 2: Changes in serum (a) estrone sulfate and (b) estradiol

(a) (b)

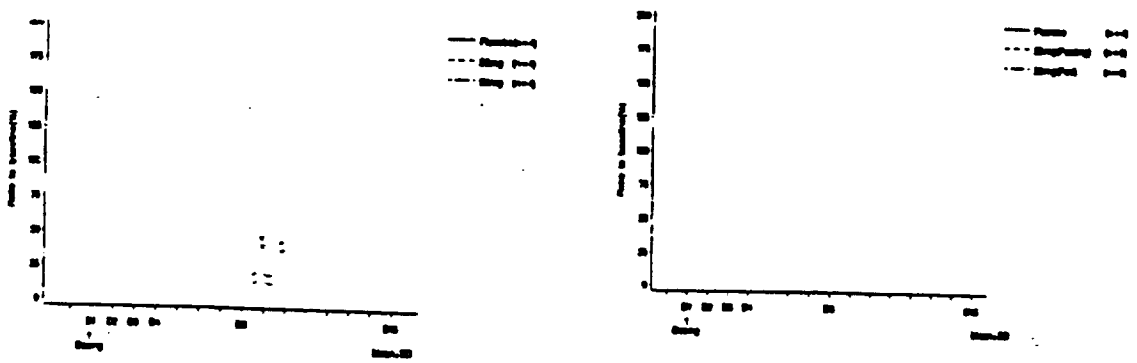


Figure 3: Changes in serum (a) estrone and (b) estrone sulfate

(a) (b)

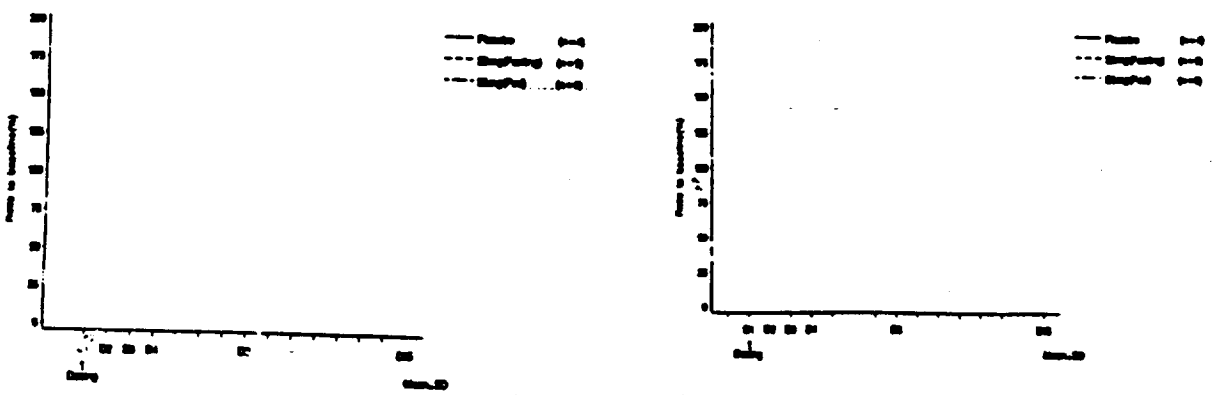


Figure 4: Mean plasma profiles for exemestane

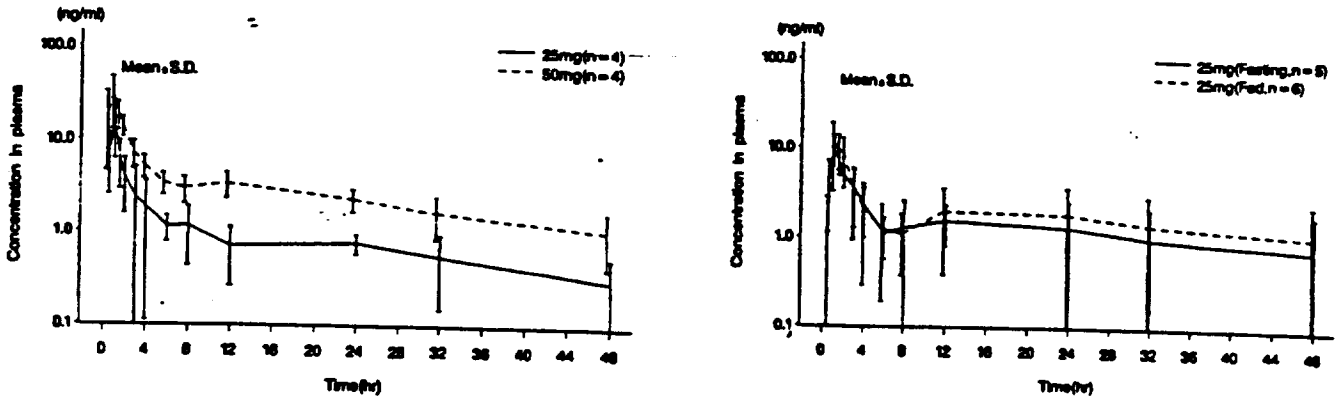
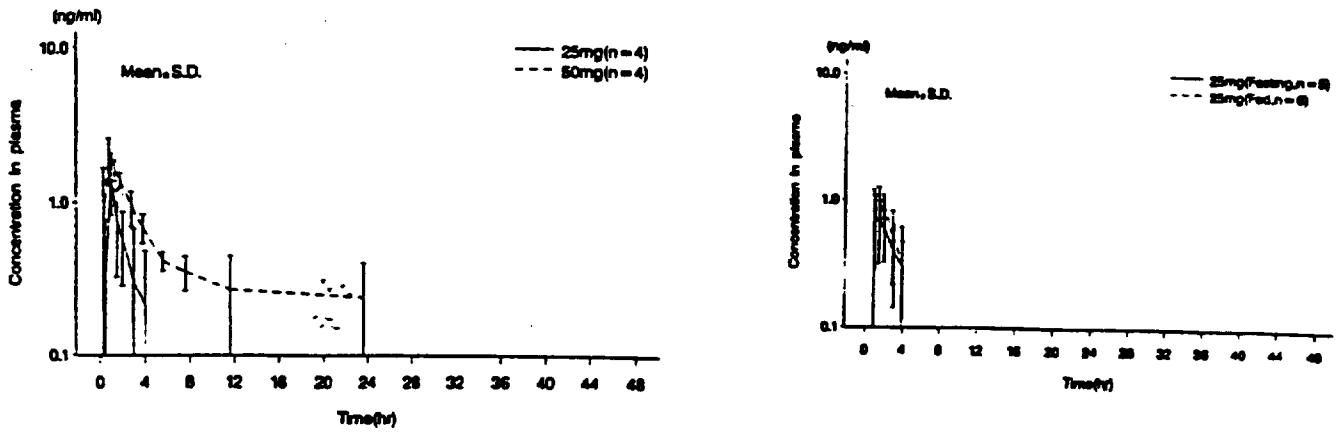


Figure 5: Mean plasma profiles for hydroexemestane



CONCLUSIONS: The results obtained from the study showed that:

1. Co-admistration of exemestane with a standard breakfast 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.
2. 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.

SINGLE / MULTIPLE DOSE PHARMACOKINETIC STUDY

STUDY 95-OEXE-022 VOLUME: 1.52

INVESTIGATOR AND LOCATION: [ ]

STUDY DATE: September 1995 - July 1998.

OBJECTIVES: (1) To obtain information on the plasma pharmacokinetics of exemestane after single and repeated daily oral administration of 25 mg sugar-coated tablet to postmenopausal patients with advanced breast cancer (ABC); (2) To compare the results of the present study with those obtained in previous assessments of exemestane pharmacokintics in healthy postmenopausal women.

FORMULATIONS:
25 mg sugar-coated tablet of exemestane, Batch No. B12F10 and Batch No. E12F02

STUDY DESIGN: Open, multicenter, single and repeated dose pharmacokinetcs study in postmenopausal patients with advanced breast cancer (ABC). The patients received a single oral dose of 25 mg of exemestane and exemestane pharmacokintics were evaluated. Following repeated daily treatment (25 mg/day), exemestane pharmacokinetics were evaluated at steady state at any time from day 15 of daily administration, but not beyond, the week 8 of the study. Blood samples (5 ml) were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 h after both single and repeated administration; and 48, 72 and 120 h after single dosing.

ASSAYS:
[

DATA ANALYSIS: AUC, Cmax, t_{lag}, $t_{1/2}$, R_A (accumulation ratio), CL/F, Vz/F and Tmax were calculated for exemestane.

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

Table 1:

Comparison of the pharmacokinetic parameters (mean ±SD, 95% confidence intervals of the mean values in square brackets) calculated following single oral administration of exemestane at 25 mg dose to postmenopausal ABC patients (this study) and postmenopausal healthy subjects (data obtained from the previous studies Le Coz 1997 and Jannuzzo 1997).

Parameter	ABC patients (n=6)		healthy subjects (n=20)	
t_{max} (h)	1.02±0.81	[0.17-1.87]	2.1±1.4	[1.44-2.75]
C_{max} (ng/mL)	40.440±40.553	[-2.118-82.998]	17.4±14.0	[10.848-23.952]
AUC (ng·h/mL)	76.712±44.736	[29.766-123.659]	47.9±20.2	[38.446-57.354]
$t_{1/2,z}$ (h)	19.24±10.22	[8.52-29.96]	23.52±14.49	[16.74-30.30]
CL/F (L/h)	415±202	[202-628]	594±194	[503-685]
V_z/F (L)	11692±7478	[9140-28906]	19790±13261	[13594-25996]

Table 2:

Comparison of the pharmacokinetic parameters (mean ±SD, 95% confidence intervals of the mean values in square brackets) calculated following repeated daily oral administration of exemestane at 25 mg dose to postmenopausal ABC patients (this study) and postmenopausal healthy subjects (data obtained from the previous study Jannuzzo 1997).

Parameter	ABC patients (n=9)		healthy subjects (n=8)	
$t_{max,ss}$ (h)	1.16±0.78	[0.56-1.76]	2.9±2.9	[0.5-5.3]
$C_{max,ss}$ (ng/mL)	29.571±24.859	[10.463-48.679]	11.4±6.6	[5.9-16.9]
$AUC(0\text{-}24h)_{ss}$ (ng·h/mL)	75.405±29.407	[52.802-98.008]	41.4±18.5	[25.9-56.9]
CL/F_{ss} (L/h)	391±184	[250-531]	715±296	[468-962]
$R_{A,Cmax}$	0.82±0.42	[0.38-1.26]	073±0.27	[0.50-0.96]
$R_{A,AUC(0\text{-}24\,h)}$	1.08±0.17	[0.90-1.26]	0.87±0.21	[0.69-1.05]

Figure 1:

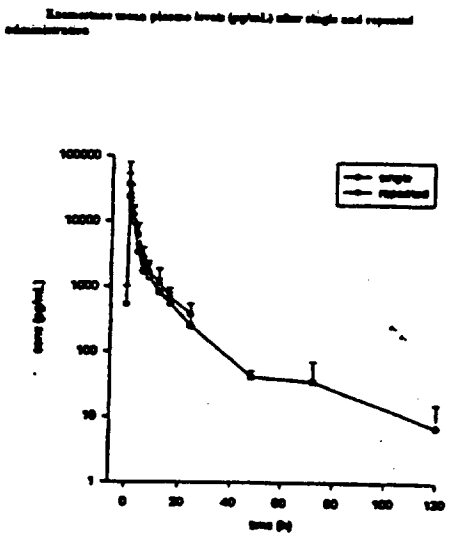
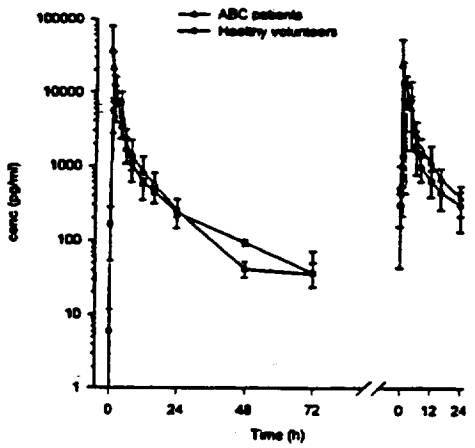


Figure 2:

Comparison between mean (±SD) plasma levels (pg/mL) of exemestane after single (left) and repeated daily (right) administration of the drug to the ABC patients with those observed in healthy subjects (January 1997)



CONCLUSIONS: Comparison of the data obtained from this study with those obtained from healthy postmenopausal volunteers (Study 94-OEXE-012 and Study 95OEXE-013) show that:

1. 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% in AUC and (iv) a 30% decrease in CL/F in ABC patients compared to healthy postmenopausal volunteers.
2. 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% 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.

RENAL IMPAIRMENT STUDY

STUDY 95-OEXE-016 VOLUME: 1.51

INVESTIGATOR AND LOCATION:

STUDY DATE: 4 April 1996 to date

OBJECTIVES: To assess the pharmacokinetics of exemestane in postmenopausal volunteers with moderate or severe renal impairment after administration of one exemestane 25 mg sugar coated tablet as a single oral dose.

FORMULATIONS/TREATMENTS:
Exemestane was supplied as 25 mg sugar-coated tablets by the applicant. The certificate of analysis (Batch C12F09 - expiry date April 1998) is provided.
Volunteers were given a single oral dose of 25 mg of exemestane as sugar-coated tablets on day 1 following a standard breakfast.

STUDY DESIGN: This is an open, multicenter study. As per the study protocol, eighteen postmenopausal volunteers (six healthy subjects, six subjects with moderate renal impairment, and six subjects with severe renal impairment) were to receive a single oral dose of 25 mg of exemestane as sugar-coated tablets after a standard breakfast. Seven subjects with severe renal impairment and three healthy volunteers have completed the study to date.
Blood samples for pharmacokinetic assessments were collected at the following times:
- just before drug intake (time 0)
- at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72 , 120, and 168 h post dosing.

Urine was collected before administration (blank sample) and over the following time intervals after drug intake: 0-24, 24-48, 48-72 and 72-96 h.

ASSAYS:

DATA ANALYSIS: Pharmacokinetic analyses were carried out using a non-compartmental approach. For the calculations the actual sampling times were used.
After exemestane administration, the maximum plasma concentration C_{max} and the corresponding time t_{max} were read for each subject directly from the raw data. The area under the plasma concentration vs. time curve, AUC, was determined by the linear trapezoidal rule

up to the last detectable concentration $C(t_z)$ at time t_z, and denoted $AUC(0\text{-}t_z)$; beyond that time the AUC was determined by extrapolation from $C(t_z)$ assuming monoexponential decay.
The ratios of systemic clearance (CL/F) and volume of distribution of the terminal phase (V_z/F) to absolute bioavailability (F) were calculated.
The amount of exemestane excreted in urine [Ae (0-96h)] was measured and renal clearance was calculated as CL_R = Ae (0-96 h) / AUC (0-96 h).

RESULTS: Mean plasma pharmacokinetic parameters of exemestane are shown in Tables 1. All subjects with renal impairment were considered as a single group in this preliminary report.

Only 3 healthy postmenopausal subjects have been enrolled in this study. Data from previous studies in healthy volunteers (Le Coz 1997, Jannuzzo 1997) carried out with the same analytical method are available. The pooled data (n = 12 and n = 8) of these healthy volunteers were used for the evaluation of the effect of renal impairment on exemestane pharmacokinetics. Exemestane pharmacokinetic parameters calculated for the healthy volunteers of this study were in reasonable agreement with those obtained in the previous studies, except for C_{max} values which appeared lower.

A significant increase in the systemic exposure to exemestane was observed in subjects with renal impairment compared with healthy volunteers (Fig 1). The graph of CL/F vs. CL_{CR} is consistent with this conclusion (Fig. 2). A significant trend is also apparent between the values of CL_R vs. CL_{CR} (Fig. 3).

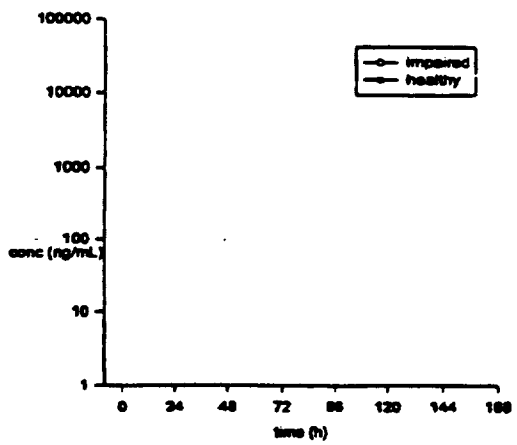


Figure 1: Mean (± SD) plasma levels of exemestane after single oral administration of 25 mg to subjects with severe renal impairment (n = 7) and healthy subjects (n=3).

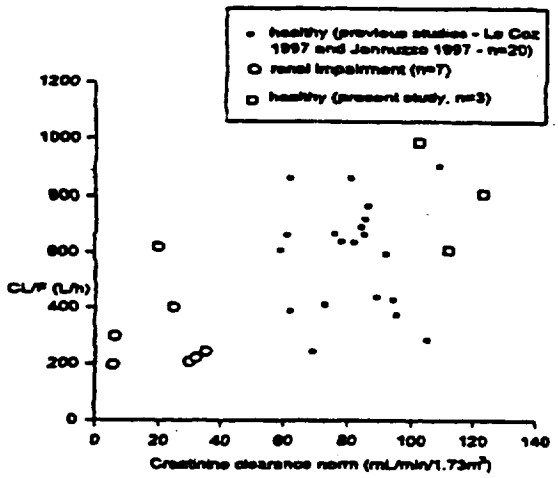


Figure 2. Exemestane CL/F vs. normalized creatinine clearance values of subjects with severe renal impairment and of healthy subjects from the present study and healthy subjects from previous studies.

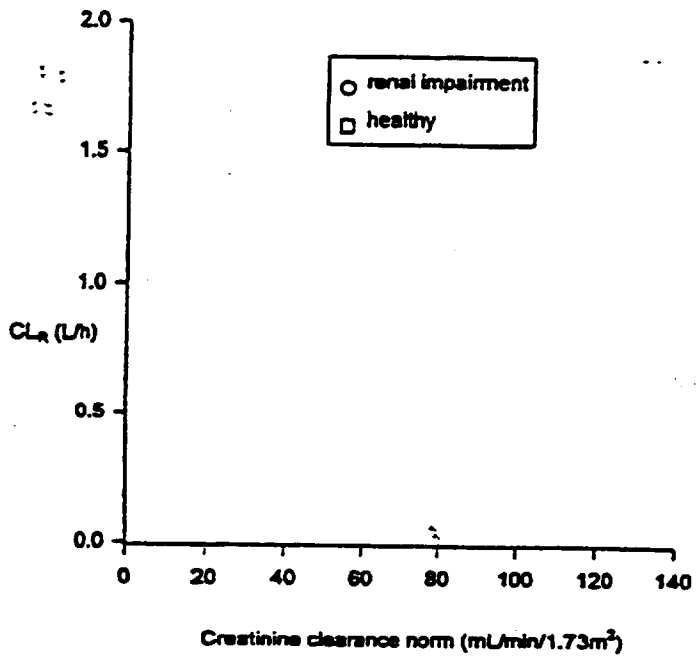


Figure 3: Exemestane CL_R of the subjects with severe renal impairment and of the healthy subjects vs. normalized creatinine clearance values.

Table 1. Pharmacokinetic parameters calculated following oral administration of exemestane at 25 mg single dose to postmenopausal subjects.

Parameter	Renal impairment subjects (n=7) Mean ± SD	Healthy subjects Mean ± SD	
		Current study (n=3)	Previous study (n=20)
t_{lag} (h)	0.29±0.17	0.50±0.43	
Cmax (pg/mL)	16743±7204	7120±2948	17441 ±13963
Tmax (h)	1.69±0.45	1.67±0.29	2.1 ± 1.4
AUC(0-t_z) (pg•h/mL)	90426±32889	31316±8287	
$T_{1/2,z}$ (h)	36.84±16.61	27.23±9.99	24 ± 14
AUC (pg•h/mL)	92613±32121	32367±7975	47939 ± 20230
%$EXTR_{AUC}$	3.29±4.49	3.48±2.34	
CL/F (L/h)	312±152	803±190	594 ± 194
Vd/F (L)	18874±19420	31215±12402	
Ae(0-72h) (ng)	10574±8601	32781±7542	
% dose	0.04±0.03	0.13±0.03	
CL_R (L/h)	0.14±0.13	1.13±0.44	

CONCLUSIONS: The results obtained from this preliminary study showed that:

1. The systemic exposure of exemestane was increased by a factor of 2-3 in subjects with renal impairment compared to the healthy postmenopausal volunteers. Considering that the renal pathway is a minor elimination route of the unchanged drug (≤ 0.10% of the dose excreted unchanged in urine), the differences in the renal function may not explain the observed differences in the systemic exposure to exemestane. Other factors (e.g. a decreased intrinsic clearance or an increased plasma protein binding in patients with renal failure) may be involved. Plasma protein binding is often altered in patients with impaired renal function. This leads to the recommendation that the PK should be described and analyzed with respect to the unbound concentrations of the drug.
2. No assay validation could be found in the study report.

3. This is a preliminary report. As per the study protocol, eighteen postmenopausal volunteers (six healthy subjects, six subjects with moderate renal impairment, and six subjects with severe renal impairment) were to be enrolled in the study. However, only seven subjects with severe renal impairment and three healthy volunteers have completed the study in the report. The number of patients enrolled in the study should have been sufficient to detect PK differences large enough to warrant dosage adjustments. When the study is completed, the final report should be submitted. The final judgement will be based on that report.

HEPATIC IMPAIRMENT STUDY

STUDY 95-OEXE-015 **VOLUME:** 1.49-1.50

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: December 31, 1996 to date

OBJECTIVES: To assess the pharmacokinetics of exemestane in postmenopausal volunteers with moderate or severe hepatic impairment after administration of exemestane 25 mg sugar-coated tablet as a single oral dose.

FORMULATIONS/TREATMENTS:
Exemestane was supplied as 25 mg sugar-coated tablets by the applicant. The certificates of analysis (Batch C12F09 - expired date April 1998, Batch E12F02 - expired date February 2000) are provided.
Volunteers were given a single oral dose of 25 mg of exemestane as sugar-coated tablets on day 1 following a standard breakfast.

STUDY DESIGN: Open, multicenter, multinational, single dose study. The subjects were given exemestane as a single oral dose of 25 mg after a standard breakfast. Blood samples for pharmacokinetic assessment were collected immediately prior to dosing and up to 168 h post-dosing. Urine samples were collected immediately before dosing and every 24 h up to 72 h post-dosing. Exemestane was assayed in the biological fluids using [redacted]

ASSAYS: [redacted]

DATA ANALYSIS: Pharmacokinetic analyses were carried out using a non-compartmental approach. For the calculations the actual sampling times were used.
After exemestane administration, the maximum plasma concentration C_{max} and the corresponding time t_{max} were taken directly from the raw data for each subject. The area under the plasma concentration versus time curve, AUC, was determined by the linear trapezoidal rule up to the last detectable concentration $C(t_z)$ at time t_z, and denoted $AUC(0\text{-}t_z)$; beyond that time the AUC was determined by extrapolation from $C(t_z)$ assuming monoexponential decay.

The ratios of systemic clearance (CL/F) and volume of distribution of the terminal phase (Vz/F) to absolute bioavailability (F) were calculated.
The amount of exemestane excreted in urine [Ae (0-72h)] was measured and renal clearance was calculated as CL_R = Ae (0-72 h) / AUC (0-72h).

RESULTS: At the time of preliminary report, plasma levels of exemestane were available in 6 healthy volunteers, in 8 subjects with moderate and in 3 subject with severe hepatic impairment. Urinary data are available in 2 healthy subjects, in 3 subjects with moderate hepatic impairment, and in one subject with severe hepatic impairment. Mean (±SD) plasma levels of exemestane of healthy subjects and subjects with moderate and severe hepatic impairment are shown in Fig. 1. The results of the statistical evaluation are presented in Table 1.
A decrease in CL/F was observed in patients suffering from hepatic impairment compared to healthy volunteers with a corresponding 3 fold increase in the systemic exposure. ANOVA showed that grade of liver impairment had a significant effect both on C_{max} and on AUC.
Although the half-lives were not significantly reduced (p=0.0554) in the groups of patients suffering from hepatic impairment, the variability and the bias could have a role in this and its relevance remains to be evaluated. Three subjects with moderate hepatic impairment had an apparent short terminal half-life value (in the range 6-7 h).
The urinary excretion of exemestane was low both in the two healthy volunteers (0.05 and 0.03% dose respectively) and in the four subjects with hepatic impairment (3 moderate and 1 severe, 0.18 ± 0.08 % dose) analyzed.

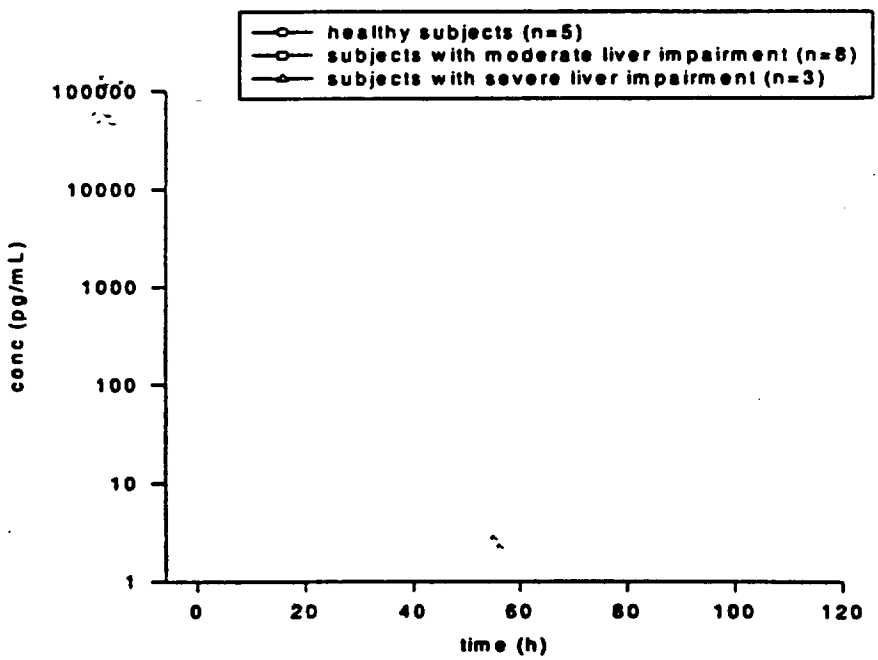


Fig. 1. Mean (±SD) plasma levels of exemestane after single oral administration of 25 mg to healthy subjects and to subjects with moderate and severe hepatic impairment.

Table 1. Statistical comparison of the main plasma pharmacokinetic parameters obtained following oral administration of exemestane at 25 mg single dose to postmenopausal healthy subjects and to subjects with moderate and severe hepatic impairment

Parameter	Means and simultaneous 90% confidence interval			1-way ANOVA
	Healthy	Moderate	Severe	
T_{max} (h) (range)[1]	1-4	1-4	1-2	p>0.05
C_{max} (ng/mL) [2]	15.150 10.426-22.014	36.865 26.673-50.952	41.533 24.484-70.453	p<0.01
AUC(0-t_z) (ng·h/mL)[2]	38.085 30.904-46.936	109.990 91.784-131.808	143.663 106.908-193.053	p<0.01
AUC (ng·h/mL) [2]	39.113 31.727-48.219	110.361 92.065-132.292	144.404 107.407-194.146	p<0.01
$T_{1/2,z}$ (h)[3]	27.67 17.69-37.65	12.49 3.85-21.13	19.39 5.28-33.50	p>0.05

[1]: Median, range and Friedman's test

[2]: geometric mean, antilog of 90% confidence intervals and ANOVA on log-transformed data

[3]: arithmetic mean, 90% confidence intervals and ANOVA on untransformed data.

CONCLUSIONS: The results obtained from the study showed that:

1. A decrease in CL/F was apparent in patients suffering from hepatic impairment compared to healthy volunteers with a corresponding 3 fold increase in the systemic exposure.

2. The grade of liver impairment had a significant effect both on C_{max} and on AUC of the drug.

3. The reduction of hepatocellular activity could increase absolute bioavailability, via a reduction of the hepatic first pass effect.

4. No assay validation could be found in the study report.

5. This is a preliminary report. Since the study is ongoing, the following points should be noted.

   - More than six patients per group of graded impaired hepatic function (mild, moderate, and severe) should be selected using established methods such as Child-Pugh.

- To the extent possible, factors such as diet, smoking, alcohol intake, ethnicity, and concomitant medications that may contribute to the variability in drug kinetics should be controlled during the study.
- For drugs which are highly extracted by the liver (extraction ratio, E > 0.7) and are extensively bound to plasma proteins (fraction unbound, fu < 20 %), the unbound fraction should be determined in each patient at least at trough and maximum plasma concentration. The clearance and volume terms should be individually corrected for plasma protein binding.
- Correlations between the degree of hepatic function, for example hepatic blood flow, serum albumin concentration or prothrombin time and various pharmacokinetic parameters (such as unbound total body clearance, unbound oral clearance, unbound apparent volume of distribution) should be sought in order to facilitate algorithm for dose adjustment.

The complete report should be submitted when it is available. The final judgement will be based on that report.

EXEMESTANE-KETOCONAZOLE INTERACTION STUDY

STUDY 95-OEXE-028 VOLUME: 1.41-1.42

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: April 29, 1996 to October 21, 1996

OBJECTIVES: To evaluate the possible involvement of CYP3A4 in exemestane metabolism in healthy postmenopausal volunteers.

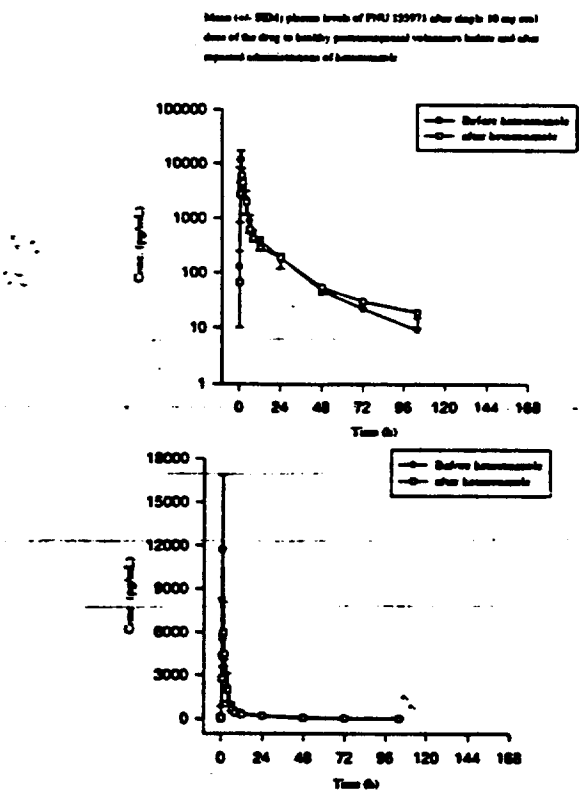
FORMULATIONS/TREATMENTS:
Exemestane was supplied as 25 mg sugar-coated tablets by the applicant. The certificate of analysis (Batch C12F01 - expiry date January 1998) is provided.
Volunteers were given a first single oral dose of 10 mg of exemestane as 2 × 5 mg sugar-coated tablets on day 1 following a standard breakfast. After a 25-day wash-out period they were given 200 mg/day ketoconazole orally for 6 days (days 26 - 31) following an overnight fast. The volunteers received a second single oral dose of 10 mg of exemestane as 2 × 5 mg sugar-coated tablets on day 29 one hour after ketoconazole administration, 15 minutes after completion of a standard breakfast.

STUDY DESIGN: This was an open, single center, single group, non-randomized study comparing exemestane pharmacokinetics before and during ketoconazole treatment.
Blood samples for pharmacokinetic assessment were collected up to 168 h after each single exemestane dose. Plasma levels of exemestane were measured using [redacted] Collection of daily urine for the measurement of the ratio of the amount of 6-β-hydroxycortisol/cortisol excreted in urine (marker for CYP3A activity) was performed at baseline (days -2, -1) and on days 27, 28 and 31, following the 2nd, the 3rd and the 6th ketoconazole administration. The two compounds were assayed using commercially available enzyme-linked immunosorbent assay (ELISA) and [redacted] kits, respectively.

ASSAYS:
[redacted]

DATA ANALYSIS: Plasma pharmacokinetic parameters were calculated using non-compartmental methods: t_{lag}, C_{max}, t_{max}, $t_{1/2,z}$, AUC, CL/F, V_z/F, AUMC/AUC were evaluated after the two single doses of exemestane. Actual sampling times were considered in the calculations. The ratio of urinary amounts of 6-β-hydroxycortisol to cortisol (calculated at baseline and on days 27, 28 and 31) was used as a marker of the CYP3A activity.
Descriptive statistics was used for the pharmacokinetic parameters (mean, SD, SEM, median, minimum, maximum). The comparison between the pharmacokinetic parameters of exemestane obtained before and during ketoconazole administration (C_{max}, $t_{1/2,z}$, AUC, CL/F, V_z/F) was performed using Student's t-test for paired data. Ninety percent confidence intervals for the ratio of AUC and C_{max} during/before ketoconazole administration were also calculated. The ratios of the amounts of 6-β-hydroxycortisol to cortisol excreted in urine before and during repeated ketoconazole administration were compared using non-parametric techniques (Friedman's test). A value of $p \leq 0.05$ was considered significant in all statistical tests.

RESULTS: The mean (± SEM) plasma levels vs. time plots of the drug are shown in the following Figure.



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.

As shown in the table below, the ratios of the amounts (Ae) of 6-β-hydroxycortisol to cortisol significantly decreased (Friedman's test, $p<0.05$) following repeated ketoconazole administration (mean ± SD; n = 5). However, there was no control group, i.e. the group without exemestane administration.

Day	Ratio 6-β-hydroxycortisol to cortisol Ae	Friedman's test
-2, -1 (average)	4.97 ± 1.86	
27	4.05 ± 2.03	$\chi 2 = 8.28$
28	2.99 ± 1.57	d.f. = 3
31	3.07 ± 1.17	p = 0.041

CONCLUSIONS: The results obtained from the study showed that:

1. 90% confidence intervals about the geometric mean ratio of the observed pharmacokinetic measures before and during ketoconazole repeated administration were 33-181% for C_{max} and 69-126% for AUC. However, considering the variability of AUC and the findings of

in vitro studies, inhibition of CYP3A4 has little effect on the overall pharmacokinetics of exemestane.

2. An efficient inhibition of CYP3A4 activity by ketoconazole was confirmed by the significant decrease in the ratio of 6-β-hydroxycortisol/cortisol excreted in urine. These findings indicate that inhibition of CYP3A4 activity does not significantly increase the bioavailability of exemestane and does not significantly inhibit the metabolism of exemestane.
3. The assay and its validation for exemestane described in the study report are not adequate. The analytical procedure should describe in detail the steps necessary to perform each analytical test. All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate.

DRUG PRODUCT DISSOLUTION TESTING

Selection of dissolution method and specification: Exemestane is poorly soluble in all aqueous media simulating gastrointestinal fluids such that sink conditions cannot be reached even at minutes from the 25 mg tablet in water, simulated gastric fluid pH 1.2 and phosphate buffer 6.8 (Table 1). The sponsor then investigated the possibility of enhancing the solubility of exemestane in aqueous media by addition of sodium lauryl sulfate (Table 2). The dissolution data obtained from the formulations used for the pivotal bioequivalence study are shown on Tables 3-6.

Table 1:

Dissolution test results of Exemestane 25 mg sugar coated tablets (batch D12F06 - A4 process) in three different dissolution media

SMP.	WATER				SGF without enzymes pH 1.2				Phosphate Buffer pH 6.8			
	15'	30'	45'	60'	15'	30'	45'	60'	15'	30'	45'	60'
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
MIN.	57.17	72.03	72.03	74.51	41.48	56.30	64.33	69.22	34.73	53.07	62.33	68.08
MAX.	62.37	76.55	83.97	88.23	58.53	61.40	72.85	78.57	41.11	58.89	68.60	74.85
C.V.	2.74%	3.50%	4.62%	5.07%	7.26%	2.71%	3.27%	3.31%	4.56%	2.92%	2.69%	2.99%

SGF = Simulated Gastric Fluid

Table 2:

Dissolution profiles of Exemestane s.c. tablets (lot 8001) in different dissolution media: water and aqueous solutions containing increasing percentages of sodium lauryl sulfate (Na L.S.)

MEDIUM	TIME	SUMMARY TABLE			
		MEAN	MIN.	MAX.	RSD
WATER (*)	15'	55.66			2.58%
	30'	73.27			3.01%
	[illegible]	[illegible]			[illegible]
	60'	85.15			2.27%
	120'	95.31			1.69%
Na L.S. 0.125% (*)	15'	68.24			3.72%
	30'	78.96			2.87%
	[illegible]	[illegible]			[illegible]
	60'	88.78			4.22%
	120'	95.15			3.87%
Na L.S. 0.15% (*)	15'	78.49			3.80%
	30'	80.59			3.62%
	[illegible]	[illegible]			[illegible]
	60'	88.29			4.07%
	120'	94.65			5.20%
Na L.S. 0.20% (*)	15'	76.33			3.27%
	30'	85.25			4.92%
	[illegible]	[illegible]			[illegible]
	60'	91.85			4.57%
	120'	97.64			3.41%
Na L.S. 0.25% (*)	15'	85.95			1.63%
	30'	94.09			1.07%
	[illegible]	[illegible]			[illegible]
	60'	98.54			0.57%
	120'	100.61			1.24%
Na L.S. 0.5% (§)	15'	89.46			2.48
	30'	93.44			2.59
	[illegible]	[illegible]			[illegible]

(*) test carried out on 6 tablets
(§) test carried out on 12 tablets

Table 3:

EXEMESTANE SUGAR-COATED TABLETS 25 mg BATCH D12706

DISSOLUTION PROFILE RESULTS ON TWELVE TABLETS

MANUFACTURING DATE: JULY 1996 ANALYSIS DATE: OCTOBER 1996

Number SAMPLES	SAMPLING POINTS		
	15 minutes	30 minutes	45 minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			

SAMPLE POINT	MINIMUM	MEAN	MAXIMUM	CV (%)
15'		85.27		3.56
30'		93.31		2.60
45'		97.97		2.09

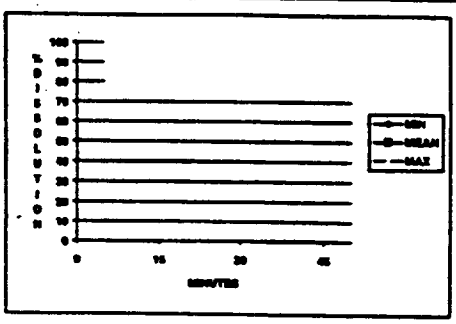


Table 4:

EXEMESTANE SUGAR-COATED TABLETS 25 mg BATCH D12707

DISSOLUTION PROFILE RESULTS ON TWELVE TABLETS

MANUFACTURING DATE:JULY 1996 ANALYSIS DATE: OCTOBER 1996

Number SAMPLES	SAMPLING POINTS		
	15 minutes	30 minutes	45 minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			

SAMPLE POINT	MINIMUM	MEAN	MAXIMUM	CV (%)
15'		87.24		2.54
30'		93.98		1.37
45'		96.74		1.28

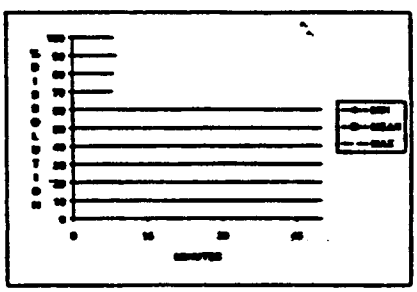


Table 5:

EXEMESTANE SUGAR-COATED TABLETS 25 mg BATCH E12F01

DISSOLUTION PROFILE RESULTS ON TWELVE TABLETS

MANUFACTURING DATE: JANUARY 1997; ANALYSIS DATE: OCTOBER 1998

Number SAMPLES	SAMPLING POINTS		
	15 minutes	30 minutes	45 minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			

SAMPLE POINT	MINIMUM	MEAN	MAXIMUM	CV (%)
15'		86.66		3.42
30'		93.14		2.18
45'		94.30		2.02

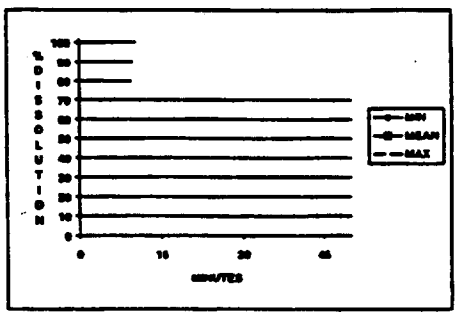


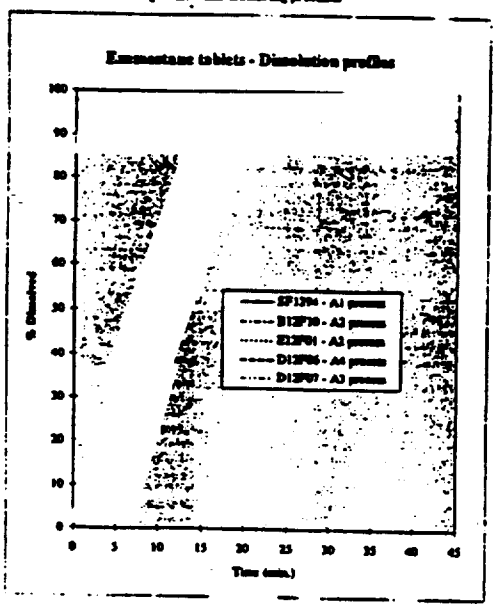
Table 6:

Exemestane sugar -coated tablets 25 mg - dissolution profiles

BATCH	MFG. PROCESS	SAMPLE POINT	MINIMUM	MEAN	MAXIMUM	CV (%)
SF1294 (*)	A1	20'		88.2		2.63
		30'		94.7		2.54
		45'		98.7		1.41
B12F10 (*)	A2	15'		95.64		1.77
		30'		97.12		1.50
		45'		97.39		1.61
E12F01 (§)	A2	15'		86.66		3.42
		30'		93.14		2.18
		45'		94.30		2.02
D12F07 (§)	A3	15'		87.94		2.74
		30'		93.98		1.27
		45'		94.74		1.38
D12F06 (§)	A4	15'		83.27		3.76
		30'		92.21		2.44
		45'		93.92		2.49

(§) carried out on twelve tablets. These results are relevant to a re-check carried out in October 1998. The initial time tests (on 6 tablets for lots D12F06 and D12F07 and on 12 tablets on lot E12F01) gave practically the same values.

(*) carried out on six tablets



Based on the above results the sponsor is proposing the following method and specifications:

Dosage Form, Strength: sugar coated tablets, 25 mg

Dissolution Apparatus: USP, Apparatus I (basket)

Speed of Rotation: 100 rpm

Dissolution Medium: 0.5% (w/v) sodium lauryl sulfate aqueous solution at 37° C

Volume: 900 ml

Sampling Times: minutes

Dissolution analytical method:

Dissolution Specifications: NLT % at minutes

COMMENTS: Based on the in vitro dissolution data submitted to the NDA the dissolution specification should be changed to Q % at minutes.

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