

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

**20-541/S-006**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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**NDA 20-541**

**Submission Date:**

November 1, 1999  
November 24, 1999  
February 1, 2000  
February 10, 2000

**Drug Name:** Arimidex (ZD1033, Anastrozole)  
**Formulation:** 1 mg tablets  
**Sponsor:** Zeneca Pharmaceuticals  
1800 Concord Pike, PO Box 15437  
Wilmington, DE 19850-5437  
**Reviewer:** John Duan, Ph.D.  
**Type of Submission:** Supplemental New Drug Application

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This is a review of the Clinical Pharmacology and Biopharmaceutics (CPB) studies submitted in the sNDA 20-541 to support use of arimidex as the first-line treatment of postmenopausal women with advanced breast cancer.

### SYNOPSIS

Arimidex is a selective nonsteroidal aromatase inhibitor. The aromatase enzyme complex catalyzes the synthesis of estrogens from androgens. Since estrogens promote growth of certain breast tumors, inhibition of estrogen synthesis by aromatase enzyme is an effective treatment for hormone-dependent breast cancer. The approved (NDA20-541) indication is the treatment of advanced breast cancer in postmenopausal women who have progressed following tamoxifen therapy. This sNDA presents data to support the safety and effectiveness of Arimidex 1 mg daily, for the first-line treatment of postmenopausal women with advanced breast cancer.

In the approved NDA20-541, the applicant showed that inhibition of aromatase activity is primarily due to anastrozole, the parent drug. Studies with radiolabeled drug have demonstrated that orally administered anastrozole is well absorbed into the systemic circulation with 83 to 85% of the radiolabel recovered in urine and feces. Food does not affect the extent of absorption. Elimination of anastrozole is primarily via hepatic metabolism (approximately 85%) and to a lesser extent, renal excretion (approximately 11%), and anastrozole has a mean terminal elimination half-life of approximately 50 hours in postmenopausal women. The major circulating metabolite of anastrozole, triazole, lacks pharmacologic activity. The pharmacokinetic parameters are similar in patients and in healthy postmenopausal volunteers. The pharmacokinetics of anastrozole are linear over the dose range of 1 to 20 mg and do not change with repeated dosing. Consistent with the 2-day terminal elimination half-life, plasma

concentrations approach steady-state levels at about 7 days of once daily dosing and steady-state levels are approximately three- to four-fold higher than levels observed after a single dose of ARIMIDEX. Anastrozole is 40% bound to plasma proteins in the therapeutic range. Studies in postmenopausal women demonstrated that anastrozole is extensively metabolized with about 10% of the dose excreted in the urine as unchanged drug within 72 hours of dosing, and the remainder (about 60% of the dose) is excreted in urine as metabolites. Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. Three metabolites of anastrozole have been identified in human plasma and urine. The known metabolites are triazole, a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide of anastrozole itself.

The section of Human Pharmacokinetics and Bioavailability of this sNDA presented three clinical pharmacology trials involving a total of 88 subjects.

In addition, based on the agreement reached in a teleconference held on February 1, 1999, a bioequivalence study (6157IL/0002) is submitted, which compares two Nolvadex formulations.

This review is completed by Question Based Review approach.

***1. What are the major differences between the current sNDA and approved NDA?***

The major difference between this sNDA and the approved NDA is the indication. The sNDA is for the first-line treatment of postmenopausal women with advanced breast cancer whereas the approved NDA is for the treatment of advanced breast cancer in postmenopausal women who have progressed following tamoxifen therapy.

***2. What additional studies to characterize the pharmacokinetics are submitted in the current sNDA?***

The applicant conducted a study to investigate the safety, pharmacologic actions, and pharmacokinetics in single and repeated oral administration of ZD1033 0.5 mg and 1 mg in postmenopausal healthy female volunteers. This was an open, randomized study with two fixed doses of ZD1033 in single administration or repeated dosing for 14 days. Pharmacokinetics was evaluated by calculation of  $C_{max}$ ,  $t_{max}$ ,  $AUC_{TLDC}$ ,  $AUC_{inf}$ , and  $t_{1/2}$  in single administration and accumulative rate and  $t_{1/2}$  in repeated administration. Hormone concentration was compared with baseline value and between the two dose groups at the same measuring points to assess the effects on hormone dynamics. Gross exposure of estradiol (defined as AUC of estradiol concentration time curve for a day) was compared between the two dose groups on Day 1 and the whole day on Day 14 for assessment.

The pharmacokinetic parameters obtained in this study were consistent with those obtained in the previous phase I studies. Although the drug concentration data and estradiol and other hormone measurements are available, a PK/PD model to assess possible relationship between drug levels and/or hormone levels has not been established. An effort by the reviewer regarding this aspect is ongoing.

**3. What additional information to update the package insert is submitted in the current sNDA?**

The applicant submitted two additional studies. One is to investigate the race difference and another is to detect drug interaction between anastrozole and warfarin.

**4. Did the data show the difference between Japanese and Caucasian?**

The applicant conducted an open, parallel-group trial to compare the pharmacodynamic effect (on serum estradiol) of anastrozole 1 mg (daily for 16 days) in Japanese and Caucasian healthy post-menopausal women volunteers. A total of 48 (24 Japanese and 24 Caucasian) healthy post-menopausal women volunteers entered this trial.

By t-test, there were no statistically significant differences between Japanese and Caucasian healthy post-menopausal women volunteers in the effect of anastrozole (1 mg daily for 16 days) on serum estradiol and estrone sulphate concentrations, or on steady-state plasma anastrozole  $C_{min}$  (after 16 days of dosing). However, the 90% confidence intervals of the ratios of these values fall outside the 80-125% range as shown in the following table.

Endpoint	Japanese glsmean (n=22)	Caucasian glsmean (n=23)	Ratio of glsmeans <sup>a</sup>	90% CI	p-value
Serum estradiol (pmol/l)	2.80	3.22	0.87	0.76 to 1.00 (0.74 to 1.03) <sup>d</sup>	0.1026 <sup>b</sup>
Serum estrone sulphate (pmol/l)	37.21	33.85	1.10	0.88 to 1.37 (0.84 to 1.43) <sup>d</sup>	0.4752 <sup>b</sup>
$C_{min}$ (ng/ml)	30.41	25.69	1.18	0.99 to 1.40 (0.97 to 1.44) <sup>d</sup>	0.0938 <sup>c</sup>

<sup>a</sup> Ratio of glsmeans is presented as Japanese glsmean/Caucasian glsmean.

<sup>b</sup> Derived from ANCOVA.

<sup>c</sup> Student's t-test.

<sup>d</sup> 95% confidence interval calculated by the applicant

$C_{min}$  Minimum anastrozole plasma concentration at the end of the dosing interval. Glmean Geometric least squares mean.

The data showed a trend of elevation of anastrozole concentrations in Japanese women compared to the Caucasians. This difference could be due to the difference in the body size between the two populations.

**5. Is there any drug interaction between anastrozole and warfarin?**

The applicant submitted the results of a randomized, double-blind, placebo-controlled, 2-way cross-over trial. The trial comprised 2 treatment periods of 11 days separated by a 3-week washout period. Volunteers were randomized to receive either anastrozole in Treatment Period 1 and placebo in Treatment Period 2, or vice versa. In addition, all volunteers received warfarin 25 mg (5 x 5-mg tablets) on Day 3 of each treatment period.

The results of analysis of plasma AUC, CL/F and  $t_{1/2}$  to assess the effect of concomitant administration of anastrozole on the pharmacokinetics of warfarin (R and S enantiomers) are summarized in the following Table by the applicant.

Parameter	Anastrozole		Placebo		Treatment effect	95% CI	p-value
	n	glsmean	n	glsmean			
<b>R-warfarin</b>							
AUC (ng•h/ml)	16	93619.99	15	91127.91	1.027 <sup>a</sup>	0.988 to 1.068	0.160
CL/F (ml/min)	16	2.23	15	2.29	0.974 <sup>a</sup>	0.937 to 1.012	0.163
$t_{1/2}$ (h)	16	55.40 <sup>b</sup>	15	55.15 <sup>b</sup>	0.254 <sup>a</sup>	-2.083 to 2.592	0.818
<b>S-warfarin</b>							
AUC (ng•h/ml)	16	57129.21	15	55676.34	1.026 <sup>a</sup>	0.979 to 1.076	0.259
CL/F (ml/min)	16	3.65	15	3.74	0.974 <sup>a</sup>	0.929 to 1.021	0.249
$t_{1/2}$ (h)	16	39.38 <sup>b</sup>	15	40.98 <sup>b</sup>	-1.596 <sup>c</sup>	-6.189 to 2.996	0.466

<sup>a</sup> glsmean of the anastrozole phase divided by the glsmean of the placebo phase

<sup>b</sup> lsmean

<sup>c</sup> lsmean of the anastrozole phase minus the lsmean of the placebo phase

AUC area under the curve

CI confidence interval

CL/F apparent oral clearance

glsmean geometric least squares mean

lsmean least squares mean

Therefore, administration of anastrozole resulted in no statistically significant changes in the pharmacokinetics of either R- or S-warfarin as compared to placebo.

The effects of concomitant administration of anastrozole on the anticoagulant activity of warfarin are summarized by the applicant in the following Table.

**Table. Statistical comparison on anastrozole and placebo groups**

Parameter	Anastrozole		Placebo		Treatment effect <sup>a</sup>	95% CI	p-value
	n	glsmean	n	Glsmean			
PT (sec)							
AUC <sub>(8-49)</sub>	16	17.45	15	18.36	0.951	0.860 to 1.052	0.299
166 h	16	11.27	15	12.15	0.928	0.876 to 0.983	0.015
240 h	16	11.56	15	11.31	1.023	0.987 to 1.059	0.193
APTT (sec)							
AUC <sub>(8-49)</sub>	16	34.96	15	36.07	0.969	0.918 to 1.023	0.237
166 h	16	29.43	14 <sup>b</sup>	31.72	0.928	0.889 to 0.968	0.002
240 h	16	29.94	15	29.74	1.007	0.968 to 1.047	0.722
TT (sec)							
AUC <sub>(8-49)</sub>	16	18.86	15	18.68	1.010	0.979 to 1.042	0.505
166 h	16	18.72	14 <sup>b</sup>	19.05	0.983	0.935 to 1.034	0.474
240 h	16	19.96	15	18.75	1.017	0.980 to 1.054	0.350
Factor VII (%)							
AUC <sub>(8-22)</sub>	16	51.09	15	46.04	1.110	0.982 to 1.254	0.088
AUC <sub>(22-94)</sub>	16	30.94	15	28.67	1.079	0.908 to 1.284	0.355
166 h	16	108.96	15	98.72	1.104	0.970 to 1.256	0.123
240 h	16	97.81	15	107.26	0.912	0.821 to 1.012	0.079

a gmean of the anastrozole phase divided by the gmean of the placebo phase  
 b Value not recorded for Volunteer 0006.  
 aPTT activated partial thromboplastin time  
 AUC area under the pharmacodynamic parameter-time curve  
 CI confidence interval  
 glsmean geometric least squares mean  
 PT prothrombin time  
 TT thrombin time

Based on these results, there was no evidence to suggest that anastrozole has clinically relevant effects on the pharmacokinetics or anticoagulant activity of warfarin. Although the difference in PT and aPTT at 166 hours was statistically significant between anastrozole and placebo treatment groups, anastrozole had no clinically relevant effect on the clotting mechanisms as assessed by PT (prothrombin time), aPTT (activated partial thromboplastin time), TT (thrombin time) and factor VII.

**6. Are the two formulations of tamoxifen used in clinical trials bioequivalent?**

In the two clinical trials to evaluate Arimidex as a first-line agent in treatment of postmenopausal women with breast cancer, two Nolvadex (tamoxifen citrate) formulations were used as the comparator. One formulation is manufactured and marketed in the US and contains mannitol as an excipient. The other formulation is manufactured in the UK and marketed in Europe and rest of the world and contains lactose as an excipient. Based on the agreement between the Agency and the applicant, the bioequivalence between these two formulations has to be established.

The applicant conducted an open, randomized, 2-center 2-period crossover bioequivalence trial. A total of 28 postmenopausal women with advanced breast cancer completed this trial.

Patients were randomized to be given 1 of 2 formulations of tamoxifen: the ROW sales formulation (tamoxifen 20 mg [F6293]) or the US sales formulation (tamoxifen 20 mg [F12061]), both taken orally once daily for 3 months. Patients were then given the crossover formulation for the following 3 months. Patients underwent pharmacokinetic assessments during the month 3 and month 6 visits (at the end of each period). At each of these visit, blood samples were collected to obtain a 24-hour pharmacokinetic profile.

The results of statistical comparisons of tamoxifen and N-desmethyltamoxifen pharmacokinetic parameters are presented in the following tables.

**Table. Statistical comparisons of tamoxifen pharmacokinetic parameters.**

Parameters	N	ROW sales formulation (F6293)	US sales formulation (F6293)	Ratio (ROW/US)	90% CI of ratio
AUC <sub>0-24h</sub> (ng•h/mL)	28	3250.6	3083.4	1.05	0.99-1.12
C <sub>max</sub> (ng•h/mL)	28	184.2	181.0	1.02	0.95-1.09

**Table. Statistical comparisons of N-desmethyltamoxifen pharmacokinetic parameters.**

Parameters	N	ROW sales formulation (F6293)	US sales formulation (F6293)	Ratio (ROW/US)	90% CI of ratio
AUC <sub>0-24h</sub> (ng• h/mL)	28	6258.5	6102.2	1.03	0.97-1.08
C <sub>max</sub> (ng• h/mL)	28	334.0	329.1	1.01	0.97-1.07

Therefore, the US sales formulation (F12061) and the rest of the world (ROW) sales formulation manufactured in the UK (F6293) of tamoxifen were bioequivalent based upon measurements of AUC<sub>0-24</sub> and C<sub>max</sub> for tamoxifen and the major metabolite N-desmethyltamoxifen.

## COMMENTS

### General

1. Generally, we recommend single-dose pharmacokinetic study to assess bioequivalence because a single-dose study is more sensitive in assessing release of the drug substance from two different formulations into systemic circulation. However, the multiple-dose study conducted by the applicant was adequate, since appropriate dosage administration and sampling were carried out to document attainment of steady state. Therefore, the bioequivalence between the US sales formulation and ROW (rest of the world) formulation has been established.
2. Although there were no statistically significant differences between Japanese and Caucasian healthy post-menopausal women volunteers in the effect of anastrozole (1 mg daily for 16 days) on serum estradiol and estrone sulphate concentrations, or on steady-state plasma anastrozole C<sub>min</sub> (after 16 days of dosing), the 90% confidence intervals of the ratios of these values fall outside the 80-125% range. Whether this difference is due to body size should be analyzed.

### Labeling

In Clinical Pharmacology, Special Population Section, the following statements:

Should be changed to:

Race: Estradiol and estrone sulfate levels were similar between Japanese and Caucasian post-menopausal women who received 1 mg of anastrozole daily for 16 days. Anastrozole mean steady state minimum plasma concentrations in Caucasian and Japanese post-menopausal women were 25.7 and 30.4 ng/mL, respectively.

In Clinical Pharmacology, Drug-drug Interaction Section, the following statements:

3,  
-1.

Should be changed to:

Effect on Corticosteroids: In multiple daily dosing trials with 3, 5, and 10 mg, the selectivity of anastrozole was assessed by examining effects on corticosteroid synthesis. For all doses, anastrozole did not affect cortisol or aldosterone secretion at baseline or in response to ACTH. No glucocorticoid or mineralocorticoid replacement therapy is necessary with anastrozole.

The following paragraph

Should be changed to:

In a study conducted in 16 male volunteers, anastrozole did not alter the pharmacokinetics as measured by  $C_{max}$  and AUC, and anticoagulant activity as measured by prothrombin time, activated partial thromboplastin time, and thrombin time of both R- and S-warfarin.

#### RECOMMENDATION

1. This supplemental NDA is approvable from Clinical Pharmacology and Biopharmaceutics perspective.
2. The applicant should make proper changes based on the labeling comments.

ISI

Atiqur Rahman, Ph.D.

Team Leader  
Division of Pharmaceutical Evaluation I

8/30/00  
Date

ISI

John Duan, Ph.D.

Reviewer  
Division of Pharmaceutical Evaluation I

8/23/00  
Date

CC: NDA 20-541 original  
HFD-150 Division File  
HFD-150 AChapman  
HFD-150 WOdujinrin  
HFD-860 MMehta, ARahman, JDuan  
CDR

19 pages redacted from this section of  
the approval package consisted of draft labeling

## APPENDIX II. INDIVIDUAL STUDY SYNOPSIS

### 1. Clinical Pharmacology study (A15-12)

**Study title:** ZD1033 Single and multiple dose study in healthy postmenopausal women

**Investigator & location:** Dr Hiroki Koyama, Director of Osaka Medical Center for Cancer and Cardiovascular Diseases.

**Study period:** February 1995 to March 1995.

**Study formulations:** ZD1033 0.5 mg tablet: Lot No. ADM34571/94; ZD1033 1 mg tablet: Lot No. ADM34531/94.

#### **Objectives:**

To investigate the safety, pharmacologic actions, and pharmacokinetics in single and repeated oral administration of ZD1033 0.5 mg and 1 mg in postmenopausal healthy female volunteers.

**Subjects:** 24 healthy postmenopausal women. Single administration; 0.5 mg, 6 subjects, 1 mg, 6 subjects. Repeated dosing for 14 days; 0.5 mg, 6 subjects, 1 mg, 6 subjects.

#### **Study Design:**

This was an open, randomized study with two fixed doses of ZD1033 in single administration or repeated dosing for 14 days.

#### *Single administration study*

ZD1033 0.5 mg or 1 mg was administered once orally in fasting. The subjects did not eat for 10 hours before dosing and took a tablet with 150 ml water.

#### *Repeated administration*

ZD1033 0.5 mg or 1 mg was administered once per day for 14 days orally within 30 minutes after breakfast. A tablet was taken with 150 ml water.

#### *Endpoints:*

For Safety, subjective findings, blood pressure, pulse rate, body temperature, standard 12-lead ECG, and results of clinical laboratory tests were monitored.

Pharmacokinetics was evaluated by calculation of  $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-TLDC}$ ,  $AUC_{0-inf}$  and  $t_{1/2}$  in single administration and accumulative rate and  $t_{1/2}$  in repeated administration.

Hormone dynamics: Hormone concentration was compared with baseline value and between the two groups at the same measuring points to assess the effects on hormone dynamics. Gross

exposure amount of estradiol was compared between the two groups on Day 1 and the whole day on Day 14 for assessment

*Statistic methods:*

The paired t-test was used to compare measured values before and after dosing. However, plasma hormone concentration (estradiol only) was compared between the two groups by Dunnett test that considers multiplicity. The significance level was  $p < 0.05$ .

**Results:**

*Assay performance:* In-study validation results for Arimidex assay are presented in the following table.

*Safety:*

There was no case of withdrawal or dropout from this trial.

In the single administration study, mild dull headache was observed in one of the 6 subjects in the 1 mg group which resolved without any treatment. This symptom was possibly related to ZD1033. No findings of blood pressure, pulse rate, body temperature, standard 12-lead ECG and clinical laboratory values were considered to be clinically significant.

In the repeated administration study, three subjects in the 0.5 mg group had symptoms: swollen feeling in the fingers; right lower abdominal pain, nausea, dull headache, and malaise. In the 1 mg group, one subject showed subjective findings of hot flushes, swollen feeling (hands and legs), and sweating. All of these symptoms were mild and resolved without treatment. In both 0.5 mg and 1 mg dose groups, no findings of clinical significance were observed including blood pressure, pulse rate, body temperature, standard 12-lead ECG and clinical laboratory values.

*Pharmacokinetics:*

$C_{max}$  in single administration of 0.5 mg and 1 mg was  $8.3 \pm 1.1$  (mean  $\pm$  SD) and  $17.8 \pm 2.35$  ng/ml,  $t_{max}$  was  $1.2 \pm 0.41$  and  $1.3 \pm 0.52$  hours, and  $t_{1/2}$  was  $52.5 \pm 20.4$  and  $56.3 \pm 10.1$  hours, respectively.

In the repeated administration study, accumulative ratio in 0.5 mg and 1 mg administration was  $3.9 \pm 0.6$  (mean  $\pm$  SD) and  $3.7 \pm 0.84$  and  $t_{1/2}$  was 56.8 to 57.7 and 51.8 to 55.9 hours, respectively. Pharmacokinetic parameters obtained in this trial were consistent with those obtained in the phase I study conducted previously in breast cancer patients and western clinical studies.

*Results of hormone dynamics:*

In the single administration study, Subject S3 had a plasma estradiol concentration that violated the inclusion criteria, and thus excluded from the analysis of hormone dynamics. Significant decreases from baseline were seen in plasma estradiol and estrone concentrations, which were considered to be due to the pharmacologic action of ZD1033. There were no differences between the 0.5 mg group and the 1 mg group at any measuring point. No other effect of ZD1033 on hormone concentration was evident.

In the repeated administration, based on the results of measurements by the Hospital, gross exposure of estradiol in the 1 mg group was significantly low on Day 14 compared with the 0.5 mg group ( $p=0.031$ ), when gross exposure of estradiol of the day was defined as the area under the concentration-time curve (AUC) for a day. Also, analysis using geometric mean value of estradiol revealed that the 1 mg group showed significant low value ( $p=0.016$ ) on Day 14 from the geometric mean value (rate) vs. the value obtained from the 0.5 mg group. However, the comparison between the two groups at each measuring point showed a significant difference only after three hours from dosing on Day 14. The difference appeared to be minor. Plasma estrone concentration showed a decrease due to the pharmacologic action of ZD1033. No other hormone concentration showed obvious effects of ZD1033.

**COMMENTS:**

1. The pharmacokinetic parameters obtained in this study were consistent with those obtained in the previous phase I studies.
2. Actions to reduce estradiol in plasma concentration demonstrated that there was difference between the two groups in the exposure rate for a day, however, there were no significant differences between the two groups in the concentration at any measuring point. From this, a good clinical effect can be expected from ZD1033 0.5 mg administration as well. Therefore, it is necessary to investigate administration of ZD1033 0.5 mg and 1 mg in postmenopausal female patients with breast cancer.
3. A PK/PD model could be generated based on the concentration data and estradiol and other hormone measurements.

**APPEARS THIS WAY  
ON ORIGINAL**

## **2. Special population (race) study (Study #1033IL/0035 [A-15-13])**

**Study title:** A Trial to Compare the Pharmacodynamic Effects and Pharmacokinetics of Steady-State ZD1033 (Anastrozole) in Japanese and Caucasian Healthy Post-Menopausal Women Volunteers (1033IL/0035 [A-15-13]).

**Investigator & location:** RA Yates, Clinical Pharmacology Unit, Zeneca Pharmaceuticals, Macclesfield, Cheshire, SK10 4TG, UK.

**Study period:** February 1998 to June 1998.

**Study formulation:** Anastrozole 1 mg (batch numbers

### **Objectives:**

The primary objective was to compare the pharmacodynamic effect (on serum estradiol) of anastrozole 1 mg (daily for 16 days) in Japanese and Caucasian healthy post-menopausal women volunteers.

The secondary objectives were to compare the pharmacodynamic effect (on estrone sulphate), and the pharmacokinetics (minimum plasma concentration [ $C_{min}$ ]) of anastrozole 1 mg (daily for 16 days) dose in Japanese and Caucasian healthy post-menopausal women volunteers.

Additional secondary endpoint was comparison of the pharmacodynamics of serum estrone. However, there were technical problems with the estrone assay. Hence, serum estrone assessments were not conducted.

### **Subjects:**

A total of 48 (24 Japanese and 24 Caucasian) healthy post-menopausal women volunteers entered this trial. The mean age of the Japanese volunteers was 60.9 years (range 50 to 73 years) and their mean weight was 54.2 kg (range 39 to 68 kg). The mean age of the Caucasian volunteers was 61.5 years (range 52 to 75 years) and their mean weight was 66.0 kg (range 46 to 87 kg). None of the volunteers withdrew from the trial.

### **Study Design:**

This was an open, parallel-group trial comparing serum estradiol, serum estrone sulphate, and steady-state plasma anastrozole  $C_{min}$  in healthy Japanese and Caucasian post-menopausal women volunteers.

Blood samples were taken to assess the following: serum estradiol (primary endpoint); serum estrone sulphate and the plasma anastrozole  $C_{min}$  (secondary endpoints). Results were listed and summarized; each endpoint was compared between Japanese and Caucasian volunteers using Student's t-test or analysis of covariance (ANCOVA).

Safety was assessed by the recording of adverse events, clinical laboratory tests, subjective symptomatology and medical examinations. All safety data were listed and summarized; no formal statistical analysis was carried out.

**Results:**

*Assay performance:* Validation results for Arimidex assay are presented in the following table.

*Pharmacodynamics and pharmacokinetics:*

There were no statistically significant differences in serum concentrations of estradiol and estrone sulphate between Japanese and Caucasian healthy post-menopausal women volunteers who received anastrozole at a dose of 1 mg daily for 16 days. However, the 90% confidence interval of the ratios of these values fall outside the range. Similarly, although there was no statistically significant difference in steady-state plasma anastrozole C<sub>min</sub> values between the 2 populations, the 90% CI fall outside the range. (see following table).

**Analysis of serum estradiol, serum estrone sulphate and steady-state plasma anastrozole C<sub>min</sub> in post-menopausal volunteers**

Endpoint	Japanese glsmean (n=22)	Caucasian glsmean (n=23)	Ratio of glsmeans <sup>a</sup>	90% CI	p-value
Serum estradiol (pmol/l)	2.80	3.22	0.87	0.76 to 1.00 (0.74 to 1.03) <sup>d</sup>	0.1026 <sup>b</sup>
Serum estrone sulphate (pmol/l)	37.21	33.85	1.10	0.88 to 1.37 (0.84 to 1.43) <sup>d</sup>	0.4752 <sup>b</sup>
C <sub>min</sub> (ng/ml)	30.41	25.69	1.18	0.99 to 1.40 (0.97 to 1.44) <sup>d</sup>	0.0938 <sup>c</sup>

<sup>a</sup> Ratio of glsmeans is presented as Japanese glsmean/Caucasian glsmean.

<sup>b</sup> Derived from ANCOVA.

<sup>c</sup> Student's t-test.

<sup>d</sup> 95% confidence interval calculated by the applicant

C<sub>min</sub> Minimum anastrozole plasma concentration at the end of the dosing interval. Glmean Geometric least squares mean.

**Safety:** Anastrozole at a dose of 1 mg daily for 16 days was well tolerated by both Japanese and Caucasian healthy post-menopausal women. Adverse events were consistent with symptoms that could be expected to be commonly observed in post-menopausal women over the course of 5 to 6 weeks, and with the overall safety profile of anastrozole. There were no deaths, no withdrawals due to adverse events and no serious adverse events. Various adverse drug reactions were reported at both centers but these were mild-to-moderate in nature and consistent with those

already noted in the Summary of Product Characteristics (i.e., prescribing information). There were no clinically significant differences between the Japanese and Caucasian populations in any of the safety parameters monitored, although fewer adverse events and adverse drug reactions were reported by Japanese than Caucasian volunteers.

#### Comments

1. By t-test, there were no statistically significant differences between Japanese and Caucasian healthy post-menopausal women volunteers in the effect of anastrozole (1 mg daily for 16 days) on serum estradiol and estrone sulphate concentrations, or on steady-state plasma anastrozole  $C_{min}$  (after 16 days of dosing). However, the 90% confidence intervals of the ratios of these values fall outside the \_\_\_\_\_ range.
2. The data suggested that a trend towards elevated anastrozole concentrations in Japanese women compared to the Caucasians. This could be due to the difference in body size between two populations.
3. There were no clinically significant differences between the 2 populations in the safety parameters monitored.

APPEARS THIS WAY  
ON ORIGINAL

### 3. Drug interaction study (Study #1033IL/0033)

**Study title:** A Randomized, Placebo-Controlled, Double-Blind, Cross-over Trial in Healthy Male Volunteers to Assess the Effect of Anastrozole (ARIMIDEX™) on the Pharmacokinetics and Anticoagulant Activity of Warfarin (1033IL/0033).

**Investigator & location:** Michael Seiberling MD, Innovex (Biodesign) GmbH, Obere Hardstrasse 8-16, D-79114, Freiburg, Germany (Center 0001).

**Study period:** November 1996 to January 1997

**Study formulation:** Anastrozole 1-mg tablets: formulation number F11292; batch number ..... or matching placebo: formulation number F11314; batch number ..... Warfarin 5-mg tablets: formulation number F12201; batch number .....

**Objectives:** The primary objective of this trial was to assess the effect of steady-state anastrozole concentrations on the pharmacokinetics and anticoagulant activity of warfarin. The secondary objective of the trial was to confirm the absence of effect of anastrozole on clotting mechanisms.

**Subjects:** A total of 16 healthy male volunteers aged between 18 and 62 years inclusive were recruited into the trial.

#### Study Design:

This was a randomized, double-blind, placebo-controlled, 2-way cross-over trial conducted at a single center. The trial comprised 2 treatment periods of 11 days separated by a 3-week washout period. Volunteers were randomized to receive either anastrozole in Treatment Period 1 and placebo in Treatment Period 2, or vice versa. They received anastrozole 7 mg as a loading dose (7 x 1-mg tablets) or matching placebo on Trial Day 1 of each treatment period, and anastrozole 1 mg or matching placebo on Trial Days 2 to 11 of each treatment period. In addition to their randomized treatment, all volunteers received warfarin 25 mg (5 x 5-mg tablets) on Day 3 of each treatment period. Warfarin was administered 2 hours after anastrozole.

Blood samples for pharmacokinetic and pharmacodynamic assessment were taken at frequent intervals during each treatment period. The safety of volunteers was monitored throughout the trial.

The primary pharmacokinetic endpoints were the area under the plasma concentration-time curve from time 0 to infinity (AUC) for the R and S enantiomers of warfarin. The secondary pharmacokinetic endpoints were the terminal elimination half-life ( $t_{1/2}$ ) and apparent oral clearance (CL/f) for R-warfarin and S-warfarin. All pharmacokinetic endpoints were analyzed using an analysis of variance (ANOVA) model, fitting for the effects of volunteers, periods and treatments (anastrozole or placebo). AUC and CL/f data were log-transformed prior to analysis as previous experience has shown them to be log-normally distributed. Half-life ( $t_{1/2}$ ) data were not log-transformed prior to analysis.

The primary pharmacodynamic endpoint was prothrombin time (PT) following the administration of warfarin, assessed using the prothrombin time  $AUC_{(8-94)}$ , and the prothrombin time at 166 and 240 hours after dosing. The secondary pharmacodynamic endpoints were: (a) activated partial thromboplastin time (aPTT) and thrombin time (TT) following the administration of warfarin, assessed using the  $AUC_{(8-94)}$ , and results at 166 and 240 hours after dosing; (b) factor VII concentration following the administration of warfarin, assessed using the  $AUC_{(8-22)}$ , and the  $AUC_{(22-94)}$ , and the results at 166 and 240 hours after dosing; (c) PT, aPTT, TT and factor VII concentration on Trial Day 3 before dosing with warfarin. All pharmacodynamic endpoints were log-transformed prior to analysis and were to be analyzed using an ANOVA or analysis of covariance (ANCOVA) model, fitting for the effects of volunteers, periods and treatments (anastrozole or placebo). The usefulness of Day 1 pre-dose values in increasing the precision of any treatment effects was investigated. Safety was assessed by clinical chemistry, hematology and urinalysis tests.

## Results:

### Assay performance:

The results of analysis of plasma AUC, CL/F and  $t_{1/2}$  to assess the effect of concomitant administration of anastrozole on the pharmacokinetics of warfarin (R and S enantiomers) are summarized in the following Table.

Table. Statistical comparison of anastrozole and placebo groups

Parameter	Anastrozole		Placebo		Treatment effect	95% CI	p-value
	n	glsmean	n	glsmean			
<b>R-warfarin</b>							
AUC (ng·h/ml)	16	93619.99	15	91127.91	1.027 <sup>a</sup>	0.988 to 1.068	0.160
CL/F (ml/min)	16	2.23	15	2.29	0.974 <sup>a</sup>	0.937 to 1.012	0.163
$t_{1/2}$ (h)	16	55.40 <sup>b</sup>	15	55.15 <sup>b</sup>	0.254 <sup>a</sup>	-2.083 to 2.592	0.818
<b>S-warfarin</b>							
AUC (ng·h/ml)	16	57129.21	15	55676.34	1.026 <sup>a</sup>	0.979 to 1.076	0.259
CL/F (ml/min)	16	3.65	15	3.74	0.974 <sup>a</sup>	0.929 to 1.021	0.249
$t_{1/2}$ (h)	16	39.38 <sup>b</sup>	15	0.98 <sup>b</sup>	-1.596 <sup>c</sup>	-6.189 to 2.996	0.466

<sup>a</sup> glsmean of the anastrozole phase divided by the glsmean of the placebo phase  
<sup>b</sup> lsmean

<sup>c</sup> lsmean of the anastrozole phase minus the lsmean of the placebo phase.

AUC area under the curve

CI confidence interval

CL/F apparent oral clearance

glsmean geometric least squares mean

lsmean least squares mean

There was no carry-over of warfarin between treatments and no evidence of any anastrozole carry-over between treatments.

Administration of anastrozole resulted in no statistically significant changes in the pharmacokinetics of either R- or S-warfarin as compared to placebo, as assessed by AUC, CL/F and  $t_{1/2}$ .

*Pharmacodynamics:* The effects of concomitant administration of anastrozole on the anticoagulant activity of warfarin are summarized in the following Table.

**Table. Statistical comparison on anastrozole and placebo groups**

Parameter	Anastrozole		Placebo		Treatment effect <sup>a</sup>	95% CI	p-value
	n	glsmean	n	glsmean			
PT (sec)							
AUC <sub>(8-49)</sub>	16	17.45	15	18.36	0.951	0.860 to 1.052	0.299
166 h	16	11.27	15	12.15	0.928	0.876 to 0.983	0.015
240 h	16	11.56	15	11.31	1.023	0.987 to 1.059	0.193
APTT (sec)							
AUC <sub>(8-49)</sub>	16	34.96	15	36.07	0.969	0.918 to 1.023	0.237
166 h	16	29.43	14 <sup>b</sup>	31.72	0.928	0.889 to 0.968	0.002
240 h	16	29.94	15	29.74	1.007	0.968 to 1.047	0.722
TT (sec)							
AUC <sub>(8-49)</sub>	16	18.86	15	18.68	1.010	0.979 to 1.042	0.505
166 h	16	18.72	14 <sup>b</sup>	19.05	0.983	0.935 to 1.034	0.474
240 h	16	19.06	15	18.75	1.017	0.980 to 1.054	0.350
Factor VII (%)							
AUC <sub>(8-22)</sub>	16	51.09	15	46.04	1.110	0.982 to 1.254	0.088
AUC <sub>(22-94)</sub>	16	30.94	15	28.67	1.079	0.908 to 1.284	0.355
166 h	16	108.96	15	98.72	1.104	0.970 to 1.256	0.123
240 h	16	97.81	15	107.26	0.912	0.821 to 1.012	0.079

<sup>a</sup> glsmean of the anastrozole phase divided by the glsmean of the placebo phase

<sup>b</sup> Value not recorded for Volunteer 0006.

aPTT activated partial thromboplastin time

AUC area under the pharmacodynamic parameter-time curve

CI confidence interval

Glsmean geometric least squares mean

PT prothrombin time

TT thrombin time

There was no carry-over of warfarin between treatments and no evidence of any anastrozole carry-over between treatments.

There was no significant difference between treatment with anastrozole compared to placebo in the mean prothrombin time, thrombin time, activated partial thromboplastin time, or factor VII concentrations prior to warfarin dosing.

The prothrombin time  $AUC_{(8-94)}$  and the prothrombin time at 240 hours postdose were not significantly different between treatments. There was a significant reduction in the prothrombin time at 166 hours after dose with anastrozole administration as compared to placebo. Though there was a significant reduction in the prothrombin time, the magnitude of the effect was at most 12.4%.

There was no significant treatment effect on the thrombin time  $AUC_{(8-94)}$ , or in the thrombin times determined 166 and 240 hours after dosing in the presence of anastrozole or placebo.

The activated thromboplastin time  $AUC_{(8-94)}$  and the activated thromboplastin time at 240 hours postdose were not significantly different between the two treatments. There was a significant reduction in the mean activated thromboplastin time at 166 hours after dose with anastrozole administration as compared to placebo. Though the reduction was significant, the magnitude of the effect was at most 11.1%.

There was no significant treatment effect on the factor VII  $AUC_{(8-22)}$  or  $AUC_{(22-94)}$  or in the percentage of factor VII determined 166 and 240 hours after dosing in the presence of anastrozole or placebo.

*Safety:* No deaths occurred during the trial. There was one withdrawal from the trial due to an adverse event (Volunteer 0008). No serious adverse events were experienced during this trial. A total of 42 adverse events were reported, 22 of these were reported in 12 subjects receiving anastrozole (3 before and 19 after being dosed with warfarin), and 20 were in 6 volunteers receiving placebo (9 before and 11 after dosing with warfarin).

The most commonly reported adverse event in the trial was headache, with 12 reports from 9 volunteers. Headache was reported by 8 volunteers (50%) on anastrozole (7 before and 1 after taking warfarin), and 4 volunteers (26.7%) on placebo (2 before and 2 after warfarin); 3 volunteers experienced headaches on both treatments.

Both of these drugs have received Regulatory and Licensing approval, and safety problems were not expected in this trial. The only predictable events were hemorrhage (associated with warfarin) and gastrointestinal disturbance (associated with anastrozole). The former was not seen, and there was no excess of gastrointestinal symptoms in subjects taking anastrozole. There were no significant adverse events attributable to trial treatment.

#### Comments

1. The mean plasma concentrations of anastrozole achieved throughout the warfarin dosing and sampling period were within the range seen in post-menopausal women with advanced breast cancer taking the clinically recommended dose of the drug.
2. The trial was well designed to detect interaction between anastrozole and warfarin likely to be seen in normal clinical practice. There were no statistically or clinically significant differences between the pharmacokinetics of warfarin administered with anastrozole and with

placebo. There were small but statistically significant differences in some of the pharmacodynamic effects of warfarin when it was co-administered with anastrozole as compared to placebo (showing decreases in anticoagulant activity with anastrozole), but these were not clinically significant.

3. Overall there was no evidence to suggest that anastrozole has clinically relevant effects on the pharmacokinetics or anticoagulant activity of warfarin. Anastrozole had no effect on the clotting mechanisms as assessed by PT, aPTT, TT and factor VII.

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#### 4. Bioequivalence study (Study # 6157IL/0002)

**Study title:** A Study to Compare the Bioequivalence of Two Formulations of 20 mg NOLVADEX Tablets Taken Once Daily in Postmenopausal Women with Breast Cancer.

**Investigator & location:** Gerald Batist MD, Jewish General Hospital, 3755 Cote Ste-Catherine, Montreal, Quebec, H3T 1E2 (0001); Pierre Dube MD, Hopkal Maisonneuve Rosemont, 5415 Boul L'Assomption, Montreal, Quebec, H1T 2M4 (0002)

**Study period:** February 1995 to March 1995.

**Study formulation:** the ROW sales formulation (tamoxifen 20 mg [F6293]) and the US sales formulation (tamoxifen 20 mg [F12061])

#### **Objectives:**

The objective of this trial was to compare the pharmacokinetic characteristics and establish the bioequivalence of two 20-mg formulations of tamoxifen (Rest of the world [ROW] sales formulation manufactured in the UK [F6293] and US sales formulation [F12061]).

**Subjects:** A total of 32 postmenopausal women with advanced breast cancer were enrolled to ensure that 24 patients completed this trial.

#### **Study Design:**

This was an open, randomized, 2-center 2-period crossover bioequivalence trial. A total of 32 postmenopausal women with advanced breast cancer were enrolled to ensure that 24 patients completed this trial.

Patients were randomized to be given 1 of 2 formulations of tamoxifen: the ROW sales formulation (tamoxifen 20 mg [F6293]) or the US sales formulation (tamoxifen 20 mg [F12061]), both taken orally once daily for 3 months. Patients were then given the crossover formulation for the following 3 months.

**Pharmacokinetic assessments:** Pharmacokinetic assessments of tamoxifen and N-desmethyltamoxifen, a metabolite of tamoxifen, included the steady-state area under the plasma concentration-time curve from 0 to 24 hours ( $AUC_{0-24}$ ), the maximum plasma concentration ( $C_{max}$ ), and the time to reach  $C_{max}$  ( $t_{max}$ ). The concentrations at the end of a dosing interval ( $C_{min}$ ) were used for the assessment of steady state.

Patients underwent pharmacokinetic assessments during the month 3 and month 6 visits (at the each end of the period). At each of these 3-day visits, blood samples were collected to obtain 3 consecutive assessments of trough plasma concentrations ( $C_{min}$ ) and a 24-hour pharmacokinetic profile. Blood samples were obtained at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 16, 20, and 24 hours after dosing.

**Safety assessments:** Safety assessments included adverse event monitoring and laboratory assessments.

**Results:**

*Assay performance:*

*Demography:* Thirty-two female patients aged 50 through 75 years entered the trial (mean age 59.9 years). Most patients (68.8%) were aged 65 years or less and all subjects were Caucasians. Four patients withdrew from trial treatment, and 28 patients completed the trial.

*Pharmacokinetics:*

The results of statistical comparisons of tamoxifen and N-desmethyltamoxifen pharmacokinetic parameters are presented in the following tables.

**Table. Statistical comparisons of tamoxifen pharmacokinetic parameters.**

Parameters	N	ROW sales formulation (F6293)	US sales formulation (F6293)	Ratio (ROW/US)	90% CI of ratio
AUC <sub>0-24h</sub> (ng•h/mL)	28	3250.6	3083.4	1.05	0.99-1.12
C <sub>max</sub> (ng•h/mL)	28	184.2	181.0	1.02	0.95-1.09
t <sub>max</sub> (hr) median	28	3.0	4.0		
Range		0.5-10	1.0-16.0		

**Table. Statistical comparisons of N-desmethyltamoxifen pharmacokinetic parameters.**

Parameters	N	ROW sales formulation (F6293)	US sales formulation (F6293)	Ratio (ROW/US)	90% CI of ratio
AUC <sub>0-24h</sub> (ng•h/mL)	28	6258.5	6102.2	1.03	0.97-1.08
C <sub>max</sub> (ng•h/mL)	28	334.0	329.1	1.01	0.97-1.07
t <sub>max</sub> (hr) median	28	3.0	4.0		
Range		0-16	0-24.0		

There were no major differences in the steady-state concentrations of tamoxifen or its major metabolite N-desmethyltamoxifen following the administration of the 2 tamoxifen 20-mg tablet formulations (ROW sales formulation [F6293] and US sales formulation [F12061]). This was further confirmed by statistical analysis, which showed that the 2 formulations were

bioequivalent in the rate and extent of absorption. As a result, the US sales formulation (F12061) and the ROW sales formulation (F6293) are expected to be clinically equivalent.

*Safety:* A total of 17 (56.7%) patients had adverse events while using the ROW sales formulation and 10 (32.3%) patients had adverse events while using the US sales formulation. Two patients had serious adverse events: 1 patient had a serious adverse event while taking the US sales formulation and 1 patient had a serious adverse event while taking the ROW sales formulation. Three (9.7%) patients had drug-related adverse events while taking the US sales formulation and 4 (13.3%) patients had drug-related adverse events while taking the ROW sales formulation. No individual adverse event was reported by more than 3 patients while using either treatment formulation. The majority of adverse events was mild or moderate in intensity and was considered to be unrelated to trial treatment. No patient died or withdrew from trial treatment because of an adverse event.

**Conclusions:**

Both the US sales formulation (F12061) and the ROW sales formulation manufactured in the UK (F6293) of tamoxifen were bioequivalent based upon measurements of  $AUC_{0-24}$  and  $C_{max}$  at steady-state for tamoxifen and the metabolite N-desmethyltamoxifen. Both formulations were well tolerated by postmenopausal women with breast cancer. The adverse events that occurred during this trial were consistent with the known safety profile of tamoxifen in this patient population.

**Comments:**

1. This was a multiple dose bioequivalence study. Generally, we recommend single-dose, pharmacokinetic studies to assess BE because they are more sensitive in assessing release of the drug substance from the drug product into systemic circulation. This multiple-dose study design was adequate, since appropriate dosage administration and sampling were carried out to document attainment of steady state.
2. The reviewer got the similar results using the raw data provided.

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