CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-541/S-010

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-541	SUBMISSION DATES Original NDA 3/4/02
DRUG NAME:	Arimidex™ (anastrozole)	Original amendment 4/2/02
DOSAGE STRENGTH:	1 mg tablet	Original amendment 4/18/02
APPLICANT:	AstraZenica	
REVIEWER:	John Duan, Ph.D.	
TEAM LEADER:	N.A.M. Atiqur Rahman, Ph.D.	
TYPE OF SUBMISSION:	NDA supplement	

I. EXECUTIVE SUMMARY

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. Arimidex is currently approved for the treatment of advanced breast cancer in postmenopausal women. This sNDA presents data to support the safety and effectiveness of Arimidex 1 mg daily, for use as adjuvant therapy following primary treatment for early breast cancer in postmenopausal women.

The studies in the Clinical Pharmacology and Biopharmaceutics section of the current submission investigated the effects of anastrozole on the pharmacokinetics of tamoxifen and the effect of tamoxifen on the pharmacokinetics of anastrozole. The studies showed that anastrozole had no effect on the pharmacokinetics of tamoxifen. On the other hand, co-administration of anastrozole 1 mg with tamoxifen 20 mg resulted in an estimated 27% decrease in anastrozole levels. The applicant presented the results from another study to show the observed interaction following the co-administration of anastrozole 1 mg with tamoxifen 20 mg did not impact upon its estradiol suppressive effects thus to conclude that the observed reduction of anastrozole concentration is not expected to be of clinical significance. However, the clinical significance of the reduction of the levels of anastrozole could not be concluded based on these studies because the relationship between the effects of estradiol suppression and clinical endpoints has not been established. Further, estrogen suppression may reach the maximum through the once daily dosing even though the drug level is reduced, considering that the half life of anastrozole is about 50 hours. From this standpoint, a labeling addition in CLINICAL PHARMACOLOGY Drug-drug Interaction section is recommended to indicate the reduction of anastrozole level when co-administrated with tamoxifen.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-541 supplement and find the Clinical Pharmacology and Biopharmaceutics Section acceptable. The following **comments** should be sent to the sponsor.

1. The clinical significance of the reduction of the levels of anastrozole could not be concluded through the studies submitted in the "hpbio' section because the relationship between the

effects of estradiol suppression and clinical endpoints has not been established. Further, estrogen suppression may reach the maximum through the once daily dosing even though the drug level is reduced, considering that the half life of anastrozole is about 50 hours.

2. The enzymes responsible for the metabolism of anastrozole by N-dealkylation and hydroxylation have not been identified. We recommend you conduct studies to characterize the enzymes to update the package insert.

Comments to the medical officer

1. The studies in the current submission showed that anastrozole had no effect on the pharmacokinetics of tamoxifen.

2. Co-administration of anastrozole 1 mg with tamoxifen 20 mg resulted in an estimated 27% decrease in anastrozole levels. The clinical significance of the reduction of the levels of anastrozole could not be concluded through the current studies. This comment is based on the following considerations.

   - Estrogen suppression may reach the maximum through the once daily dosing even though the drug level is reduced, considering that the half life of anastrozole is about 50 hours.
   - The relationship between the effects of estradiol suppression and clinical endpoints has not been established.

Labeling Recommendations

1. The following paragraph should be added to the **CLINICAL PHARMACOLOGY Drug-drug Interactions** Section as the last paragraph.

Co-administration of anastrozole and tamoxifen reduced anastrozole plasma concentration by 27% compared to those achieved with anastrozole alone; however, the coadministration did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. (see **PRECAUTIONS Drug Interactions).**

2. The following statements in **PRECAUTIONS Drug Interactions** Section:

Should be changed to:

Estrogen-containing therapies ——— should not be ——— with ARIMIDEX as they may diminish its pharmacological action (see **CLINICAL PHARMACOLOGY Drug-drug Interactions**).

/S/

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

/S/

Atiqur Rahman, Ph.D. Date
Team Leader
Division of Pharmaceutical Evaluation I

CC: NDA 20541 original
HFD-150 Division File
HFD-150 ABiard
HFD-150 PCortzar
HFD-860 MMehta, PMarroum, ARahman, JDuan
CDR

II. Table of Contents

III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Anastrozole is a potent and selective nonsteroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone. Inhibition of aromatase activity is primarily due to anastrozole, the parent drug.

Studies with radio labeled 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.

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. Several minor (less than 5% of the radioactive dose) metabolites have not been identified. The major circulating metabolite of anastrozole, triazole, lacks pharmacologic activity. The enzymes responsible for the metabolism of anastrozole by N-dealkylation and hydroxylation have not been identified.

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 pharmacokinetics of anastrozole are linear over the dose range of 1 to 20 mg and do not change with repeated dosing. Consistent with the approximately 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 pharmacokinetics have been investigated in postmenopausal female volunteers and patients with breast cancer. The pharmacokinetic parameters are similar in patients and in healthy postmenopausal volunteers. No age related effects were seen over the range <50 to >80 years.

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

Anastrozole pharmacokinetics have been investigated in subjects with renal insufficiency. Anastrozole renal clearance decreased proportionally with creatinine clearance and was approximately 50% lower in volunteers with severe renal impairment (creatinine clearance < 30

mL/min/1.73m^2) compared to controls. Since only about 10% of anastrozole is excreted unchanged in the urine, the reduction in renal clearance did not influence the total body clearance.

Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Anastrozole pharmacokinetics have been investigated in subjects with hepatic cirrhosis related to alcohol abuse. The apparent oral clearance (CL/F) of anastrozole was approximately 30% lower in subjects with stable hepatic cirrhosis than in control subjects with normal liver function. However, plasma anastrozole concentrations in the subjects with hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials, so that no dosage adjustment is needed.

Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 *in vitro* with Ki values which were approximately 30 times higher than the mean steady-state C_{max} values observed following a 1 mg daily dose. Anastrozole had no inhibitory effect on reactions catalyzed by cytochrome P450 2A6 or 2D6 *in vitro*. Administration of a single 30 mg/kg or multiple 10 mg/kg doses of anastrozole to subjects had no effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. Based on these *in vitro* and *in vivo* results, it is unlikely that co-administration of ARIMIDEX 1 mg with other drugs will result in clinically significant inhibition of cytochrome P450 mediated metabolism.

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

Mean serum concentrations of estradiol were evaluated in multiple daily dosing trials with 0.5, 1, 3, 5, and 10 mg of ARIMIDEX in postmenopausal women with advanced breast cancer. Clinically significant suppression of serum estradiol was seen with all doses. Doses of 1 mg and higher resulted in suppression of mean serum concentrations of estradiol to the lower limit of detection (3.7 pmol/L). The recommended daily dose, ARIMIDEX 1 mg, reduced estradiol by approximately 70% within 24 hours and by approximately 80% after 14 days of daily dosing. Suppression of serum estradiol was maintained for up to 6 days after cessation of daily dosing with ARIMIDEX 1 mg.

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.

In multiple daily dosing trials with 5 and 10 mg, thyroid stimulating hormone (TSH) was measured; there was no increase in TSH during the administration of ARIMIDEX. ARIMIDEX does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

The studies in the current submission investigated the effects of anastrozole on the pharmacokinetics of tamoxifen and the effect of tamoxifen on the pharmacokinetics of

anastrozole. The studies showed that anastrozole had no effect on the pharmacokinetics of tamoxifen. On the other hand, co-administration of anastrozole 1 mg with tamoxifen 20 mg resulted in an estimated 27% decrease in anastrozole levels. The applicant presented the results from another study to show the observed interaction following the co-administration of anastrozole 1 mg with tamoxifen 20 mg did not impact upon its estradiol suppressive effects thus to conclude that the observed reduction of anastrozole concentration is not expected to be of clinical significance. However, the clinical significance of the reduction of the levels of anastrozole could not be concluded through these studies because the relationship between the effects of estradiol suppression and clinical endpoints has not been established. Further, estrogen suppression may reach maximum with once daily dosing, considering that the half life of anastrozole is about 50 hours, even though the drug level is reduced.

IV. QUESTION BASED REVIEW

1. Is there any effect of anastrozole on the pharmacokinetics of tamoxifen?

No. The applicant submitted two studies (study 1033IL/0029 and 1033IA/0031) in which the effect of anastrozole on the pharmacokinetics of tamoxifen was evaluated. Same conclusion that anastrozole had no effect on the pharmacokinetics of tamoxifen was obtained from both studies.

There was no evidence of a significant difference between the anastrozole group and the placebo group for tamoxifen concentrations whilst on trial therapy (Days 14 and 28) or after completing trial therapy (Day 42) in trial 1033IL/0031 as shown in the following table.

Table Analysis of tamoxifen serum concentrations

	Geometric lsmean (ng/ml)	Treatment effect[a]	95% confidence interval	p-value
Anastrozole (n=15)[b]	125.0356			
		1.0060	0.8921 to 1.1345	0.9190
Placebo (n=18)	124.28689			

[a] Ratio of anastrozole geometric lsmean to the placebo geometric lsmean
[b] Patient 0002/0002 was not post-menopausal and was therefore excluded from the analysis.

In trial 1033IA/0029, the patients had one blood sample taken after having been on trial treatment for at least 3 months. The following table shows the comparison of steady state trough level of tamoxifen and its major metabolite N-desmethyltamoxifen between two treatment groups, i.e., the anastrozole 1 mg plus tamoxifen 20 mg group and tamoxifen 20 mg group.

Table. Statistical analysis of the comparison of Cmin values between treatment groups: Anastrozole 1 mg plus tamoxifen 20 mg versus tamoxifen 20 mg

Comparison subjects	Ratio of geometric means	90% Confidence Interval
Tamoxifen	1.01	0.91 to 1.11
N-desmethyltamoxifen	1.05	0.94 to 1.16

As shown, anastrozole 1 mg had no effect on the concentrations of either tamoxifen or N-desmethyltamoxifen.

Therefore, the conclusion that anastrozole 1 mg has no significant influences on the pharmacokinetics of tamoxifen is confirmed by both studies.

2. Is there any effect of tamoxifen on the pharmacokinetics of anastrozole?

Yes. The study 1033IA/0029 investigated the steady state trough concentrations of anastrozole between the anastrozole 1 mg plus tamoxifen 20 mg group and anastrozole 1 mg alone group, and showed the effect.

The following table presents the results of the statistical analyses for the comparisons of plasma trough concentrations between the two treatment groups.

Table. Statistical analysis of the comparison of anastrozole Cmin values between treatment groups.

Treatment comparison	Ratio of geometric means	90% C I
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg	0.73	0.67 to 0.80

As shown, the geometric mean concentration of anastrozole was 27% lower in the anastrozole 1-mg plus tamoxifen 20-mg combination group than in the anastrozole 1-mg alone arm.

3. What is the clinical significance of the reduction of anastrozole level when co-administrated with tamoxifen?

The applicant presented the results from another study (1033ID/0029) to show the observed interaction following the co-administration of anastrozole 1 mg with tamoxifen 20 mg did not impact upon its estradiol suppressive effects.

Table. Statistical analysis of the comparison of estradiol concentrations.

Treatment comparison	Ratio of glsmeans	90% CI
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg	1.00	0.91 to 1.09

From this result, the applicant concluded that the observed reduction of anastrozole concentration is not expected to be of clinical significance. However, the clinical significance of the reduction of the levels of anastrozole could not be concluded through these studies because the relationship between the effects of estradiol suppression and clinical endpoints has not been established. Further, estrogen suppression may reach the maximum through the once daily dosing even though the drug level is reduced, considering that the half life of anastrozole is about 50 hours.

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

(10-33)

APPENDIX II. INDIVIDUAL STUDY REVIEW

1. STUDY 1033IA/0029

STUDY TITLE: A Randomized, Double-blind Trial to Assess the Pharmacokinetics of ARIMIDEX Alone, NOLVADEX Alone, or ARIMIDEX and NOLVADEX in Combination, When Used as Adjuvant Treatment for Breast Cancer in Postmenopausal Women (1033IA/0029).

INVESTIGATORS AND CLINICAL SITES:
Professor M Dowsett, Academic Department of Biochemistry, The Royal Marsden Hospital, Fulham Road, Kensington, London, SW3 6JJ, United Kingdom (Center 0118) Principal investigator for Protocol Number 1033IL/0029 (ATAC main trial): Professor M Baum, University College London Medical School, The Middlesex Hospital, Mortimer Street, London, W1N 8AA, United Kingdom (Centre 0001)

STUDY PERIOD: 08 June 1998 to 03 March 1999

OBJECTIVES:
To assess the effect of anastrozole on the pharmacokinetics of tamoxifen and to assess the effect of tamoxifen on the pharmacokinetics of anastrozole.

DOSAGES:
Patients were given once-daily oral doses of one of the following.

- Anastrozole (1 mg) (batch numbers: F011292, 11292) and tamoxifen placebo (F011003, 12062),
- Tamoxifen (20 mg) (F006293, 12061) and anastrozole placebo (F011314, 11314),
- anastrozole (1 mg) plus tamoxifen (20 mg).

SUBJECT:
Postmenopausal women who were candidates to receive adjuvant hormonal treatment for invasive primary breast cancer and who were entered into the ATAC main trial and were suitable for pharmacokinetic assessment.

A total of 357 patients from 26 centers received treatment; demographic details are presented in the following Table.

Age, weight, and race of patients at entry: all randomized patients

Demographic characteristic	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole 1 mg plus tamoxifen 20 mg
	(N = 138)	(N = 113)	(N = 106)
Mean age (SD) (years)	65.4(8.9)	63.1(9.7)	63.6(9.3)
Mean body weight (SD) (kg)	71.7 (14.5)	73.0 (13.8)	71.0 (13.1)
Caucasian (n [%])	132(95.7)	106(93.8)	103(97.2)

SD Standard deviation.

STUDY DESIGN:
This was a randomized, double-blind, multi-center trial. A subset of patients who were already participating in the ATAC main trial (protocol number 1033IL/0029) was recruited. Patients were randomized on a 1:1:1 basis into 1 of 3 treatment arms, i.e., anastrozole (ARIMIDEX) alone, tamoxifen (NOLVADEX) alone, or a combination of anastrozole and tamoxifen. Participation in this trial involved having one blood sample taken after the patient had been taking trial treatment for at least 3 months.

Following the initial pharmacokinetic assessments, an additional evaluation was undertaken to assess the effects of anastrozole, with or without tamoxifen, on estradiol suppression. This information was obtained from a separate ATAC sub-protocol (protocol number 1033ID/0029) and required blood samples to be taken from patients at baseline and after 3 months of treatment, allowing baseline and steady-state estradiol concentrations to be determined.

The primary endpoints of this trial were the trough (steady-state Cmin) plasma concentrations of anastrozole, tamoxifen, and N-desmethyltamoxifen (major metabolite of tamoxifen), measured at 24±4 hours after taking the previous dose. Blood samples for these assessments were therefore drawn before patients had taken their trial treatment for that day. Data for these endpoints were analyzed by analysis of variance.

RESULTS:

Assay methods:
The plasma concentrations of anastrozole were measured using —— %
——. The following table summarizes the validations of the method.

Linear Range ng/mL	Accuracy (%)	Precision (%CV)	
		Intra-assay	Inter-assay
——	94.4-104	0.4-16.1	5.9-8.1

The concentrations of tamoxifen were measured with a —— method. The method has a quantitation range of —— ng/mL for tamoxifen, with recovery of tamoxifen from spiked serum ranging from 79% to 93%.

Data exclusion:
Ten patients (of whom, 7 [5.1%] were randomized to receive anastrozole 1 mg, 2 [1.8%] to tamoxifen 20 mg, and 1 [0.9%] to the combination of anastrozole 1 mg plus tamoxifen 20 mg) were excluded from the pharmacokinetic analyses because the results of laboratory tests did not correspond with those that would be anticipated from their recorded treatment allocation. Two patients (1 patient [0.7%] receiving anastrozole 1 mg and 1 patient [0.9%] taking anastrozole 1 mg plus tamoxifen 20 mg) withdrew from this sub-protocol.

Pharmacokinetics and Pharmacodynamics:
The following Table summarizes the steady-state trough plasma concentrations of anastrozole, tamoxifen, and N-desmethyltamoxifen and the results of the statistical analyses.

Table. Steady-state trough plasma concentrations (Cmin [ng/mL]) of anastrozole, tamoxifen, and N-desmethyltamoxifen

	Anastrozole 1 mg (N = 131)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 105)	Tamoxifen 20 mg (N = 111)
Anastrozole			
n	130	104	
Mean (standard deviation)	37.4 (15.2)	27.7 (11.3)	
Geometric mean (CV%)	34.7 (40.6)	25.5 (44.3)	
Ratio of geometric means[a]	0.73		
90% confidence interval	0.67 to 0.80		
Tamoxifen			
n		99	104
Mean (standard deviation)		103.8 (45.6)	103.8 (40.9)
Geometric mean (CV%)		95.3 (43.7)	94.8 (49.2)
Ratio of geometric means[a]		1.01	
90% confidence interval		0.91 to 1.11	
N-desmethyltamoxifen			
n		76	76
Mean (standard deviation)		293.8 (98.9)	286.6 (107.8)
Geometric mean (CV%)		277.6 (35.7)	265.1 (43.7)
Ratio of geometric means[a]		1.05	
90% confidence interval		0.94 to 1.16	

[a] Combination group:monotherapy group.
CV Coefficient of variation.

As shown in the above table, co-administration of anastrozole 1 mg with tamoxifen 20 mg did not affect the steady-state plasma trough concentrations of tamoxifen or N-desmethyltamoxifen. Co-administration of anastrozole 1 mg with tamoxifen 20 mg resulted in an estimated 27% decrease in anastrozole levels.

Serum estradiol concentrations were not determined in this sub-protocol; however, the applicant analyzed estradiol concentrations from a similar ATAC sub-protocol, evaluating bone mineral density (1033ID/0029). Geometric mean serum estradiol levels were 21.5 and 18.5 pmol/L prior to treatment and 4.44 and 3.63 pmol/L after 3 months of treatment for the anastrozole 1-mg and the anastrozole 1-mg plus tamoxifen 20-mg treatment groups, respectively. Excluding 3 patients with estradiol concentrations of 585, 321, and 291 pmol/L at 3 months, geometric mean estradiol concentrations were 21.1 pmol/L prior to treatment and 3.75 pmol/L following 3 months of treatment with anastrozole 1 mg. The following Table presents the results of the statistical analysis for the comparison of estradiol concentrations between these two groups.

Table. Statistical analysis of the comparison of estradiol concentrations.

Treatment comparison	Ratio of glsmeans	90% CI
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg	0.86	0.71 to 1.04
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg (excluding data from 3 patients)	1.00	0.91 to 1.09

Although the observed interaction following the co-administration of anastrozole 1 mg with tamoxifen 20 mg did not appear to impact upon its estradiol suppressive effects, the relationship between the effects of estradiol suppression and clinical endpoints has not been established. The clinical significance of the reduction of the levels of anastrozole can not be concluded from this standpoint.

COMMENTS:

1. The study showed that anastrozole had no effect on the pharmacokinetics of tamoxifen.

2. The clinical significance of the reduction of the levels of anastrozole could not be concluded through the current study according to the following considerations.

   - Estrogen suppression may reach the maximum through the once daily dosing even though the drug level is reduced, considering that the half life of anastrozole is about 50 hours.
   - The relationship between the effects of estradiol suppression and clinical endpoints has not been established.

3. The assay descriptions and validations for anastrozole, tamoxifen, N-desmethyltamoxifen, and estradiol are not complete.

2. STUDY 1033IL/0031

STUDY TITLE: A randomized, double-blind, parallel-group trial to evaluate the effect of anastrozole (ARIMIDEX) 1 mg on the pharmacokinetics of tamoxifen in post-menopausal women with breast cancer (1033IL/0031)

INVESTIGATORS AND CLINICAL SITES: Dr J Tobias, Meyerstein Institute of Oncology, Middlesex Hospital, London, England (Center 0001)

STUDY PERIOD: February 26, 1996 to July 25, 1996

OBJECTIVES:

Primary objectives:

- To assess the effect of anastrozole on the pharmacokinetics of tamoxifen
- To assess the safety and tolerability of the combination of anastrozole and tamoxifen therapy.

Secondary objective:

- To informally assess the effect of tamoxifen on the action of anastrozole.

DOSAGES: All patients continued to receive tamoxifen 20 mg orally once daily throughout the trial. They were randomized to receive in addition once daily oral doses of one of the following for a period of 28 days.

- anastrozole 1 mg (formulation number F11292; batch number 9111N)
- matching placebo (formulation number F11314; batch number P 0114/03)

SUBJECT:

Thirty-nine patients with breast cancer, who were receiving tamoxifen as adjuvant therapy, were recruited from 3 centers in the UK. Nineteen patients were randomized to the anastrozole group and 20 to the placebo group. Of these, 5 patients (3 anastrozole group and 2 placebo group) were withdrawn before they received randomized treatment. As the analysis was by treatment received, these patients were not included.

STUDY DESIGN:

This was a randomized, double-blind, parallel-group, multi-center trial in which post-menopausal women with breast cancer who were receiving tamoxifen as adjuvant therapy were randomized to receive in addition either anastrozole or placebo for 28 days. The pharmacokinetics of tamoxifen were compared between the groups.

Blood samples were to be taken from Days -7 to 42 throughout the trial to measure the concentrations of tamoxifen, desmethyltamoxifen, anastrozole and estradiol. Steady-state pharmacokinetics were to be characterized for tamoxifen in the presence and absence of anastrozole, and for anastrozole in the presence of tamoxifen. Biochemical and hematological variables and adverse events were monitored throughout the trial.

The primary endpoints of this trial were plasma tamoxifen levels, desmethyltamoxifen levels and estradiol proportion. The treatment comparison of interest was between the anastrozole and placebo groups, both in the presence of tamoxifen. All endpoints were analyzed using analysis of variance. All endpoints were log (base e) transformed before the analysis. The results were back-transformed and presented in terms of the adjusted geometric means (glsmeans), treatment effect (being the ratio of anastrozole to placebo), the 95% confidence limits and associated p-value. The anastrozole kinetic data were listed and summarized only. Informal comparisons were made with data from a previous Phase III trial (1033IL/0004). Safety data were listed and summarized.

RESULTS:

Assay methods:

The plasma concentrations of anastrozole were measured using —— The following table summarizes the validations of the method.

Linear Range ng/mL	Accuracy (%)	Precision (%CV)	
		Intra-assay	Inter-assay
——	94.4-104	0.4-16.1	5.9-8.1

The concentrations of tamoxifen were measured with —— method. The following table summarizes the validations of the method.

Sensitivity (ng/mL)	Recovery (%)	Precision (%CV)
——	79-93	2.18

The estradiol plasma concentrations were measured by radiommunoassay using a specific antiserum. The following table summarizes the validations of this method.

Sensitivity (pmol/L)	Within-assay variability (%)	Between-assay variability (%)
——	9.4	12.8

The assay descriptions and validations are not complete.

Pharmacokinetics and Pharmacodynamics:

The analysis of the tamoxifen is presented in the following Table.

Table Analysis of tamoxifen serum concentrations

	Geometric lsmean (ng/ml)	Treatment effect[a]	95% confidence interval	p-value
Anastrozole (n=15)[b]	125.0356			
		1.0060	0.8921 to 1.1345	0.9190
Placebo (n=18)	124.28689			

[a] Ratio of anastrozole geometric lsmean to the placebo geometric lsmean

[b] Patient 0002/0002 was not post-menopausal and was therefore excluded from the analysis.

There was no evidence of a significant difference between the anastrozole group and the placebo group for tamoxifen concentrations whilst on trial therapy (Days 14 and 28) or after completing trial therapy (Day 42).

The result of the analysis of the estradiol proportion is summarized in the following Table. Estradiol proportion is defined as the mean of the levels of estradiol measured during treatment (Days 14 and 28), divided by the mean of the levels of estradiol measured at baseline (Days -7 and 0).

Table. Analysis of estradiol proportion

	Geometric lsmean (pmol/l)	Treatment effect[a]	95% confidence interval	p-value
Anastrozole (n=15)[b]	0.1319			
		0.1426	0.1120 to 0.1816	<0.0001
Placebo	0.9247 (n=18)			

[a] Ratio of anastrozole geometric lsmean to the placebo geometric lsmean [b] Patient 0002/0002 was not post-menopausal and was therefore excluded from the analysis.

There was a significant difference between the anastrozole group and the placebo group in the during-treatment estradiol proportion, adjusted for baseline ($p<0.0001$).

COMMENTS:

1. The study confirmed that anastrozole had no effect on the pharmacokinetics of tamoxifen. However, the concentrations of the major metabolite of tamoxifen N-desmethyltamoxifen was not measured.

2. The conclusion through the comparison of this trial with other trial that tamoxifen co-administration does not affect the steady-state plasma concentrations of anastrozole is controversial to the conclusion of study 029.

3. The assay descriptions and validations are not complete.

APPENDIX III. FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-541	Brand Name	Arimidex
OCPB Division (I, II, III)	I	Generic Name	Anastozole
Medical Division	Oncology Drug Products	Drug Class	non-steroidal aromatase inhibitor.
OCPB Reviewer	John Duan	Indication(s)	Breast cancer
OCPB Team Leader	Atique Rahman	Dosage Form	Tablet
		Dosing Regimen	1mg QD
Date of Submission	3/4/02	Route of Administration	Oral
Estimated Due Date of OCPB Review	8/4/02	Sponsor	AstraZenica
PDUFA Due Date	9/4/02	Priority Classification	
Division Due Date	8/4/02		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
acute dose:				
chronic dose:				
Patients-				
acute dose:				
chronic dose:				
Dose proportionality -				
Fasting / non-fasting acute dose:				
Fasting / non-fasting chronic dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:	X	1	1	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; acute / multi dose:	X	1		
replicate design; acute / multi dose:				
Food-drug interaction studies:		[redacted]		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3	2	

Filability and QBR comments

	"X" if yes	***Comments***
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	N/A	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1. Does tamoxifen affect the pharmacokinetics of anastrozole? 2. Does anastrozole affect the pharmacokinetics of tamoxifen?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**John Duan 3/10/02**	
Secondary reviewer Signature and Date	**Atique Rahman 3/10/02**	

CC: NDA 20-541, HFD-850 (Electronic Entry or Lee), HFD-150 (CSO), HFD-860 (Rahmana, Mehta), CDR

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/s/

John Duan
8/13/02 04:11:56 PM
BIOPHARMACEUTICS

Atiqur Rahman
8/14/02 05:38:49 PM
BIOPHARMACEUTICS