NDA 20541

NDA20-541

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

In response refer to File Number F96-00376

This is in response to your request dated Jan. 5, 1996, in which you requested revised documents pertaining to the approval of Arimidex (anastrozole), NDA 20-541, approved Dec. 27, 1995. Your request was received in the Center for Drug Evaluation and Research on Jan. 12, 1996.

✓ Enclosed is/are the document/documents you requested.

____ A search of the records of the Center for Drug Evaluation and Research
- ___ did not locate any disclosable documents responsive to your request.
- ___ did not locate any documents responsive to your request.
- ___ did not locate an approved New Drug Application nor an approved Abbreviated New Drug Application for this/these product/products.
- ___ Summary Basis of Approval are no longer prepared
- ___ did not locate a record an any such inspection by this Center.
- ___ found that final printed labeing is not yet available.

✓ Due to severe resource restrictions, this/these documents are only available on microfiche. Paper copy cannot be provided. You may wish to view the document at your local library or request a local company provide paper copies from the fiche.

____ The minutes of the meeting/meetings you requested are still in preparation and are not yet available.

____ The document you requested is available from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161, 703-487-4650.

____ The portion of your request regarding _____ has been referred to the Agency's Freedom of Information Staff Office (HFI-35). They can be reached at 301-443-6310, ext 101.

✓ In order to reduce processing time and costs, certain material may have been deleted from the record(s) furnished to you, because a preliminary review indicated that the deleted material is not required to be publicly disclosed. If, however, you wish to review any deleted material, identify the specific deletion and submit an additional request for this information.

✓ This concludes your request.

____ You can expect a further response from _____.

The following charges will be included in a monthly invoice:
Reproduction $_____ Search $_____ Review $_____ Other _____
Total $_____ DO NOT SUBMIT PAYMENT UNTIL YOU RECEIVE AN INVOICE

If there are any problems with this response, please notify us in writing of your specific problem(s). Please reference the above file number.

Sincerely yours,

Bernice Carter

Bernice Carter
Freedom of Information Officer
Center for Drug Evaluation
and Research, HFD-19

AP Ltr

Proposed LBCG

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 27 1995

NDA 20-541

Zeneca Pharmaceuticals
1800 Concord Pike
P.O. Box 15437
Wilmington, Delaware 19850-5437

Attention: Frances M. Kelleher, Ph.D.
Manager, Drug Registration
Drug Regulatory Affairs Department

Dear Dr. Kelleher:

Please refer to your March 28, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arimidex (anastrozole) 1 mg Tablets.

We acknowledge receipt of your amendments dated April 10, May 1 and 3, June 30, July 26, October 19, November 3 and 7 and December 6, 12 and 14, 1995.

This new drug application provides for the treatment of advanced breast cancer in post-menopausal women who have progressed following tamoxifen citrate therapy.

In addition, we note your commitment in your letter dated December 7, 1995 to complete and submit results on two ongoing clinical trials as soon as possible.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-541. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Leslie Vaccari, Project Manager, at (301) 594-5778.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE Package insert, bottle labeling

cc:
Original NDA 20-541
HFD-150/Div. files
DISTRICT OFFICE
HFD-150/LVaccari
HFD-2/M.Lumpkin
HFD-100 (with labeling)
HF-2/medwatch (with labeling)
HFD-80 (with labeling)
HFD-244/TAcker (with labeling)
HFD-635 (with labeling)
HFD-9/JTracy (with labeling)

Drafted by: LVaccari /12-12-95/FT12-22-95

R/D Initialed by: DPease/12-13-95
RJustice/12-21-95
JBeitz/12-13-95
SKim/12-21-95
RWood/12-21-95
PAndrews/12-14-95
MBrowers/12-14-95
DeGeorge/12-19-95
SWang/12-14-95
CGnecco/12-18-95

final: RDeLap/12-21-95

APPROVAL Robert J. DeLap 12/22/95

12/27/95

Response to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

PROFESSIONAL INFORMATION BROCHURE

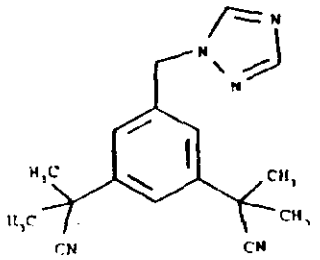
ARIMIDEX®

(anastrozole) Tablets

Rev A-6 12/95

DESCRIPTION

ARIMIDEX® (anastrozole) tablets for oral administration contain 1 mg of anastrozole, a non-steroidal aromatase inhibitor. It is chemically described as 1,3-Benzenediacetonitrile, α, α, α', α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Its molecular formula is $C_{17}H_{19}N_5$ and its structural formula is:



Anastrozole is an off-white powder with a molecular weight of 293.4. Anastrozole has moderate aqueous solubility (0.5 mg/mL at 25°C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrile.

Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogens. In post-menopausal women the principal source of circulating estrogen (primarily estradiol) is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissues such as adipose tissue, with further conversion of estrone to estradiol. Many breast cancers also contain aromatase; the importance of tumor-generated estrogens is uncertain.

Treatment of breast cancer has included efforts to decrease estrogen levels by ovariectomy pre menopausally and by use of anti-estrogens and progestational agents both pre and post-menopausally; and these interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

is a potent and selective non-steroidal aromatase inhibitor, which significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone.

OSED LABELING | PROPOSEI IONS | COMMENTS

...onse to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

Pharmacokinetics: 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. Elimination of anastrozole is primarily via hepatic metabolism (approximately 85%) and to a lesser extent, renal excretion (approximately 11%), with a mean terminal elimination half-life of approximately 50 hours in postmenopausal women. The pharmacokinetic parameters are similar in patients and in healthy postmenopausal volunteers. The pharmacokinetics of anastrozole were are linear over the dose range of 1 to 20 mg. After 7 days of and so not change with repeated dosing.

Food does not affect the extent of absorption

and anastrozole has

The major circulating metabolite of anastrozole, triazole, lacks pharmacologic activity.

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

L Anastrozole is 40% bound to plasma proteins in the therapeutic range.

Response to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

Table 1

Pharmacokinetic Parameters	Mean (CV%)

Response to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

Table 1 (Continued)

*Median (Range)
ND - Not Determined
Cmin - Steady state minimum plasma anastrozole concentration

DSED LABELING	PROPOSED IONS	COMMENTS
Response to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews		

and excretion:

Metabolism: 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. 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

and the remainder excreted in urine as metabolites. (about 60% of the dose)

← 1st pt next page (on renal adjustments)

91 Because renal elimination is not a significant pathway of elimination, ~~clearance remains unchanged~~ total body clearance of anastrozole in renal impairment, dosing adjustment in patients with renal dysfunction is not necessary (see Special Populations and DOSAGE AND ADMINISTRATION sections). Dosage adjustment is also unnecessary in patients with stable hepatic cirrhosis (see Special Populations and DOSAGE AND ADMINISTRATION sections).

Special Populations

Geriatric: Anastrozole pharmacokinetics have been investigated in postmenopausal female volunteers and patients with breast cancer

No age related effects were seen over the range < 50 to > 80 years.

Race: Anastrozole pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: 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% anastrozole is excreted unchanged in the urine, the reduction in renal clearance did not influence the total body clearance. (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: 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 (see DOSAGE AND ADMINISTRATION), so that no dosage adjustment is needed

nse to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

Drug-Drug Interactions: Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 *in vitro* with Ki values which were approximately 30 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 cytochrome P450

Pharmacodynamic Effects: 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.

Effects on corticosteroids:

In multiple daily dosing trials with 3, 5, and 10 mg.

the selectivity of anastrozole was assessed in effects on corticosteroid synthesis.

For all doses, anastrozole did not effect cortisol or aldosterone secretion. No glucocorticoid or mineralocorticoid replacement therapy is necessary with anastrozole.

at baseline or in response to ACTH

Other endocrine effects:

In multiple daily dosing trials with 5 and 10 mg, thyroid stimulating hormone (TSH) was measured; there was no ~~effect on thyroid function with~~ during the administration of ARIMIDEX.

increase in TSH

ARIMIDEX does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

Clinical Studies

~~Two~~ well-controlled clinical trials in postmenopausal women with advanced breast cancer following tamoxifen therapy for either advanced or early breast cancer. Some of the patients had also received previous cytotoxic treatment. Eligible patients with measurable and non-measurable disease were randomized to receive either a single daily dose of 1 mg or 10 mg of ARIMIDEX or megestrol acetate 40 mg four times a day. The studies were double-blinded with respect to ARIMIDEX. Time to progression and objective response rates were the primary efficacy variables. Objective response rates were calculated based on the Union Internationale Contre le Cancer (UICC) criteria.

Anastrozole was studied in 2 (0004, a North American study 0005, a predominantly European study) who had progressive disease

Most patients were ER positive; a smaller fraction were ER unknown or ER negative. The ER negative patients were eligible only if they had had a positive response to tamoxifen.

The rates of prolonged (more than 24 weeks) Stable disease progression and survival were also calculated.

Only patients with measurable disease could be considered responders.

Response to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

. Both trials included over 375 patients; demographics and other baseline characteristics were similar for the 3 treatment groups in each trial. Patients in the 0005 trial had responded better to prior tamoxifen treatment.

[illegible] the patients entered who had prior tamoxifen therapy for advanced disease (58% in Trial 0004; 57% in Trial 0005), 18% of these patients in Trial 0004 and 42% in Trial 0005 were reported by the primary investigator to have responded. In Trial 0004, 81% of patients were ER-positive, 13% were ER-unknown, and 6% were ER-negative. In Trial 0005, 58% of patients were ER-positive, 37% were ER-unknown, and 5% were ER-negative. In Trial 0004, 60% of patients had measurable disease compared to 80% in Trial 0005. The sites of metastatic disease were similar among treatment groups for each trial. On average, 40% of the patients had soft tissue metastases; 60% had bone metastases; and 40% had visceral (15% liver) metastases.

As shown in the table below, similar results were observed among treatment groups and between the two trials. None of the within trial differences were statistically significant.

Response to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

	ARIMIDEX 1 mg	ARIMIDEX 10 mg	Megestrol Acetate 160 mg
Trial 0004 (N. America)	(n=128)	(n=130)	(n=128)
Median Follow-up (days)	179	182	176
Time to Progression (days)	170	143	151
Objective Response (all patients) (%)	10.2	5.4	5.5
Stable Disease for >24 weeks (%)	26.6	23.8	29.7
Progression (%)	48.4	50.0	51.6
Trial 0005 (Europe, Australia)	(n=135)	(n=118)	(n=125)
Median Follow up (days)	192	185	182
Time to Progression (days)	132	156	120
Objective Response (all patients) (%)	10.4	12.7	10.4
Stable Disease for >24 weeks (%)	23.7	21.2	22.4
Progression (%)	58.5	50.8	56.0

in each treatment group in both studies

Approximately 1/3 of the patients had either an objective response or stabilization of their disease for greater than 24 weeks. In patients who had an objective response, over 60% of the patients responded for greater than 6 months, and over 15% responded for greater than 12 months.

Among the 263 patients who received Arimidex 1mg there were 6 complete responders and 21 partial responders.

time to progression

OSED LABELING

Response to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

PROPOSED . .SIONS

COMMENTS

(Arimidex/Megestrol)

To compare the three treatments, hazard ratios (ratio of the likelihood of progression for two treatments over the period of study) and odds ratios for response rates, were calculated for the pooled studies. These show that, in general, the 3 treatments were similar in efficacy, but that confidence intervals were fairly wide. There is, in these data, no indication that Arimidex 10 mg is superior to Arimidex 1 mg.

for time to progression

together with their confidence intervals

for the ARIMIDEX 1 mg comparison to megestrol acetate, the hazard ratio was 0.97 [0.75, 1.24] (p=0.76); for ARIMIDEX 10 mg compared to megestrol acetate, the hazard ratio was 0.92 [0.71, 1.19] (p=0.47). The odds ratio and confidence intervals of the comparison between each dose of ARIMIDEX and megestrol acetate for objective response rate demonstrate that both ARIMIDEX 1 mg and ARIMIDEX 10 mg were similar in efficacy to the comparator. For the ARIMIDEX 1 mg comparison to megestrol acetate, the odds ratio was 1.32 [0.66, 2.65] (p=0.37); for the ARIMIDEX 10 mg comparison to megestrol acetate, the odds ratio was 1.15 [0.55, 2.36] (p=0.68). There were too few deaths occurring across treatment groups of both trials to draw conclusions on overall survival differences.

INDICATIONS AND USAGE

ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX.

CONTRAINDICATIONS

None known.

(Arimidex/megestrol)

There were no differences in response seen between women over or under 65

There were too few non-white patients studied to draw conclusions about racial differences in response rates.

. . nse to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

WARNINGS

ARIMIDEX can cause fetal harm when administered to a pregnant woman. has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about 3/4 and 1.5 times the recommended hum · dose, respectively, on a mg/m^2 basis). Studies in both rats and rabbits at doses equal to or greater than 0.1 and 0.02 mg/kg/day, respectively (about 3/4 and 1/3, respectively, the recommended human dose on a mg/m^2 basis), administered during the period of organogenesis that will increase pregnancy loss (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses); effects were dose related in rats. Placental weights were significantly increased in rats at doses 0.1 mg/kg/day or more.

Anastrozole

showed

anastrozole

Evidence of fetotoxicity, including delayed fetal development (i.e., incomplete ossification and depressed fetal body weights), was observed in rats administered doses of 1 mg/kg/day (which produced plasma C_{max} and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). There was no evidence of teratogenicity in rats administered doses up to 1.0 mg/kg/day.

anastrozole

In rabbits, caused pregnancy failure at doses equal to or greater than 1.0 mg/kg/day (about 16 times the recommended human dose on a mg/m^2 basis); there was no evidence of teratogenicity in rabbits administered 0.2 mg/kg/day (about 3 times the recommended human dose on a mg/m^2 basis).

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There are no adequate and well-controlled studies in pregnant women using ARIMIDEX. If ARIMIDEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS

General: Before starting treatment with ARIMIDEX, pregnancy must be excluded (see WARNINGS).

ARIMIDEX should be administered under the supervision of a qualified physician experienced in the ...t anticancer agents

Laboratory Tests: Three-fold elevations of mean serum gamma glutamyl transferase (GT) levels have been observed among patients with liver metastases receiving ARIMIDEX. These changes were likely related to the progression of liver metastases in these patients, although other contributing factors could not be ruled out.

or megestrol

ponse to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

(See Clinical Pharmacology)

Drug Interactions: Anastrozole inhibited *in vitro* metabolic reactions catalyzed by cytochromes P450 1A2, 2C8/9, and 3A4 / but only at relatively high concentrations

Anastrozole did not inhibit P450 2A6 or the polymorphic P450 2D6 in human liver microsomes. Anastrozole ~~also~~ did not alter the pharmacokinetics of antipyrine. Based on these *in vivo* and *in vitro* studies, it is unlikely that co-administration of a 1 mg dose of ARIMIDEX with other drugs will result in clinically significant drug · inhibition of cytochrome P450.- mediated metabolism of the other drugs.

Although there have been no formal interaction studies other than with antipyrine,

Drug/Laboratory Test Interactions: No clinically significant changes in the results of clinical laboratory tests have been observed.

long term animal

Carcinogenesis: No studies have been conducted to assess the carcinogenic potential of ARIMIDEX.

Mutagenesis: ARIMIDEX has not been shown to be mutagenic in *in vitro* tests (Ames and E. coli bacterial tests, CHO-K1 gene mutation assay) or clastogenic either *in vitro* (chromosome aberrations in human lymphocytes) or *in vivo* (micronucleus test in rats).

...ponse to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

Impairment of Fertility: Studies to investigate the effect of ARIMIDEX on fertility have not been conducted; however, chronic studies indicated hypertrophy of the ovaries and the presence of follicular cysts in rats administered doses equal to or greater than 1 mg/kg/day (which produced plasma and $AUC_{0\text{-}24\ hr}$ that were 19 and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). In addition, hyperplastic uteri were observed in chronic studies of female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma C_{max} and $AUC_{0\text{-}24\ hr}$ that were 22 times and 16 times higher than the respective values found in post-menopausal humans at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in humans.

anastrozole

anastrozole

Pregnancy: Pregnancy Category D: (See WARNINGS).

Nursing Mothers: It is not known if anastrozole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARIMIDEX is administered to a nursing woman. (See WARNINGS and PRECAUTIONS.)

Pediatric Use: The safety and efficacy of ARIMIDEX in pediatric patients have not been established.

Geriatric Use: 50 % of patients in studies 0004 and 0005 were 65 or older. Response rates and time to progression were similar for the over 65 and younger patients.

ADVERSE REACTIONS

ARIMIDEX was generally well tolerated in two well-controlled clinical trials (i.e., Trials 0004 and 0005), with less than 3.3% of the ARIMIDEX-treated patients and 4.0% of the megestrol acetate-treated patients withdrawing due to an adverse event.

The principal adverse events were common with Arimidex than megestrol and were diarrhea,

Adverse events reported in greater than 5% of the patients in any of the treatment groups in these two well-controlled clinical trials, regardless of causality, are presented below:

Number (n) and Percentage of Patients with Adverse Event[1]

Adverse Event	ARIMIDEX 1 mg (n = 262)		ARIMIDEX 10 mg (n = 246)		Megestrol Acetate 160 mg (n = 253)	
	n	%	n	%	n	%
Asthenia	42	(16.0)	33	(13.4)	47	(18.6)
Nausea	41	(15.6)	48	(19.5)	28	(11.1)
Headache	34	(13.0)	44	(17.9)	24	(9.5)
Hot Flushes	32	(12.2)	29	(10.6)	21	(8.3)
Pain	28	(10.7)	38	(15.4)	29	(11.5)
Back Pain	28	(10.7)	26	(10.6)	19	(7.5)
Dyspnea	24	(9.2)	27	(11.0)	53	(20.9)
Sweating	24	(9.2)	26	(10.6)	16	(6.3)
Cough Increased	22	(8.4)	18	(7.3)	19	(7.5)
Diarrhea	22	(8.4)	18	(7.3)	7	(2.8)
Constipation	18	(6.9)	18	(7.3)	21	(8.3)
Abdominal Pain	18	(6.9)	14	(5.7)	18	(7.1)
Anorexia	18	(6.9)	19	(7.7)	11	(4.3)
Bone Pain	17	(6.5)	26	(31.8)	19	(7.5)
Pharyngitis	16	(6.1)	23	(9.3)	15	(5.9)
Dizziness	16	(6.1)	12	(4.9)	15	(5.9)
Rash	15	(5.7)	15	(6.1)	19	(7.5)
Dry Mouth	15	(5.7)	11	(4.5)	13	(5.1)
Peripheral Edema	14	(5.3)	21	(8.5)	28	(11.1)
Pelvic Pain	14	(5.3)	17	(6.9)	13	(5.1)
Depression	14	(5.3)	6	(2.4)	5	(2.0)
Chest Pain	13	(5.0)	18	(7.3)	13	(5.1)
Paresthesia	12	(4.6)	15	(6.1)	9	(3.6)
Vaginal Hemorrhage	6	(2.3)	4	(1.6)	13	(5.1)
Weight Gain	4	(1.5)	9	(3.7)	30	(11.9)
Sweating	4	(1.5)	3	(1.2)	16	(6.3)
Increased Appetite	0	(0)	1	(0.4)	13	(5.1)

[1] A patient may have more than one adverse event.

onse to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics Pharmacokinetics and Medical Reviews

Other less frequent (2% to 5%) adverse experiences reported in patients receiving ARIMIDEX 1 mg in either *Trial 0004* or *Trial 0005* are listed below. These adverse experiences are listed by body system and are in order of decreasing frequency within each body system regardless of causality.

assessed

Body as a Whole:

Flu syndrome; Fever; Neck pain; Malaise; Accidental injury; Infection

Cardiovascular: Hypertension; Thrombophlebitis

Hepatic: Gamma GT increased, SGOT increased; and SGPT increased

Hematologic: Anemia; Leukopenia

Metabolic and Nutritional: Alkaline phosphatase increased; Weight loss

Mean serum total cholesterol levels increased by 0.5 mmol/L among patients receiving ARIMIDEX. Increases in LDL cholesterol have been shown to contribute to these changes.

Musculoskeletal: Myalgia; Arthralgia; Pathological fracture

Nervous: Somnolence; Confusion; Insomnia; Anxiety; Nervousness

Respiratory: Sinusitis; Bronchitis; Rhinitis

Skin and Appendages: Hair thinning; Pruritus

Urogenital: Urinary tract infection; breast pain

The incidences of the following adverse event groups were statistically analyzed: weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flushes, and vaginal dryness. These six groups, and the adverse events captured in the groups, were prospectively defined;

potentially causally related to one or both of the therapies because of their pharmacology,

The results are shown in the table below.

					54	
					35	
			28		35	
	9		4			
Vaginal Dryness	5	(1.9)	3	(1.2)	2	(0.8)
Weight Gain	4	(1.5)	10	(4.1)	30	(11.9)

More patients treated with megestrol acetate reported weight gain as an adverse event compared to patients treated with ARIMIDEX
(p<0.0001).

[illegible] other differences were not statistically significant.

...sponse to 9/28/95 Biopharmaceutics/Pharmacokinetics Review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

An examination of the magnitude of change in weight in all patients was also conducted. Thirty-four percent (87/253) of the patients treated with megestrol acetate experienced weight gain of 5% or more and (27/253) of the patients treated with megestrol acetate experienced weight gain of 10% or more.

11%

On average, this 5 to 10% weight gain represented between 6 and 12 pounds.

No patients receiving ARIMIDEX or megestrol acetate discontinued treatment due to drug-related weight gain.

Among patients treated with ARIMIDEX 1 mg, 13% [33/262] experienced weight gain of 5% or more and 3% [6/262] experienced weight gain of 10% or more.

OVERDOSAGE

Clinical trials have been conducted with ARIMIDEX, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of ARIMIDEX that results in life threatening symptoms has not been established. In rats, lethality was observed after single oral doses that were greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m^2 basis) and was associated with severe irritation to the stomach (necrosis, gastritis, ulceration, and hemorrhage).

There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consider that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because ARIMIDEX is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

COMMENTS

PROPOSE TISIONS

OPOSED LABELING

ponse to 9/28/95 Biopharmaceutics/Pharmacokinetics review; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

DOSAGE AND ADMINISTRATION

The dose of ARIMIDEX is one 1 mg tablet taken once a day.

Patients treated with ARIMIDEX do not require glucocorticoid or mineralocorticoid replacement therapy.

(See clinical Pharmacology

Patients with Hepatic Impairment: Hepatic metabolism accounts for approximately 85% of anastrozole elimination

Although clearance of anastrole was decreased in with cirrhosis patients due to alcohol abuse, plasma anastrozole concentrations stayed in the usual range seen in patients without disease. Therefore,

No changes in dose are recommended for patients with mild-to-moderate hepatic impairment although patients should be monitored for side effects. ARIMIDEX has not been studied in patients with severe hepatic impairment.

Patients with Renal Impairment: No changes in dose are necessary for patients with renal impairment.

nse to 9/28/95 Biopharmaceutics/Pharmacokinetics ...iew; 10/31/95 Pharmacology/Toxicology Review; 11/6/95 Chemistry Review; and 12/1/95 Biopharmaceutics/Pharmacokinetics and Medical Reviews

HOW SUPPLIED

White, biconvex, film-coated tablets containing 1 mg of anastrozole. The tablets are impressed on one side with a logo consisting of a letter "A" (upper case) with an arrowhead attached to the foot of the extended right leg of the "A" and on the reverse with the tablet strength marking "Adx 1". These tablets are supplied in bottles of 30 tablets (NDC 0310-0201-30)

Store at controlled room temperature, 20°-25°C (68°-77°F) [see USP].

ZENECA Pharmaceuticals
A Business Unit of ZENECA Inc.
Wilmington, Delaware 19850-5437 USA

Rev A-6 12/95
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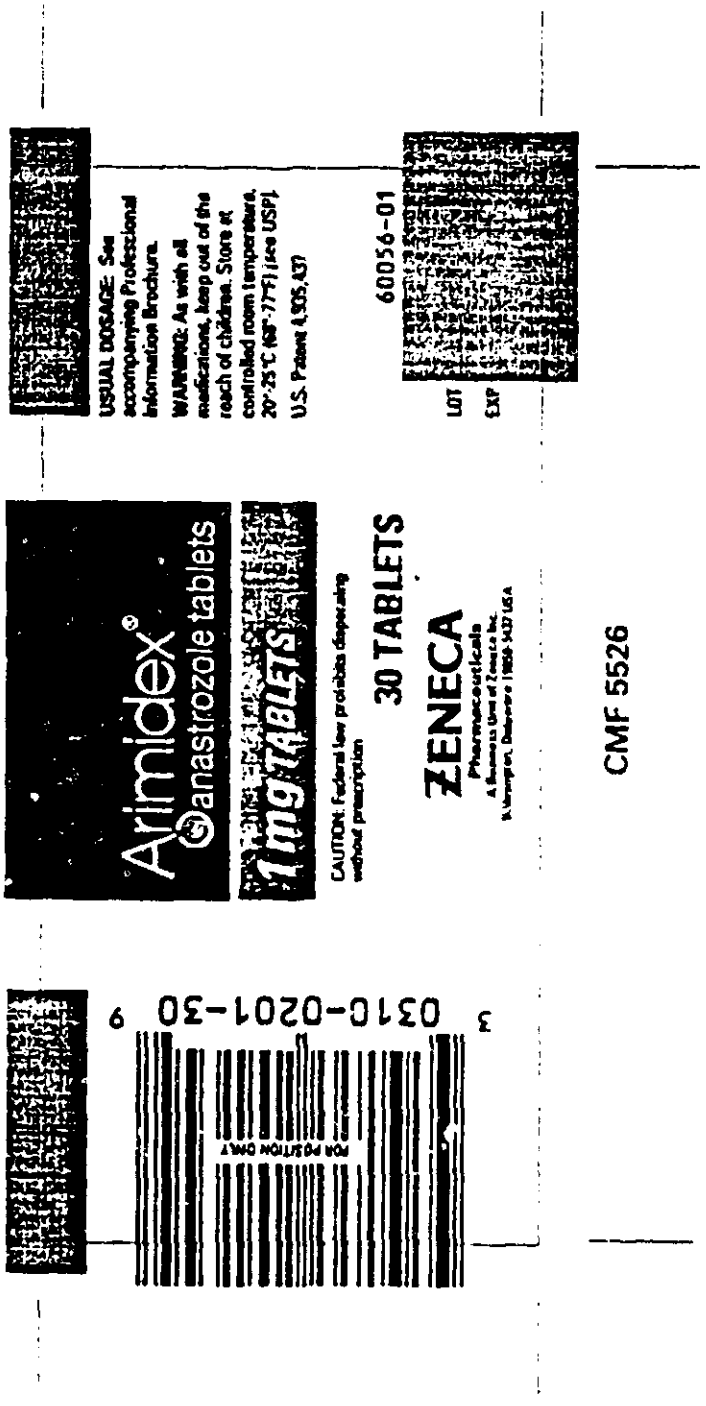
USUAL DOSAGE: See accompanying Professional Information Brochure.
WARNING: As with all medications, keep out of the reach of children. Store at controlled room temperature, 20°-25°C (68°-77°F) [see USP].
U.S. Patent 4,935,437
60056-01
LOT
EXP
Arimidex®
anastrozole tablets
1mg TABLETS
CAUTION: Federal law prohibits dispensing without prescription
30 TABLETS
ZENECA
Pharmaceuticals
0310-0201-30
CMF 5526

Printed in

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1. General Information and Timeline

Drug Name:	ARIMIDEX® (Anastrozole)
Applicant:	ZENECA Limited
NDA Submission Date:	March 29, 1995
Electronic Data Files Installed:	April 3, 1995, SAS for Windows
Pharmacologic Category:	Aromatase Inhibitor
Proposed Indication:	Breast Cancer, Metastatic, Tamoxifen-failure
30-Day Meeting:	April 19, 1995
45-Day Filing Meeting:	May 12, 1995
Safety Update (4-month):	July 26, 1995
Electronic Data Files Installed: (for Safety Update)	July 30, 1995
ODAC Meeting:	October 16, 1995

2. Description of Clinical Data Sources

Volume 1.1 of the March 29, 1995 submission contains the index to the application. Volume 1.2 contains the proposed text of the labeling for anastrozole, summaries of CMC and nonclinical pharmacologic, toxicologic, and pharmacokinetic evaluations, summaries of human pharmacokinetic, bioavailability and clinical data, and a discussion of the benefit/risk relationship and proposed postmarketing studies. The volumes devoted to the clinical section are 1.68 - 1.108 and are summarized below:

Clinical Pharmacology Studies:	1.68 to 1.73
Controlled Studies: -1033IL/0004 -1033IL/0005	 1.74 to 1.89 1.90 to 1.102
Other Studies:	1.103
Integrated Summary of Effectiveness:	1.104
Integrated Summary of Safety:	1.105 to 1.108
Integrated Summary of Benefits and Risks	1.108
4-Month Safety Update	5.1 to 5.13

For each of the two controlled trials, the study reports contain the protocol and amendments, a list of investigators and their curricula vitae, sample case report forms, randomization scheme, relevant publications and individual patient data listings. The data cut-off date for the original NDA submission was September 15, 1994; for the 4-Month Safety Update it was March 31, 1995.

The electronic CANDA was constructed using SAS for Windows software. It contains all the information submitted as hard copy as well as the complete patient case report forms for deaths and withdrawals occurring on the two controlled trials and on seven clinical pharmacology studies. Data files have been installed on a separate server so that several reviewers have access to files at the same time. ZENECA has also provided the review team with a high quality laser printer.

3. Introduction

ZENECA Limited proposes that 1 mg of Arimidex® (anastrozole) administered orally once daily be approved for the treatment of :

> "advanced breast cancer in postmenopausal women who have progressed following tamoxifen therapy".

Anastrozole is a potent and selective oral non-steroidal aromatase inhibitor with a long elimination half-life allowing once-daily dosing. Early clinical pharmacology trials begun in July 1991 demonstrated that anastrozole significantly lowered serum estradiol levels without affecting glucocorticoid or mineralocorticoid secretion. Although these trials were not designed to assess efficacy, 3 of 17 (18%) postmenopausal patients with breast cancer (Trial 0007) had no evidence of disease progression while on continued treatment (10 mg/day) for 24, 25, and 28 months as of the cut-off date (September 15, 1994). Thus, it was concluded that inhibition of estrogen and resulting estradiol concentrations in postmenopausal women produced a beneficial effect in women with breast cancer.

- **Efficacy**

After the minimal dose that achieved maximal suppression of serum estradiol was defined as 1 mg/day, two similar controlled clinical trials were conducted in the absence of a phase 2 trial. The phase 3 trial population was restricted to postmenopausal women who had failed first-line hormonal treatment with tamoxifen in the adjuvant or advanced setting. Treatment arms consisted of either anastrozole 1 or 10 mg once a day (double-blind) compared to standard treatment with open-label megestrol acetate (MEGACE™, Bristol Myers Squibb) 40 mg orally four times daily. Time to progression and objective response rates were primary efficacy variables. Other objective efficacy variables were time to treatment failure, duration of response, survival, and quality of life assessments.

Trial 0004 enrolled 386 patients from 49 centers in the US and Canada between March 3, 1993 and June 24, 1994. The median duration of follow-up was 179 and 182 days for the 1 mg and 10 mg anastrozole groups, and 176 days for the megestrol acetate group. The median time to progression in the three arms was 170, 143, and 151 days. The objective response rates in the three arms were: 10.2%, 5.4% and 5.5%. There were no statistically significant differences across treatment groups in primary efficacy variables.

Trial 0005 enrolled 378 patients from 73 centers in Europe, South Africa and Australia between April 22, 1993 and June 24, 1994. The median time to progression in the three arms was 132, 156, and 120 days. The objective response rates in the three arms were: 10.4%, 12.7% and 10.4%. Again, there were no statistically significant differences across treatment groups in primary efficacy variables. There were too few deaths across treatment groups in either Trial 0004 or 0005 to allow conclusions to be drawn on survival differences

- **Safety Issues**

At the time of data cut-off, a total of 737 subjects had received anastrozole. A wide range of single doses of anastrozole were given to 124 volunteers in clinical pharmacology studies (0.000005 to 60 mg). Multiple doses were given to 613 subjects, of which 508 were treated on controlled trials. Total exposure to anastrozole in the trial program was equivalent to 238 subject-years. Megestrol acetate was administered to 253 patients.

Six adverse event groups were prospectively defined Anastrozole 1 mg was associated with a significantly lower incidence of weight gain than megestrol acetate ($p < 0.0001$). The incidence of other anticipated adverse events (edema, thromboembolic disease, gastrointestinal disturbance, hot flushes, and vaginal dryness) was similar in patients treated with anastrozole 1 mg or megestrol acetate.

Review of all drug-related adverse events revealed that the most frequent events (in descending order) in patients treated with anastrozole were: hot flushes, asthenia, headache, nausea, pain, dizziness, alopecia, diarrhea, and dyspnea Of these, the incidence of alopecia was 6-7 times more frequent with anastrozole 1 mg than with megestrol acetate Increased appetite occurred in only 1 patient treated with anastrozole.

The most frequent drug-related adverse events occurring with megestrol acetate treatment were, in descending order: weight gain, dyspnea, hot flushes, asthenia, headache, increased appetite, nausea, sweating, vaginal hemorrhage, peripheral edema, pain, leukorrhea, dizziness, and dry mouth. Compared to anastrozole 1 mg, the incidence of dyspnea, peripheral edema, vaginal hemorrhage, and sweating was 2- to 3-fold higher with megestrol acetate; the incidence of weight gain was 8-fold higher.

Anastrozole was equally well tolerated in elderly (>65 years) and middle-aged patients. There was some evidence of increased nausea and vomiting in patients with hepatic impairment treated with the 1 mg dose as compared to patients with normal hepatic function. However, no changes in dose appear necessary for patients with mild to moderate hepatic impairment; anastrozole is not recommended for patients with severe hepatic dysfunction.

No changes in dose are recommended for patients with renal impairment. No significant drug interactions mediated by the inhibition of cytochrome P450 are expected.

- **Sponsor's Conclusions Regarding Controlled Trials**

Results of the clinical program support the use of anastrozole 1 mg as an alternative to megestrol acetate in the treatment of advanced breast cancer in postmenopausal women who progress following tamoxifen therapy. The pharmacologic effects of anastrozole may cause hot flushes and alopecia; gastrointestinal disturbances may also occur

- **Proposed Studies**

Accrual is expected to begin in 1995 for the following trials in postmenopausal women with metastatic breast cancer. Two trials comparing anastrozole 1 mg once daily with tamoxifen 20 mg once daily are planned in Europe and in Scandinavia. The design is double-blind; patients will remain on treatment until disease progression, then cross-over to the alternative treatment. A third trial comparing anastrozole 1 mg with formestane given IM every two weeks is also planned.

4. Controlled Trials

4.1 1033IL/0004

4.11 Protocol Review

Title: A Randomized Multicenter Efficacy and Safety Study to Evaluate Arimidex™ (ZENECA ZD1033, 1 and 10 mg) Double-blind, Compared with Open-label Megestrol Acetate in Postmenopausal Women with Advanced Breast Cancer

Principal Investigator: Aman Buzdar, MD, M.D. Anderson Cancer Center, Houston, TX

Study Dates: 3/3/93 - 6/24/94
Data Cut-off Date: 9/15/94

- **Review of Protocol Amendments**

A total of 175 patients were accrued to the original protocol prior to any amendments taking effect. The three amendments incorporated into the protocol addressed recruitment issues, patient exclusion criteria, and monitoring of adverse events, as summarized below:

Amendment 1 (9/10/93): In order to compensate for a non-uniform recruitment pattern, accrual of new patients was to be extended for six months after the 300th patient was recruited, to a maximum of 550 patients from all centers. Exclusion criteria were amended such that patients with "exposure to more than one previous cytotoxic chemotherapy regimen for advanced disease" would not be enrolled. Postmenopausal status was redefined as FSH levels > 40 IU/l instead of > 60 IU/l. After withdrawal from the study, patients would be monitored for adverse events for 2 weeks (instead of 4 weeks). A total of 210 patients were accrued after this amendment was adopted

Amendment 2 (6/14/94): Recruitment would be extended for three months after the 300th patient, to a maximum of 550 patients; all recruitment would end on June 24, 1994. Only one patient was accrued after this amendment was adopted

Amendment 3 (10/6/94): A statistical section was added dealing with evaluation of adverse events.

- **Study Design**

This was a phase 3, parallel-group, multicenter trial in postmenopausal patients with advanced breast cancer. Patients were randomized to receive either anastrozole 1 or 10 mg once daily (double-blind) or open-label megestrol acetate 40 mg four times daily.

- **Objectives**

The primary objectives were to compare two dosages of anastrozole (ZD1033), 1 mg and 10 mg once daily, with megestrol acetate (MEGACE™, Bristol-Myers Squibb) 40 mg four times daily on the following parameters: time to disease progression, tumor response, safety and tolerability. The secondary objectives were to compare treatment groups with respect to time to treatment failure, duration of response, quality of life in the first year of treatment, and survival.

- **Patient Population**

The inclusion and exclusion criteria are provided in the Appendix. In summary, eligible patients were postmenopausal women with advanced breast cancer who were eligible to receive hormonal treatment because of: disease progression while receiving tamoxifen (NOLVADEX™) as adjuvant treatment, relapse while on tamoxifen for advanced breast cancer after a minimum treatment period of 3 months, or relapse while receiving other antiestrogens. Postmenopausal was defined as age 50 or over with FSH levels > 40 IU/l or no menses for 12 months prior to therapy, or age under 50 with FSH levels > 40 IU/l. Patients could not have had prior exposure to more than one cytotoxic regimen for advanced disease (Amendment 1, 9/10/93) or more than one hormonal treatment for advanced disease.

Patients should have a baseline WHO performance status score of 0, 1, or 2, and an estimated survival of at least 3 months. Patients with estrogen receptor-negative advanced disease were excluded unless the patient showed an objective response to prior tamoxifen therapy. Patients with life-threatening visceral disease, including any brain metastases, extensive hepatic involvement or symptomatic pulmonary lymphangitic spread, were excluded.

- **Procedure**

Initially, accrual of 300 evaluable patients recruited at a uniform rate was planned. However, early in the trial, recruitment was not uniform. Thus, centers were added and accrual extended (Amendment 1, 9/10/93). Patients were allocated on a 1:1:1 basis within each center, to oral treatment with 1 mg anastrozole daily, 10 mg anastrozole daily, or 40 mg megestrol acetate four times daily. ZENECA assigned treatment in balanced blocks according to computer-generated randomization schemes produced for each center.

An independent data monitoring committee, comprised of 3 experts not employed by ZENECA (two clinicians and one statistician), periodically evaluated efficacy and safety results. The committee met on 5/3/94 to review an interim analysis of efficacy and safety for this trial and Trial 0005 and recommended that a second interim analysis be performed but that the two trials continue unchanged.

Anastrozole was supplied as film-coated, white tablets in white plastic bottles containing 35 tablets of the predetermined dose (either 1 mg or 10 mg). For the first 24 weeks, patients

assigned to anastrozole were given one bottle at monthly intervals (enough medication for 4 weeks plus a 1-week surplus); beyond 24 weeks, patients were given three bottles at 3-month invervals (enough medication for 3 months plus a 3-week surplus). Patients were instructed to take one anastrozole tablet each morning.

Patients randomized to treatment with megestrol acetate received the commercially available product packaged in white plastic bottles, each containing 250 tablets. For the first 24 weeks, patients assigned to megestrol acetate were given one bottle at 2-month intervals (enough medication for 8 weeks plus a 6.5 day surplus); beyond 24 weeks, patients were given two bottles at 3-month intervals (enough medication for 12 weeks with a 41-day surplus). Patients were instructed to take one tablet morning, midday, late afternoon, and at bedtime.

Each time medication was dispensed, a tear-off label from the bottle was attached to the patient's CRF as a record of drug assignment. Patients were required to return unused tablets at each visit to assess compliance. Pill counts were recorded for each visit on the CRF.

- **Efficacy Assessments**

Screening assessments were carried out within 4 weeks of randomization, including identification of measurable and nonmeasurable disease, as well as quality of life assessments using the Rotterdam Symptom Checklist, bone pain scores, and documentation of analgesic use, and determination of baseline estrogen and drug levels.

Efficacy assessments including, tumor measurements, quality of life assessments, estrogen and drug levels, were carried out at each patient visit (every 4 weeks for the first 24 weeks, then every 12 weeks). After disease progression, only survival was recorded at 6-month intervals. A schedule of efficacy assessments is included in the Appendix.

Radiotherapy for control of bone pain or for other reasons was permitted. Irradiated lesions were only used to assess progression.

Time to disease progression was defined as the number of days from randomization to the date when objective disease progression was first documented, or until death from any cause, whichever came first.

Objective responses required verification on two different occasions separated by 4 weeks. A CR was defined as disappearance of all tumor, clear improvement of bone lesions on scans or xrays, evidence of reossification of all lytic bone lesions, freedom from all cancer-related symptoms, and absence of new lesions. For patients with evaluable, bone-only disease, a CR was defined as remineralization of all lytic lesions, absence of bone pain off analgesics, no new pathologic fractures or bone lesions, and evidence of remodeling and normalization of bone on scans.

A PR was defined as a 50% or greater decrease in the sum of the products of the diameters of

measurable lesions, or a 30% or greater decrease in the sum of the longest diameters of unidimensional lesions. No new lesions should have appeared. Assignment of PR to evaluable disease was not permitted. Progressive disease was defined as a 25% or greater increase in the size of a measurable lesion, progression of nonmeasurable disease, appearance of a new lesion, or late hypercalcemia. Stable disease was recorded if disease progression did not occur. Increased pain due to tumor flare in the first 2 weeks of treatment was considered stable disease.

Duration of response was recorded for patients with a CR or PR and was defined as the number of days from randomization to the date of first documentation of disease progression or death. Time to treatment failure was defined as the number of days from randomization to the date of first documentation of disease progression, death or treatment withdrawal.

- **Quality of Life Assessments**

The Rotterdam Symptom Checklist (RSCL - sample provided in the Appendix) was completed by the patients at baseline, every 4 weeks for 24 weeks, then every 12 weeks until disease progression or death, up to 1 year. It was also carried out at the time of treatment withdrawal if this occurred within 1 year. The RSCL contains 38 items, each rated on a 4-point scale. The higher the score, the worse the quality of life.

Physical dimension: 22 items; scores range from 0-66;
Psychologic dimension: 8 items; scores range from 0-24;
Functional dimension: 8 items; scores range from 0-24.

Patients completed questionnaires in the waiting room prior to each trial visit, then placed them into envelopes that the study coordinator mailed to ZENECA. Patients who were unable to complete questionnaires were excused from this activity but could still participate in the trial.

Analgesic use was scored on a 4-point scale at baseline, at each visit, and at withdrawal as follows: 0 - no analgesics, 1 - non-narcotics, 2 - oral narcotics; 3 - injectable narcotics.

The severity of bone pain was scored using a 5-point scale at baseline, at each visit, and at withdrawal as follows: 0 - none, 1 - mild, 2 - moderate, 3 - severe; 4 - intractable.

Performance status was scored using the ECOG scale (0-4) at baseline, at each visit, and at withdrawal.

- **Safety Assessments**

Safety assessments including adverse events, clinical findings, and laboratory testing, were carried out at each patient visit (every 4 weeks for the first 24 weeks, then every 12 weeks). The original protocol stipulated that adverse events would be monitored until 4 weeks after withdrawal of trial treatment. This was changed to 2 weeks (Amendment 1, 9/10/93) on the

presumption that many patients would begin a cytotoxic regimen soon after withdrawal from this study. The shorter monitoring period was considered adequate since the half-life of anastrozole is 50 hours.

- **Statistical Plan**

The estimation of sample size was based on time to disease progression and objective response rate. Assuming a median time to progression of 26 weeks, a total of 300 patients (100 in each arm), recruited at a uniform rate over 12 months, with a minimum follow-up of 6 months, would be sufficient to detect a treatment difference of 14 weeks, with 80% power and a significance level of 0.05 (two-sided). Assuming an objective response rate of 25%, a treatment difference of 20% would be statistically detectable with 90% power (significance level of 0.05, two-sided).

Efficacy analyses were carried out on an intent-to-treat basis, and adjusted for the covariates of previous treatment status (adjuvant or advanced disease) and hormone receptor status. Anastrozole 1 mg and 10 mg were each compared to megestrol acetate.

Response rate, analgesic use, bone pain score, and performance status were analyzed by logistic regression. Time to progression, time to treatment failure, and death were analyzed by Cox's Proportional Hazards Model. Time to progression, time to treatment failure, death, and duration of response were also summarized using Kaplan-Meier curves, which were used to estimate the median time for each of these endpoints for each treatment group. The Rotterdam Symptom Checklist scores were analyzed as follows: physical and psychological scores at weeks 12 and 24 by analysis of covariance and the Wilcoxon Rank-Sum test; the functional score by logistic regression (because of the large proportion of patients with a maximum positive score of 24 at baseline, and no change in score on study). Analgesic use, bone pain score, and performance status at weeks 12 and 24 were also analyzed by logistic regression.

Adverse events were summarized by treatment using COSTART terms. After the adoption of Amendment 1 (9/10/93), adverse events occurring during treatment or within 2 weeks of stopping treatment were recorded. The incidence of certain anticipated events (weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flushes and vaginal dryness) was also summarized.

- **Study Conduct**

Fifty centers recruited 392 patients on this trial. However, Center 0034 (with 6 patients, two on each arm) did not follow inclusion or exclusion criteria or carefully maintain source documents. ZENECA closed this center, and with agreement with the Agency, did not include data on the 6 patients in the study report. Instead, clinical narratives were submitted for review.

4.12 Demography, Withdrawals, and Protocol Violations and Deviations

A total of 386 patients from 49 centers in North America were included in this trial. Twenty-four centers accrued ≥ 5 patients each for a total of 331 (86%) patients; the remaining 25 centers accrued < 5 patients each for a total of 55 (14%) patients. Altogether, 128 were randomized to receive 1 mg anastrozole, 130 to receive 10 mg anastrozole, and 128 to receive megestrol acetate. One patient (0015/0015) on the 10 mg anastrozole arm withdrew consent and never received treatment. This patient was included in the analysis of efficacy only. At the time of data cut-off (9/15/94), 175 (45%) patients were still on treatment. **Comment:** *Patient accrual to the study averaged 30 patients/month for the first six months, slowing to approximately 21 patients/month for the next ten months. Among centers accruing 5 or more patients, 2 of 24 centers accrued only in the last 6 months (in 1994 only). Among centers accruing less than 5 patients, 11 of 25 centers enrolled patients only in 1994 (6 enrolled 2-3 patients each, 5 enrolled one patient each).*

The median age of patients enrolled on this trial was 66 (range 29-93) and 87% of patients were Caucasian. The majority of patients (81%) had ER+ disease, while 6% had ER- disease and ER status was unknown in 13%. The WHO performance status at study entry was 0-1 in 87%. These parameters were balanced across treatment groups. Prior hormonal therapy had been administered as adjuvant therapy in a total of 164 (42.5%) patients, and as therapy for advanced disease in 222 (57.5%) patients.

The duration of tamoxifen therapy was estimated by using the interval between the start of tamoxifen therapy and date of study consent. (For this analysis, 11, 14, and 2 patients on each arm, respectively, were excluded since they either did not receive tamoxifen or the duration on tamoxifen could not be calculated.) The median duration of adjuvant tamoxifen therapy ranged from 34 months for the 1 mg anastrozole arm, to 40 months for the 10 mg anastrozole arm, and to 47 months for the megestrol arm. The median duration of tamoxifen therapy for advanced disease was similar across treatment arms (25, 26, and 22 months for each arm, respectively). The best response to prior tamoxifen treatment for advanced disease was CR in 7%, PR in 12%, stable disease in 41%, progression in 6%, and unknown in 34%. Other prior treatments for breast cancer in these patients were: surgery in 96%, chemotherapy in 45%, and radiotherapy in 58%.

Measurable disease was noted in 63% of patients, while 37% had nonmeasurable disease. Sites of metastatic disease were bone in 65%, soft tissue in 33%, and visceral in 42%. Only 14% had liver metastases. Mixed sites of disease were noted in 38%. Twenty patients had no evaluable sites of metastasis, due to prior excision or irradiation of known sites of distant disease in some cases. Again, there were no differences observed across treatment groups.

Comparison of Baseline Patient Characteristics Among Centers:
In order to evaluate potential baseline patient differences among participating centers, centers accruing ≥ 5 patients each, so-called "large centers", were compared to those accruing < 5 patients each, so-called "small centers". The following clinical features were reviewed: patients'

hormonal status at study entry, previous response to tamoxifen for advanced disease, presence of measurable disease at entry, and extent of disease at entry. For the most part, centers were well balanced in baseline patient characteristics across treatment groups.

A total of 210 patients withdrew from treatment: 181 due to disease progression, 11 due to adverse event or concurrent illness, 7 due to patient refusal or lost follow-up, 5 due to death, 4 due to other reasons, and 2 due to protocol noncompliance.

A total of 37 protocol violations were noted in 36 patients. All patients considered to be protocol violations were still included in analyses of efficacy and safety. Five patients were not candidates for hormonal treatment as defined in the protocol, 6 patients were not confirmed to be postmenopausal, 5 patients had WHO scores > 2 although their debilitation was not directly related to breast cancer, 6 patients were previously treated with more than one cytotoxic agent for advanced disease, 2 patients had prior uterine cancer, 1 patient had primary lung cancer that was misdiagnosed as metastatic breast cancer, 2 patients received concurrent therapy with other experimental drugs (Aredia), 4 patients had previously treated brain metastases, and 6 patients had ER- disease with no demonstrated response to adjuvant tamoxifen therapy. **Comment:** *The frequency of protocol violations among patients enrolled in each treatment arm was: 5% for 1 mg anastrozole, 12% for 10 mg anastrozole, and 20% for megestrol acetate. The frequency of protocol violations in "large centers" was comparable to that of "small centers".*

A total of 224 protocol deviations occurred in 167 patients. These were distributed equally across all treatment groups (with a frequency of deviations occurring in 42-44% of patients/arm), and consisted primarily of baseline or follow-up assessments that were either absent or performed outside the window of time specified in the protocol. No patient was excluded from the analysis of efficacy and safety, except for patient who never received treatment (excluded from safety analysis). **Comment:** *The frequency of protocol deviations in "large centers" was comparable to that of "small centers".*

4.13 Efficacy Results

The median duration of study treatment was 146 days (11-511 days) for the 1 mg anastrozole arm, 143 days (8-534 days) for the 10 mg anastrozole arm, and 128 days (15-472 days) for the megestrol acetate arm. The median duration of follow-up was 179 days (17-512 days) for the 1 mg anastrozole arm, 182 days (4-539 days) for the 10 mg anastrozole arm, and 176 days (30-554 days) for the megestrol acetate arm. **Comments:** *1) Calculation of all efficacy endpoints (i.e., time to progression, response duration, time to treatment failure, and time to death) were calculated from the date of randomization. Scatter plot analysis of date of randomization vs. date treatment was started shows that these dates coincide for the vast majority of patients. In fact, these often were either the exact same date or one day apart (see Appendix). 2) The extent of patient follow-up after documentation of progression or treatment failure is demonstrated in scatter plots (progression date vs. last alive date, and date of treatment failure vs. last alive date) in the Appendix.*

- **Time to Disease Progression**

A total of 64 (50%) patients treated with 1 mg anastrozole, 74 (57%) patients treated with 10 mg anastrozole, and 73 (57%) patients treated with megestrol acetate had disease progression during treatment or after treatment withdrawal. In addition, there were 11 patients (5, 1, and 5 per arm, respectively) who died before disease progression was documented; the date of death was used to calculate the time to progression in these patients. Thus, a total of 222 patients contributed to the analysis of time to progression with 164 (43%) patients censored. Median times to progression (with 97.7% confidence intervals) were: 170 days (102-266 days) for patients treated with 1 mg anastrozole, 143 days (99-222 days) for patients treated with 10 mg anastrozole, and 151 days (95-203 days) for patients treated with megestrol acetate.

Comparison of 1 mg anastrozole with megestrol acetate revealed a hazard ratio of 0.89 (CI: 0.61-1.30, p= 0.48). The hazard ratio for the comparison of 10 mg anastrozole with megestrol acetate was 1.00 (CI: 0.69-1.45, p= 0.99). There was no statistical difference between either dose of anastrozole and megestrol acetate

Subgroup Analysis. The tables below show the rate of disease progression (by patient) by prior hormonal treatment (adjuvant vs advanced disease) and by estrogen receptor status (positive, unknown, negative) at study entry.

Disease Progression by Patient

Treatment Arm	Prior Hormonal Therapy	
	Adjuvant	Advanced
Anastrozole 1 mg	36/60 (60%)	28/68 (41%)
Anastrozole10 mg	33/54 (61%)	41/76 (54%)
Megestrol Acetate 40 mg	27/50 (54%)	46/78 (59%)
All Patients	96/164 (58%)	115/222 (52%)

Treatment Arm	Estrogen Receptor Status		
	Positive	Unknown	Negative
Anastrozole 1 mg	53/109 (49%)	8/16 (50%)	3/3 (100%)
Anastrozole 10 mg	62/102 (61%)	6/20 (30%)	6/8 (75%)
Megestrol Acetate 40 mg	56/101 (56%)	8/16 (50%)	9/11 (82%)
All Patients	171/312 (55%)	22/56 (39%)	18/22 (82%)

Comments: *1) There do not appear to be any major differences in the rate of disease progression among patients who received hormonal therapy adjuvantly or for advanced disease, with the exception of patients on the 1 mg anastrozole arm (60% vs. 41%). 2) Among ER+/PR+ patients, rates of disease progression were 45% (36/80) for 1 mg anastrozole, 66% (50/76) for 10 mg anastrozole, and 59% (41/70) for megestrol; these were comparable to rates observed among all ER+ patients noted above. 3) A greater proportion of patients with ER- disease progressed on study, although the patient numbers were very small.*

Reviewer's Assessment of Time to Progression:
1) The time to progression was confirmed for all randomized patients. Dates of first observed progression were available for the 211 patients progressing either during treatment or after treatment withdrawal (Table G4.4).

2) Eleven of the 222 patients used in the sponsor's analysis of time to disease progression died before progression was formally documented as per protocol. Eight of these in fact died of disease progression at 34, 44, 53, 57, 62, 73, 86, and 224 days. The reviewer questions the rationale for including the remaining three: patient died of a small bowel infarct at 17 days, patient died of complications of aneurysm surgery at 219 days, and patient died of a pulmonary embolism at 30 days. Note that exclusion of the entire 11 patient subset or of the 3 patient subset does not significantly alter time to progression (see Appendix for additional Kaplan-Meier plots).

3) Treatment was continued for several of the patients following first documentation of disease progression (see scatter plot of progression date vs. date treatment stopped in the Appendix).

- **Objective Response Rate**

Objective responses were assigned using UICC criteria. Bidimensionally measurable disease was noted in roughly 60% of patients; only 10 patients had assessments made on the basis of unidimensional lesions. Objective response rates for all randomized patients were similar across treatment groups. In the 1 mg anastrozole arm, there were 4 CRs and 9 PRs for an overall response rate of 10.2%. In the 10 mg anastrozole arm, there was 1 CR and 6 PRs for an overall response rate of 5.4%. In the megestrol acetate arm, there were 2 CRs and 5 PRs for an overall response rate of 5.5%. The proportion of patients with a best response of stable disease $\geq$ 24 weeks was similar across treatment groups (24-30%).

Comparison of 1 mg anastrozole with megestrol revealed an odds ratio of 1.95 (CI: 0.65-5.91, p= 0.17). The odds ratio for the comparison of 10 mg anastrozole with megestrol acetate was 0.98 (CI: 0.28-3.43, p= 0.98). There was no statistical difference between either dose of anastrozole and megestrol acetate.

For patients with measurable disease, the overall response rates (CRs + PRs) were somewhat higher: 15.9% for 1 mg anastrozole, 8.9% for 10 mg anastrozole, and 8.7% for megestrol acetate.

Stable disease lasting ≥ 24 months was noted in 20%, 14% and 22%, respectively. For patients with nonmeasurable disease, the best response in this trial was disease stabilization ≥ 24 months noted in 39% of patients on 1 or 10 mg anastrozole, and in 43% of patients on megestrol acetate.

Subgroup Analysis. The tables below show the objective response rates in patients by prior hormonal treatment (adjuvant vs. advanced disease), by estrogen receptor status (positive, unknown, negative), and by disease site (soft tissue only, bone only, visceral only).

Objective Response Rate

Treatment Arm	Prior Hormonal Therapy	
	Adjuvant	Advanced
Anastrozole 1 mg	5/60 (8.3%)	8/68 (11.8%)
Anastrozole 10 mg	2/54 (3.7%)	5/76 (6.6%)
Megestrol Acetate 40 mg	4/50 (8%)	3/78 (3.9%)

Treatment Arm	Estrogen Receptor Status		
	Positive	Unknown	Negative
Anastrozole 1 mg	9/109 (8.3%)	4/16 (25%)	0/3
Anastrozole 10 mg	7/102 (6.9%)	0/20	0/8
Megestrol Acetate 40 mg	6/101 (6%)	1/16 (6.3%)	0/11

Treatment Arm	Site of Metastatic Disease		
	Soft Tissue Only	Bone Only*	Visceral Only*
Anastrozole 1 mg	4/17 (23.5%)	3/45 (6.7%)	1/14 (7.1%)
Anastrozole 10 mg	2/14 (14.2%)	0/37	2/15 (13.3%)
Megestrol Acetate 40 mg	5/16 (31.3%)	0/41	0/22

*Partial responses only

Comments: *1) There do not appear to be any major differences in objective response rates among patients who received hormonal therapy adjuvantly or for advanced disease. 2) Response was associated with ER+ status and with soft tissue involvement. Response rates for the subset of ER+/PR+ patients (7.6%, 6.6%, and 5.7% for each arm respectively) were similar to those of all ER+ patients Response rates for the subset of ER+/soft tissue only disease patients (21%, 18%, and 40% for each arm respectively) were comparable to those of soft tissue only disease patients noted above. 3) Although response rates for patients with bone*

only or visceral only disease were low across treatment arms, disease stabilization was observed at these sites. This was noted in 42%, 27%, and 42% of patients with bone only disease in each of the arms, and in 14%, 20%, and 41% of patients with visceral only disease in each of the treatment arms respectively. 4) Among patients whose previous best response to tamoxifen was either CR or PR, responses rates were 22.2%, 7.7%, 10.6%, for each arm respectively. There were no responders on this trial in patients whose best response to tamoxifen had been disease progression.

Reviewer's Assessment of Objective Response Rate:
1) Objective responses were confirmed for the 7 CRs and 20 PRs in this trial.

2) Complete responses occurred in soft tissue lesions (skin or lymph nodes) in 7 patients and in non-measurable lung disease in 1 patient. Partial responses occurred in breast, skin, lymph nodes, bone and lung lesions.

3) Partial responses in 2 patients were based on non-measurable lesions: lymph node metastases measuring < 2 cm (0030/0008 on 10 mg anastrozole and 0046/0001 on megestrol acetate) and nonmeasurable bone disease (0030/0008). As per protocol, PRs could not be assigned to these patients, only disease stabilization. In a third patient the response observed was not confirmed 4 weeks later (0045/0002 on 10 mg anastrozole). Exclusion of these patients from the group of responding patients does not alter response rates appreciably.

- **Duration of Response**

Fifteen (56%) of the 27 responders were still responding at the time treatment was stopped and were censored for the analysis of this endpoint. The duration of response among complete and partial responders ranged from 92 - >512 days for the 1 mg anastrozole group, from 112-533 days for the 10 mg anastrozole group, and from 111- >370 days for the megestrol acetate group.

Reviewer's Assessment of Response Duration:
1) Response durations were confirmed for each of the responders.

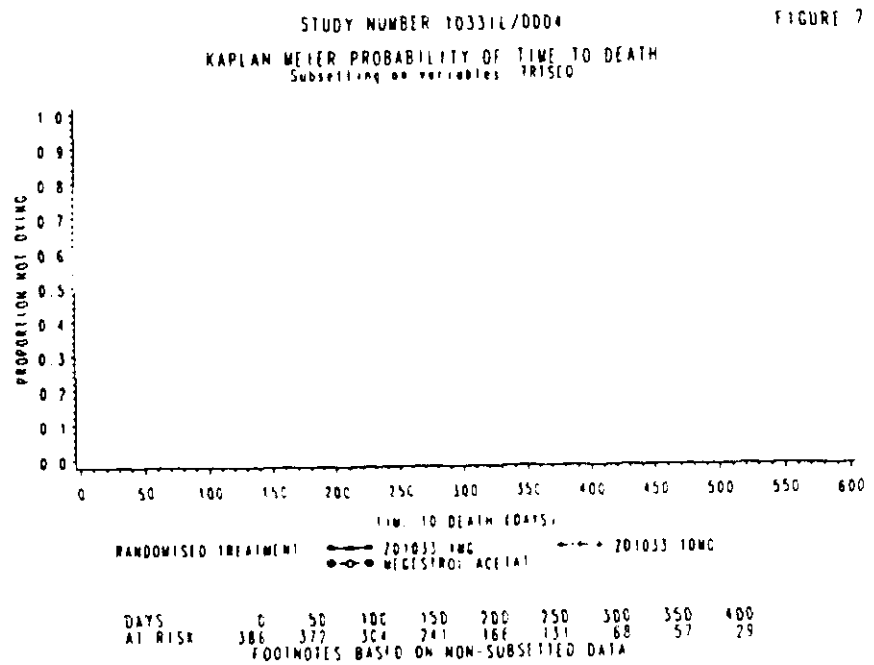
2) Five patients were in CR as of the "last alive date". Two of these patients were on the 1 mg anastrozole arm (in CR at 148 and 363 days), one was on the 10 mg anastrozole arm (276 days), and two were on the megestrol acetate arm (252 and 370 days).

3) Ten patients were in PR as of the "last alive date". Of these, five were on the 1 mg anastrozole arm (in PR at 122, 154, 277, 449, and 512 days), three were on the 10 mg anastrozole arm (168, 175, and 274 days), and two were on the megestrol acetate arm (111 and 310 days).

4) Calculation of response duration from the date of randomization rather than the date of first documentation of response inflates these response times

- **Time to Death**

A total of 17 patients treated with 1 mg anastrozole, 10 patients treated with 10 mg anastrozole, and 19 patients treated with megestrol acetate died. Median time to death could not be calculated because of the low number of deaths. **Comments:** *Scatter plots demonstrate the timing of patient deaths following first documentation of progression or treatment failure (see progression date vs. date of death, and date of treatment failure vs. date of death in the Appendix). The sponsor plans to submit an updated survival analysis in September 1995.*



Comparison of 1 mg anastrozole with megestrol acetate revealed a hazard ratio of 0.96 (CI: 0.45-2.08, p= 0.91). The hazard ratio for the comparison of 10 mg anastrozole with megestrol acetate was 0.50 (CI: 0.21-1.21, p= 0.08). There was no statistical difference between either dose of anastrozole and megestrol acetate.

Comparison of Efficacy Results Across Centers:

The "large centers" (accruing $\geq$ 5 patients each) and "small centers" (accruing < 5 patients each) were compared in terms of patient progression status, best overall response, reasons for treatment failure, and survival status. In general, centers were well balanced in these parameters across treatment arms with one notable exception. The overall death rate was far lower among "small centers" (3.6% or 2/55) as compared to "large centers" (13.3% or 44/331). This was most noticeable in the 1 mg anastrozole arm (0/19 deaths in "small centers" vs. 17/109 or 16% deaths in "large centers") and in the megestrol arm (1/18 or 6% deaths in "small centers" vs. 18/110 or 16% deaths in "large centers").

Comparison of Compliance Across Centers:
Information on drug accountability was provided for all patients treated on this trial (excluding one patient on the 10 mg anastrozole arm who never received treatment). Non-compliance was defined by the sponsor as "patients returning > 20% of pills" at an office visit. This occurred in roughly 20% of patients in each arm at the "large centers". At the "small centers", most instances of non-compliance occurred on the 10 mg anastrozole arm. The breakdown by center type is as follows:

Center	"Non-Compliant" Events
"Large Centers" *N=330 patients* *N=24 centers*	1 mg Anastrozole: 22 patients, 23 visits, 13 centers 10 mg Anastrozole: 22 patients, 28 visits, 15 centers Megestrol Acetate: 23 patients, 25 visits, 11 centers
"Small Centers" *N=55 patients* *N=25 centers*	1 mg Anastrozole: 2 patients, 3 visits, 2 centers 10 mg Anastrozole: 7 patients, 8 visits, 6 centers Megestrol Acetate: 1 patient, 1 visit, 1 center

Efficacy parameters in the 129 patients on the 10 mg anastrozole arm were evaluated in terms of compliance, with a total of 100 patients deemed "compliant" and 29 "non-compliant". In terms of best overall response, there was a higher proportion of patients with disease stabilization in the "non-compliant" group as compared to the "compliant" group (58% vs. 41%). This difference, however, did not translate into a higher rate of disease progression or death.

Protocol Violations/Deviations Among Responders:
The 27 responding patients in Trial 0004 included one with a protocol violation and 16 with one or more protocol deviations. Sufficient information was provided to infer that most of these events did not appear to affect assessment of efficacy endpoints in these patients. There were three notable exceptions: patient a CR on megestrol acetate who was "repeatedly non-compliant" with study medication; patient a PR on 1 mg anastrozole who also took Aredia: this could have affected this patient's bone pain scores and analgesic use; and patient a PR on 1 mg anastrozole who missed the visit prior to the one which demonstrated disease progression in lymph nodes: this patient's response duration, time to progression, and time to treatment failure may be inflated by four weeks.

- **Quality of Life Assessments**

The completion rate of the RSCL questionnaires at study entry, week 12 and week 24 was approximately ≥ 90% of expected. Physical quality of life at week 24 for patients treated with 1 mg anastrozole was better than for patients on megestrol acetate (p= 0.0163). Psychological quality of life at weeks 12 and 24 was better for patients treated with 1 mg anastrozole than for megestrol acetate (p= 0.0206 and p= 0.0018 respectively). Functional quality of life was similar across treatment groups at all three time points. **Comment:** *Comparisons between treatment arms were based on the numbers of patients listed below. There were comparable numbers of*

patients in each arm evaluated for each of the three RSCL domains. There were roughly half as many patients evaluable at week 24 as in week 12.

Treatment Arm	Patients with Entry and Week 12 Data			Patients with Entry and Week 24 Data		
	Phys	Psychol	Funct	Phys	Psychol	Funct
Arimidex 1 mg (N=128)	105	105	104	58	58	57
Arimidex 10 mg (N=130)	109	109	108	58	58	58
Megace 40 mg (N=128)	103	103	100	51	51	50

There was no difference in analgesic use, bone pain score, or WHO performance status at weeks 12 or 24 across treatment groups. **Comment:** *Comparisons between treatment arms were based on the numbers of patients listed below. There were comparable numbers of patients in each arm evaluated for each of these assessments. Again, there were roughly half as many patients evaluable at week 24 as in week 12.*

Treatment Arm	Patients with Entry and Week 12 Data			Patients with Entry and Week 24 Data		
	Analgesic	Bone Pain	WHO PS	Analgesic	Bone Pain	WHO PS
Arimidex 1 mg (N=128)	119	119	119	62	62	62
Arimidex 10 mg (N=130)	118	118	118	63	63	63
Megace 40 mg (N=128)	116	116	116	57	57	57

- **Endocrine Assessments**

Serum estradiol concentrations could not be statistically analyzed. Several factors such as insufficient sample volume, variable column recovery, and variability in limits of quantitation resulted in a nonhomogeneous dataset. The estradiol assays used in this trial had a higher limit of quantitation (4 to 28 pmol/l) depending on the assay run, compared to the assays used in the clinical pharmacology trials. Thus, there were many patients in each treatment group whose estradiol level at study entry was at or below the limit of assay sensitivity.

Serum estrone sulfate concentrations were suppressed by 54-85% of baseline levels in the 1 and 10 mg anastrozole arms, as compared to 26-66% of baseline levels in the megestrol acetate arm. There was no difference in estrone sulfate suppression between the two doses of anastrozole.

4.14 Safety Results

Drug-related events that occurred in any treatment group in at least 3% of patients are summarized below. Further detail regarding the safety profile of anastrozole is provided in reviews of the Integrated Summary of Safety and of the 4-Month Safety Update in Section 6.

Mild or moderate headache was noted in 15.5% of patients treated with 10 mg anastrozole, in 8.6% of patients treated with 1 mg anastrozole, and in 4.7% of patients treated with megestrol acetate. The majority of cases had an undetermined relationship to treatment.

Gastrointestinal disturbances included mild or moderate nausea in all groups (in 4-8%), mild or moderate diarrhea with anastrozole (in 2-3%), and increased appetite with megestrol acetate (in 8%).

Whereas peripheral edema occurred with similar frequency in all groups (in 2-5%), mild weight gain was more common in patients treated with megestrol acetate (15.6%) than in patients treated with anastrozole (0.8% for 1 mg, 4.7% for 10 mg).

Hot flushes were noted in 19% and 15% of patients treated with 1 mg or 10 mg anastrozole, as compared to 9% in patients treated with megestrol acetate. Mild or moderate bone pain, mild alopecia, and anorexia were also noted primarily with anastrozole. Hot flushes and alopecia are expected given the pharmacology of this agent. Megestrol acetate was more commonly associated with mild or moderate dyspnea, mild tremor, sweating, vaginal hemorrhage, and leukorrhea. A higher incidence of dyspnea with megestrol acetate is not unexpected since this agent is known to be associated with weight gain and fluid retention which can exacerbate respiratory symptoms.

- **Treatment Withdrawals**

Adverse events lead to treatment withdrawal in a total of 11 patients. Three patients withdrew from the 1 mg anastrozole arm: one with an intracranial aneurysm who died 4 weeks after withdrawal, one with exacerbation of chronic obstructive pulmonary disease who died of respiratory failure 2 weeks after withdrawal, and one who developed neuropathy. Four patients withdrew from the 10 mg anastrozole arm: one developed a vesiculobullous rash, later determined to be related to a staphylococcal infection, one developed anorexia and insomnia, one developed hypercalcemia and somnolence, and pulmonary embolus occurred in the fourth. Four patients also withdrew from the megestrol acetate arm: one developed depression, nausea and dizziness, two noted dyspnea, and pulmonary embolus occurred in the fourth.

- **Deaths on Study**

A total of 46 deaths were reported for this trial, including 37 from progression of breast cancer alone, and 9 from other causes. Eight deaths from breast cancer and six deaths from other causes occurred during treatment or within 2 weeks of stopping treatment. Twenty-nine deaths from breast cancer and three deaths from other causes occurred after the 2-week follow-up period.

The six deaths from other causes that occurred during treatment or within 2 weeks of stopping treatment were due to adverse events: intracranial hemorrhage, respiratory failure, or infarction of the small intestine (3 patients on 1 mg anastrozole), cardiac arrest (1 patient on 10 mg anastrozole), and cardiac arrest or pulmonary embolus (2 patients on megestrol acetate). Only the case of pulmonary embolus with megestrol acetate was considered by the investigator to be probably related to treatment.

Three additional patients died from other causes after the 2-week follow-up period due to kidney failure, suicide, and heart failure. All were treated on the 10 mg anastrozole arm.

No predominant cause of death other than breast cancer was identified in any of the treatment groups.

- **Laboratory Abnormalities**

There were no significant changes from study entry in mean white blood cell count, hemoglobin, and platelet count, and mean values were similar across treatment groups. The most frequently reported abnormality was anemia (defined as a decrease in hemoglobin of ≥ 3 g/dl, or any value < 9.5 g/dl) noted in 5% of patients, but this was considered to be disease-related rather than treatment-related.

There were no significant changes from study entry in mean values of alkaline phosphatase, AST, ALT, LDH, cholesterol, and sodium, and mean values were similar across treatment. Cholesterol values were high at entry for all groups and remained high during the trial (defined as $\geq 30\%$ of the ULN). No adverse events were related to cholesterol levels. Elevated alkaline phosphatase levels were universally related to bone disease; only two treatment-related elevations in alkaline phosphatase levels were noted (i.e., $\geq 3 \times$ ULN, in 1 patient each on the 1 mg anastrozole and megestrol arms). No effects on serum sodium or potassium levels suggestive of drug-induced glucocorticoid or mineralocorticoid effects were noted in this trial.

Mean body weight was similar for each group at study entry. Weight gain of 5% or more was experienced by 43 (34%) of patients on megestrol acetate; gains of 10% or more by 12 (9%) of patients on megestrol acetate. For anastrozole, weight gain of 5% or more occurred in 12% (1 or 10 mg doses), weight gain of 10% or more in only 2-4%. Mean blood pressure and pulse rate were similar in all groups at entry and during the trial.

4.25 Sponsor's Conclusions Regarding Trial 0004

There was no statistically significant difference between 1 mg or 10 mg anastrozole once daily or 40 mg megestrol acetate four times daily in any of the primary efficacy endpoints (time to progression, objective response rate, or time to treatment failure). The 1 mg anastrozole arm was associated with better physical scores in quality of life assessments, and both the 1 and 10 mg anastrozole arms were associated with better psychological scores than megestrol acetate.

All three treatments were well-tolerated. Hot flushes were more frequent in the 1 mg anastrozole arm, whereas headache, nausea, and bone pain were more common in the 10 mg anastrozole arm.

The efficacy and safety of anastrozole supports its use for the treatment of advanced breast cancer in postmenopausal women who have failed tamoxifen.

4.2 1033IL/0005

4.21 Protocol Review

Title: A Randomized Open, Multicenter [illegible] and Safety Study to Evaluate Arimidex™ (ZENECA ZD1033, 1 and 10 mg) Compared [illegible] Megestrol Acetate in Postmenopausal Women with Advanced Breast Cancer

Principal Investigator: W. Jonat, MD [illegible] Frauenklinik Eppendorf, Hamburg, Germany

Study Dates: 4/22/93 - 6/24/94
Data Cut-off Date: 9/15/94

- **Review of Protocol Amendments**

A total of 40 patients were accrued to the original protocol prior to any amendments taking effect. The first protocol amendment (6/[illegible]/94) addressed patient inclusion and exclusion criteria, and monitoring of adverse events and quality of life. Postmenopausal status was redefined as having FSH levels > 40 IU/L, instead of > 30 IU/L. Exclusion criteria were amended such that patients with "exposure to more than one previous cytotoxic chemotherapy regimen for advanced disease" would not be enrolled. After withdrawal from the study, patients would be monitored for adverse events for 2 weeks (instead of 4 weeks). Analgesic use scores, bone pain scores, and performance status scores would be assessed at baseline, week 4, 8, 12, 24, and every 12 weeks thereafter, instead of at every visit. A total of 334 patients were accrued after this amendment was adopted. **Comment:** *Four patients are not accounted for in the sponsor's listing of patient accrual relative to each protocol amendment.*

The second protocol amendment (10/5/94) dealt with blood sampling procedures and issues related to drug packaging and storage.

- **Study Design**

This was a phase 3, parallel-group, multicenter trial in postmenopausal patients with advanced breast cancer. Patients were randomized to receive either anastrozole 1 or 10 mg once daily (double-blind) or open-label megestrol acetate 40 mg four times daily.

- **Objectives**

The primary objectives were the same as for Trial 0003. These were to compare two dosages of anastrozole (ZD1033), 1 mg and 10 mg once daily, with megestrol acetate (MEGACE™, Bristol-Myers Squibb) 40 mg four times daily on the following parameters: time to disease progression, tumor response, safety and tolerability. The secondary objectives were to compare treatment groups with respect to time to treatment failure, duration of response, quality of life in the first

year of treatment, and survival

- **Patient Population**

The inclusion and exclusion criteria are similar to those of Trial 0004 and provided in the appendix. In summary, eligible patients were postmenopausal women with advanced breast cancer who were eligible to receive hormonal treatment because of: disease progression while receiving **or after completing a course of** tamoxifen (NOLVADEX™) as adjuvant treatment, or progression while on tamoxifen or other antiestrogens for advanced disease. Patients could not have had prior exposure to more than one cytotoxic regimen for advanced disease (Amendment 1, 6/15/93) or more than one previous hormone therapy for advanced disease.

Post-menopausal status, baseline WHO performance status and estimated survival was defined as in Trial 0004. Patients with estrogen receptor-negative advanced disease were excluded unless the patient showed an objective response to prior tamoxifen therapy. **Estrogen receptor-negative patients receiving adjuvant treatment were excluded.** Patients with life-threatening visceral disease were excluded. **Comment:** *Areas in bold indicate eligibility criteria that differ in this trial as compared to Trial 0004. In addition, this trial does not stipulate the minimum duration of tamoxifen therapy patients must have had prior to relapse. This was three months in Trial 0004.*

- **Procedure**

A target number of 360 evaluable patients was recruited. Patients were allocated on a 1:1:1 basis within each center, to oral treatment with 1 mg anastrozole daily, 10 mg anastrozole daily, or 40 mg megestrol acetate four times daily. ZENECA assigned treatment in balanced blocks of six according to computer-generated randomization schemes produced for each center.

An independent data monitoring committee was comprised of three experts not employed by ZENECA (two clinicians, one from the US and one from Europe, and one statistician). The committee met on 5/3/94 to review an interim analysis of efficacy and safety for this trial and Trial 0004 and recommended that a second interim analysis be performed but that the two trials continue unchanged.

Anastrozole was supplied as film-coated, white tablets in blister packs containing 7, 14, or 28 tablets of the predetermined dose (either 1 mg or 10 mg). For the first 24 weeks, patients assigned to anastrozole were given 2-month supplies of medication (enough for 8 weeks plus a 2-week surplus); beyond 24 weeks, patients were given 3-month supplies (enough medication for 12 weeks plus a 4-week surplus). Patients were instructed to take one anastrozole tablet at approximately the same time of day, with or without food.

Patients randomized to treatment with megestrol acetate received the commercially available product packaged in amber glass bottles, each containing 100 tablets. For the first 24 weeks,

patients assigned to megestrol acetate were given 2-month supplies (enough medication for 8 weeks plus a 19 day surplus); beyond 24 weeks, patients were given 3-month supplies (enough for 12 weeks with a 16-day surplus). Patients were instructed to take one tablet at 0800 hr, 1200 hr, 1600 hr and 2000 hr, with or without food.

Each time medication was dispensed, a tear-off label from the box or bottle was attached to the patient's prescription record card as a record of drug assignment. Patients were required to return unused tablets at each visit to assess compliance.

- **Efficacy Assessments**

Screening assessments were carried out within 4 weeks of randomization, including identification of measurable and nonmeasurable disease, quality of life assessments using the Rotterdam Symptom Checklist, bone pain scores, and documentation of analgesic use, and determination of baseline estradiol levels. Oral or written consent was obtained from the patients.

Efficacy assessments including, tumor measurements, performance status, analgesic use and bone pain, and estradiol levels, were carried out at each patient visit (every 4 weeks for the first 24 weeks, then every 12 weeks). The Rotterdam Symptom Checklist was performed every 12 weeks until death or disease progression, up to 1 year. An item "weight changes" was added to the standard questionnaire. After disease progression, only survival was recorded at 6-month intervals. Radiotherapy for control of bone pain or for other reasons was permitted. Irradiated lesions were only used to assess progression.

Time to disease progression, objective responses, duration of response, and time to treatment failure were defined as in Trial 0004. Cranial and liver MRI scans were not used to assess metastatic disease in this trial.

- **Quality of Life Assessments**

The Rotterdam Symptom Checklist (RSCL) was completed less frequently by the patients in this trial during the first 24 weeks (every 12 weeks instead of every 4 weeks). The instrument evaluated the same physical, psychologic, and functional dimensions, with the addition of "weight changes". Scoring of the RSCL, analgesic use, bone pain, and performance status (using the WHO scale) was the same for both controlled trials. Weight change was scored from 0 to 3, higher scores indicating worse problems due to weight.

- **Safety Assessments**

Safety assessments including adverse events, physical findings, and laboratory testing, were carried out at each patient visit (every 4 weeks for the first 24 weeks, then every 12 weeks). The original protocol stipulated that adverse events would be monitored until 4 weeks after withdrawal of trial treatment. This was amended to 2 weeks (Amendment 1, 6/15/93).

- **Statistical Plan**

The estimation of sample size was based on time to disease progression and objective response rate. Assuming a median time to progression of 26 weeks, a total of 300 patients (100 in each arm), recruited at a uniform rate over 12 months, with a minimum follow-up of 6 months, would be sufficient to detect a treatment difference of 14 weeks, with 80% power and a significance level of 0.05 (two-sided). Assuming an objective response rate of 25%, a treatment difference of 20% would be statistically detectable with 90% power (significance level of 0.05, two-sided).

Efficacy analyses were carried out on an intent-to-treat basis using methodologies outlined above for Trial 0004. Anastrozole 1 mg and 10 mg were each compared to megestrol acetate.

4.22 Demography, Withdrawals, and Protocol Violations and Deviations

A total of 378 patients from 73 centers in Europe, Australia, and South Africa were included in this trial. Thirty-one centers accrued ≥ 5 patients each for a total of 289 (76%) patients; the remaining 42 centers accrued < 5 patients each for a total of 89 (24%) patients. Altogether, 135 patients were randomized to receive 1 mg anastrozole, 118 to receive 10 mg anastrozole, and 125 to receive megestrol acetate. Two patients on the 10 mg anastrozole arm and one patient on the 1 mg anastrozole arm never received treatment. At the time of data cut-off (9/15/94), 168 (44%) patients were still on treatment. **Comment:** *Patient accrual to the study averaged 20 patients per month for the first two months, then twenty-five patients per month for the remaining 13 months. Among centers accruing 5 or more patients, 3 of 31 enrolled patients only in the last six months of the study (in 1994 only). Among centers accruing less than 5 patients, 10 of 42 centers accrued patients only in 1994 (4 enrolled 2-3 patients each, 6 enrolled one patient each).*

The median age of patients enrolled on this trial was 65 (range and 98% of patients were Caucasian. Estrogen receptor status was unknown in 37% of patients, while 58% had ER+ disease and 5% had ER- disease. The WHO performance status at study entry was 0-1 in 85%. These parameters were balanced across treatment groups. Hormonal therapy had been administered as adjuvant therapy in a total of 164 (43%) patients, and for advanced disease in 193 (51%) patients. In addition, there were 21 patients who received hormonal therapy both adjuvantly and for advanced disease.

The duration of tamoxifen therapy was calculated by using the start and stop dates of tamoxifen treatment. (For this analysis, 3, 4, and 1 patient per arm, respectively, were excluded because of data missing required for the calculation of duration of tamoxifen treatment, or because tamoxifen therapy was not recorded.) The median duration of adjuvant tamoxifen therapy was 27 months for the 1 mg anastrozole arm, 28 months for the 10 mg anastrozole arm, and 32 months for the megestrol arm. The median duration of tamoxifen therapy for advanced disease was 22 months for the 1 mg anastrozole arm, and 23 months for the 10 mg anastrozole and megestrol arms. The best response to prior tamoxifen treatment for advanced disease was CR in 14%, PR in 28%, stable disease in 43%, progression in 14%, and unknown in 2%. Other prior treatments for

breast cancer in these patients were: surgery in 90%, chemotherapy in 28%, and radiotherapy in 61%.

Measurable disease was noted in 79% of patients, while 21% had nonmeasurable disease. Sites of metastatic disease were bone in 59%, soft tissue in 43%, and visceral in 47%. Only 19% had liver metastases. Mixed sites of disease were noted in 41%. Four patients had no evaluable sites of metastasis, due to prior excision or irradiation of known sites of distant disease in 3 cases and no evaluable disease in a fourth. There were no differences observed across treatment groups.

Comparison of Baseline Patient Characteristics Among Centers:
In order to evaluate potential baseline patient differences among participating centers, centers accruing ≥ 5 patients each, so-called "large centers", were compared to those accruing < 5 patients each, so-called "small centers". The following clinical features were reviewed: patients' hormonal status at study entry, previous response to tamoxifen for advanced disease, presence of measurable disease at entry, and extent of disease at entry. For the most part, centers were well balanced in baseline patient characteristics across treatment groups. Notable exceptions to this occurred in the following comparisons. There were proportionately more ER+/PR+ patients accrued in the "small centers" as compared to the "large centers" for two of the arms: 61% vs. 32% for 1 mg anastrozole, and 56% vs. 35% for megestrol. On the other hand, there were proportionately fewer patients entered on the megestrol arm in "small centers" who had previously responded to tamoxifen: 15% vs. 42%. Extent of disease was fairly well balanced across centers except for a higher proportion of patients with visceral only disease at "small centers" in the 1 mg anastrozole arm: 32% vs. 16%.

A total of 208 patients withdrew from treatment: 163 due to disease progression, 15 due to death, 14 due to adverse event or concurrent illness, 4 due to patient refusal or lost follow-up, 10 due to other reasons, and 2 due to protocol noncompliance.

A total of 14 protocol violations were noted in 13 patients. All patients considered to be protocol violations were still included in analyses of efficacy and safety. Seven patients were not candidates for hormonal treatment as defined in the protocol, 2 patients were not confirmed to be postmenopausal, 1 patient had a WHO score > 2 although their debilitation was not directly related to breast cancer, 1 patient received concurrent therapy with other experimental drugs, 1 patient had brain metastases, and 2 patients had ER- disease with no demonstrated response to adjuvant tamoxifen therapy. **Comment:** *The distribution of patients with protocol violations was: 2% in the 1 mg anastrozole arm, 8% in the 10 mg anastrozole arm, and 2% in the megestrol acetate arm. The frequency of protocol violations was comparable among "large centers" and "small centers".*

A total of 355 protocol deviations occurred in 225 patients. These consisted primarily of baseline or follow-up assessments that were either absent or performed at incorrect times or both. Thirty patients received concurrent therapy with disallowed medications, including tamoxifen, bisphosphate, or steroids. Patient was randomized to receive anastrozole 1 mg but

actually received 10 mg; this patient was included in the efficacy analysis for the 1 mg arm and in the safety analysis for the 10 mg arm. Two patients received incorrect anastrozole doses for one dispensing period (patients). No patient was excluded from the analysis of efficacy and safety, except for patients who never received treatment (excluded from safety analysis). **Comment:** *The distribution of patients with protocol deviations was: 55% for 1 mg anastrozole, 57% for 10 mg anastrozole, and 66% for megestrol acetate. The frequency of protocol deviations was comparable among "large centers" and "small centers".*

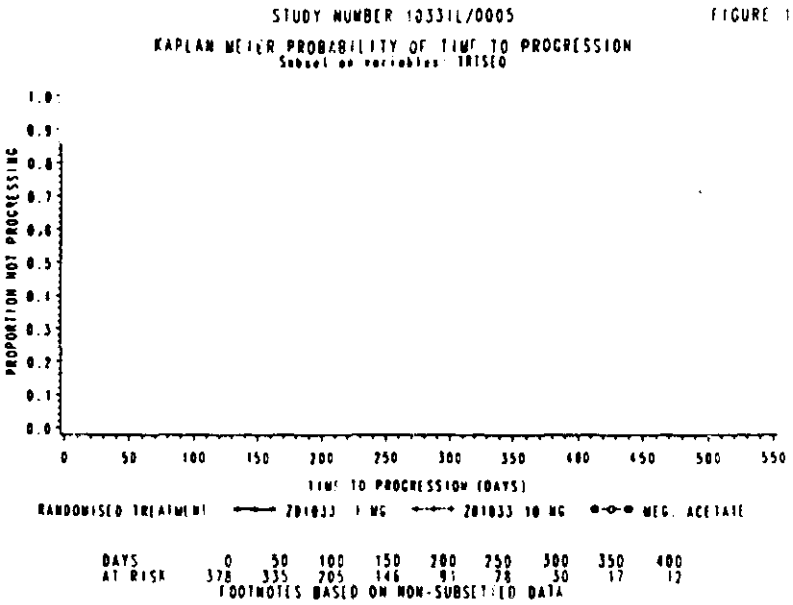
4.23 Efficacy Results

The median duration of study treatment was 137 days (5-513 days) for the 1 mg anastrozole arm, 139 days (11-485 days) for the 10 mg anastrozole arm, and 120 days (10-459 days) for the megestrol acetate arm. The median duration of follow-up was 192 days for the 1 mg anastrozole arm, 185 days for the 10 mg anastrozole arm, and 182 days for megestrol acetate. **Comments:** *1) The duration of treatment is comparable in the two controlled trials. 2) Calculation of all efficacy endpoints (i.e., time to progression, response duration, time to treatment failure, and time to death) were calculated from the date of randomization. Scatter plot analysis of date of randomization vs. date treatment was started shows that these dates coincide for the vast majority of patients. In fact, these often were either the exact same date or one day apart (see Appendix). 3) The extent of patient follow-up after documentation of progression or treatment failure is demonstrated in scatter plots (progression date vs. last alive date, and date of treatment failure vs. last alive date) in the Appendix. The duration of patient follow-up is comparable in the two controlled trials.*

- **Time to Disease Progression**

A total of 82 (61%) patients treated with 1 mg anastrozole, 66 (56%) patients treated with 10 mg anastrozole, and 78 (62%) patients treated with megestrol acetate had disease progression during treatment or after treatment withdrawal. In addition, there were 20 additional patients (8, 5, and 7 per arm, respectively) who died before disease progression was documented; the date of death was used to calculate the time to progression in these patients. Thus, a total of 246 patients contributed to the analysis of time to progression with 132 (35%) patients censored. Median times to progression were: 132 days for patients treated with 1 mg anastrozole, 156 days for patients treated with 10 mg anastrozole, and 120 days for patients treated with megestrol acetate.

Comparison of 1 mg anastrozole with megestrol acetate revealed a hazard ratio of 1.04 (CI: 0.74-1.46, p= 0.82). The hazard ratio for the comparison of 10 mg anastrozole with megestrol acetate was 0.84 (CI: 0.58-1.22, p= 0.30). There was no statistical difference between either dose of anastrozole and megestrol acetate. See Kaplan-Meier plot below.



Subgroup Analysis. The tables below show the rate of disease progression (by patient) by prior hormonal treatment (adjuvant vs advanced disease) and by estrogen receptor status (positive, unknown, negative) at study entry.

Disease Progression by Patient

Treatment Arm	Prior Hormonal Therapy	
	Adjuvant	Advanced
Anastrozole 1 mg	43/66 (65%)	39/69 (57%)
Anastrozole 10 mg	28/46 (61%)	38/72 (53%)
Megestrol Acetate 40 mg	37/52 (71%)	41/73 (56%)
All Patients	108/164 (66%)	108/193 (56%)

Treatment Arm	Estrogen Receptor Status		
	Positive	Unknown	Negative
Anastrozole 1 mg	52/84 (62%)	26/46 (57%)	4/5 (80%)
Anastrozole 10 mg	35/64 (55%)	24/46 (52%)	7/8 (88%)
Megestrol Acetate 40 mg	47/72 (65%)	28/48 (58%)	3/5 (60%)
All Patients	134/220 (61%)	78/140 (56%)	14/18 (78%)

Comments: *1) The rate of disease progression among patients who received hormonal therapy adjuvantly was somewhat higher compared to that of patients who received hormonal therapy for advanced disease. This was most pronounced for the megestrol arm. 2) Among ER+/PR+ patients, rates of disease progression were: 63% (34/54) for 1 mg anastrozole, 54% (21/39) for 10 mg anastrozole, and 65% (32/49) for megestrol; these were identical to those reported above for all ER+ patients. 3) The ER unknown group (37% of all patients enrolled) likely contained many ER+ patients, given the disease progression rates above. 4) A greater proportion of patients with ER- disease progressed on study, although the patient numbers were very small.*

Reviewer's Assessment of Time to Progression:
1) The time to progression was confirmed for all randomized patients. Dates of first observed progression were available for the 226 patients progressing either during treatment or after treatment withdrawal (Table G4.4).

2) Twenty of the 246 patients used in the sponsor's analysis of time to disease progression died before progression was formally documented as per protocol. Twelve of these patients in fact died of disease progression at 12, 21, 24, 24, 38, 56, 59, 77, 121, 141, 148, and 152 days. The reviewer questions the rationale for including the remaining eight patients:

died of respiratory/cardiac failure at 90 days
died of unknown causes, probably cardiac, at 120 days
died of pneumonia at 31 days
died of stroke at 125 days
died of stroke at 272 days
died of pneumonia at 26 days
died of intestinal perforation at 38 days
died of cardiac arrest at 141 days.

Exclusion of either the entire 20 patient subset or the 8 patient subset does not alter time to progression significantly (see additional Kaplan-Meier plots in Appendix).

3) Treatment was continued for several of the patients following first documentation of disease progression (see scatter plot of progression date vs. date treatement stopped in the Appendix).

- **Objective Response Rate**

Objective responses were assigned using UICC criteria Bidimensionally measurable disease was noted in > 75% of patients; only 4 patients had assessments made on the basis of unidimensional lesions Objective responses for all randomized patients were similar across treatment groups. In the 1 mg anastrozole arm, there were 2 CRs and 12 PRs for an overall response rate of 10.4%. In the 10 mg anastrozole arm, there were 3 CRs and 12 PRs for an overall response rate of 12.7%. In the megestrol acetate arm, there were 3 CRs and 10 PRs for an overall response rate of 10.4%. The proportion of patients with a best response of stable disease for at least 24 weeks was similar

across treatment groups (21-24%).

Comparison of 1 mg anastrozole with megestrol acetate revealed an odds ratio of 0.99 (CI: 0.40-2.50, p= 0.99). The odds ratio for the comparison of 10 mg anastrozole with megestrol acetate was 1.28 (CI: 0.51-3.20, p= 0.54). There was no statistical difference between either dose of anastrozole and megestrol acetate.

For patients with measurable disease, the overall response rates (CRs + PRs) were: 11.9% for 1 mg anastrozole, 15.7% for 10 mg anastrozole, and 11.1% for megestrol acetate. Stable disease lasting $\geq$ 24 weeks was noted in 20%, 21% and 18%, respectively. Among patients with nonmeasurable disease there were four CRs and 26 patients with disease stabilization lasting $\geq$ 24 weeks; these responses were noted in 42% of patients in the 1 mg anastrozole arm, 24% of patients in the 10 mg anastrozole arm, and 46% of patients in the megestrol acetate arm.

Subgroup Analysis. The tables below show the objective response rates in patients by prior hormonal treatment (adjuvant vs advanced disease), by estrogen receptor status (positive, unknown, negative), and by disease site (soft tissue only, bone only, visceral only).

Objective Response Rate

Treatment Arm	Prior Hormonal Therapy	
	Adjuvant	Advanced
Anastrozole 1 mg	8/66 (12.1%)	6/69 (8.7%)
Anastrozole 10 mg	4/45 (8.9%)	11/71 (15.5%)
Anastrozole 40 mg	6/52 (11.5%)	7/73 (9.6%)

Treatment Arm	Estrogen Receptor Status		
	Positive	Unknown	Negative*
Anastrozole 1 mg	9/84 (10.7%)	5/46 (10.9%)	0/5
Anastrozole 10 mg	7/64 (11.0%)	7/46 (15.2%)	1/7 (14.3%)
Megestrol Acetate 40 mg	9/72 (12.5%)	4/48 (8.4%)	0/5

*Partial response only

Objective Response Rate

Treatment Arm	Site of Metastatic Disease		
	Soft Tissue Only	Bone Only	Visceral Only*
Anastrozole 1 mg	7/15 (46.7%)	1/30 (3.3%)	2/28 (7.1%)
Anastrozole 10 mg	8/22 (36.4%)	1/29 (3.4%)	0/17
Megestrol Acetate 40 mg	6/25 (24%)	2/36 (5.6%)	1/16 (6.3%)

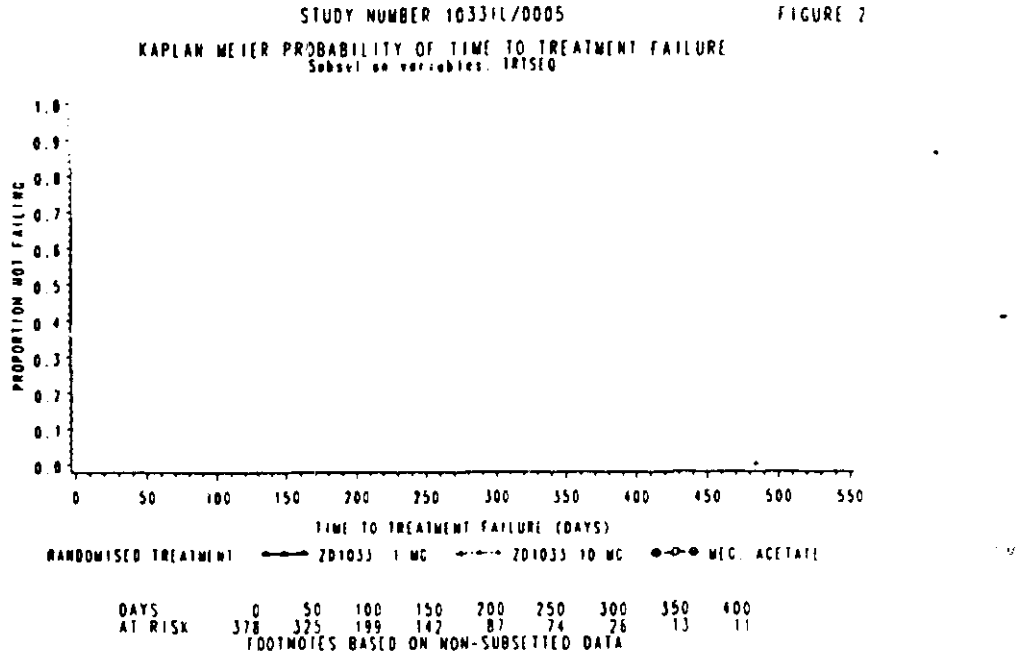
*Partial responses only

Comments: *1) There do not appear to be any major differences in objective response rates among patients who received hormonal therapy adjuvantly or for advanced disease. 2) Response was associated with ER+ status and with soft tissue involvement. Responses in the subset of patients with ER+/PR+ disease were 9.3%, 12.9%, and 10.2% for each arm respectively; these were similar to response rates for all ER+ patients noted above. Responses in the subset of patients with ER+/soft tissue only disease were: 25% (2/8) for 1 mg anastrozole, 30% (3/10) for 10 mg anastrozole, and 35.7% (5/14) for megestrol; these rates were somewhat less than what was observed for anastrozole, soft tissue only, and somewhat better for megestrol, soft tissue only, as shown in the table above. Differences may be due to the small numbers of patients with soft tissue only disease in these subsets. 3) While objective responses in patients with bone only or visceral only disease were low across treatment groups, 47%, 17%, and 33% of patients in each arm respectively had stabilization of disease $\geq$ 24 weeks at bone sites. For visceral sites, stabilization was observed in 36%, 26%, and 25% of patients in each arm respectively. 4) Among patients whose best response to previous tamoxifen had been CR or PR, response rates were 16% for each of the anastrozole arms and 11.1% for the megestrol arm. There were two responders, one on each of the anastrozole arms, whose best response to previous tamoxifen had been disease progression.*

Reviewer Assessment of Objective Response Rate:
1) Objective responses were confirmed for the 8 CRs and 34 PRs in this trial.

2) Complete responses occurred in soft tissue lesions (skin or lymph nodes) in 4 patients, in non-measurable bone lesions in 4 patients, and in nonmeasurable liver disease in 1 patient. Partial responses occurred in these same sites as well as in breast and lung.

3) Partial responses in two patients were based on nonmeasurable disease: lymph node metastases measuring < 2 cm (0036/0011 on megestrol and 0097/0003 on 1 mg anastrozole). As per protocol, responses in these patients could not be designated PRs. In two other patients the response observed was not confirmed 4 weeks later (0012/0003 on 1 mg anastrozole and 0051/0007 on megestrol). Exclusion of these patients from the group of responding patients, does not alter response rates appreciably.

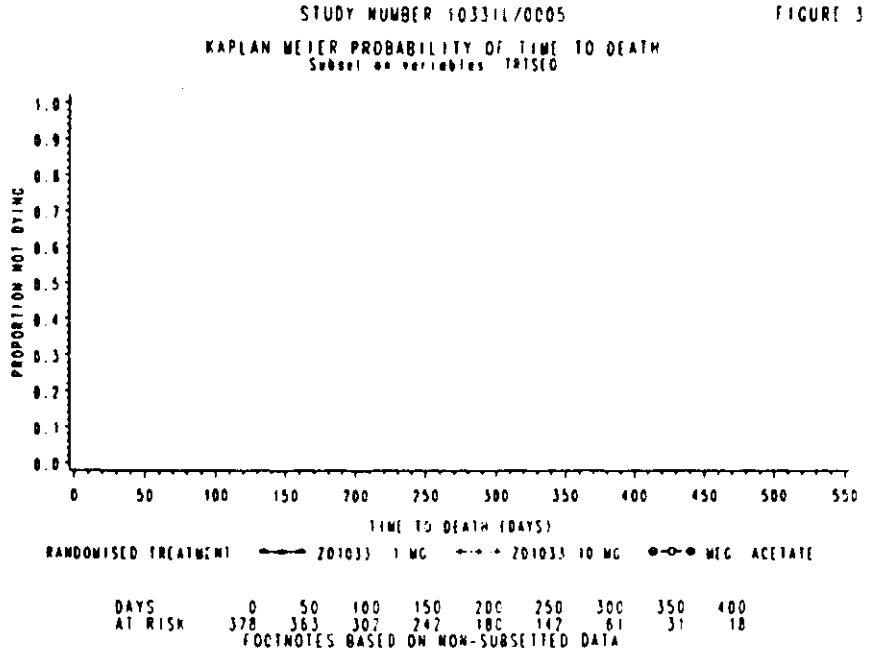


Reviewer's Assessment of Time to Treatment Failure:
1) The time to treatment failure was confirmed for all randomized patients. Dates of treatment failure were available for the 262 patients failing treatment after randomization (Table G4.4). The three patients who never received treatment were assigned a time to treatment failure of 0 days The remaining 116 (31%) patients were censored for analysis of this endpoint.

2) Treatment was continued for several of the patients following documentation of treatment failure (see scatter plot of date of treatment failure vs. date treatment was stopped in the Appendix).

- **Time to Death**

A total of 21 patients treated with 1 mg anastrozole, 22 patients treated with 10 mg anastrozole, and 28 patients treated with megestrol acetate died. Median time to death for patients on the 1 mg anastrozole or megestrol acetate arms could not be calculated because of the low number of deaths. The median time to death for patients on the 10 mg arm was 442 days. **Comments:** *Scatter plots demonstrate the timing of patient deaths following first documentation of progression or treatment failure (see progression date vs. date of death, and date of treatment failure vs. date of death in the Appendix). The sponsor plans to submit an updated survival analysis in September 1995.*



Comparison of 1 mg anastrozole with megestrol acetate revealed a hazard ratio of 0.72 (CI: 0.38-1.37, p= 0.25). The hazard ratio for the comparison of 10 mg anastrozole with megestrol acetate was 0.85 (CI: 0.44-1.62, p= 0.57). There was no statistical difference between either dose of anastrozole and megestrol.

Comparison of Efficacy Results Across Centers:

The "large centers" (accruing ≥ 5 patients each) and "small centers" (accruing < 5 patients each) were compared in terms of patient progression status, best overall response, reasons for treatment failure, and survival status. In general, centers were well balanced in these parameters across treatment arms with the following exceptions. The proportion of patients alive without progression was lower on the megestrol arm for "small centers" (19% vs. 36%), with 78% of patients in this arm progressing on treatment. At "large centers", 54% of patients progressed on treatment. (Recall that "small centers" had relatively few patients on the megestrol arm who had previously responded to tamoxifen.) Despite these differences, the overall death rate in the megestrol arm in "small centers" was in fact slightly lower than that observed in "large centers": 19% vs. 24%. In the 1 mg anastrozole arm, the death rate in "small centers" was only 8% (3/38) vs. 19% (18/97) in "large centers".

Protocol Violations/Deviations Among Responders:

The 42 responding patients in Trial 0005 included 28 with one or more protocol deviations. Sufficient information was not provided to infer that these events bore no relation to the assessment of efficacy endpoints in these patients. Since many of the deviations were due to absent follow-up assessments, it is possible that determination of disease progression could have been hampered in some patients. For example, patient a CR on 10 mg anastrozole

had study drug interrupted for an unknown length of time. Patient a PR on megestrol acetate also took bisphosphate which could have affected bone pain scores and analgesic use.

- **Quality of Life Assessments**

The completion rate of the RSCL questionnaires at study entry was ≥ 90% of expected, but ranged from 73-82% for weeks 12 and 24. Physical and functional quality of life at weeks 12 and 24 was similar for patients across treatment groups. Psychological quality of life at week 12 was better for patients treated with megestrol acetate than for patients on the 1 mg or 10 mg anastrozole arms (p= 0.0077 and p= 0.0019 respectively). However, there was no difference at week 24.

Results of the additional question on "weight changes" showed that patients were bothered by weight changes "a little" across treatment groups at weeks 12 and 24, except for the patients on the 10 mg anastrozole arm at week 24 (not bothered at all).

Comment: *Comparisons between treatment arms were based on the numbers of patients listed below. There were comparable numbers of patients in each arm evaluated for each of the three RSCL domains. There were roughly half as many patients evaluable at week 24 as in week 12. The dropout rate for patient responses to "weight change" was comparable to that for the RSCL domains given below for each of the treatment groups.*

Treatment Arm	Patients with Entry and Week 12 Data			Patients with Entry and Week 24 Data		
	Phys	Psychol	Funct	Phys	Psychol	Funct
Arimidex 1 mg (N=135)	87	87	87	49	49	50
Arimidex 10 mg (N=118)	79	76	78	43	43	42
Megace 40 mg (N=125)	76	76	76	47	47	47

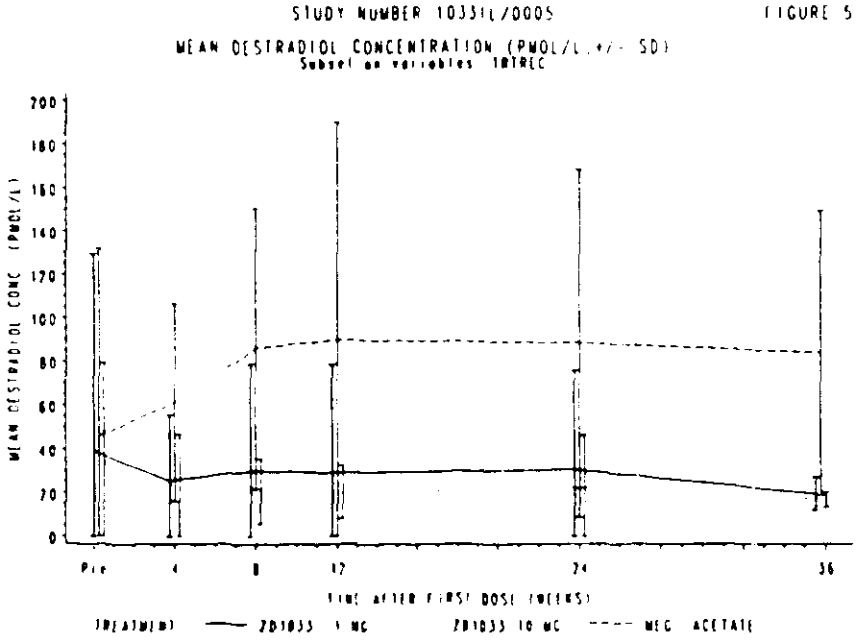
There was no difference in analgesic use across treatment groups. Bone pain scores favored both anastrozole arms over megestrol acetate at week 12 (p= 0.0602 and p=0.0105 respectively), however there was no difference across treatment groups at week 24. WHO performance status scores favored both anastrozole arms over megestrol acetate at week 12 (p= 0.0069 and 0.0702 respectively), but only the 1 mg anastrozole arm at week 24 (p=0.0457).

Comment: *Comparisons between treatment arms were based on the numbers of patients listed below. There were comparable numbers of patients in each arm evaluated for analgesic use, bone pain score and WHO performance status. Again, there were roughly half as many patients evaluable at week 24 as in week 12.*

Treatment Arm	Patients with Entry and Week 12 Data			Patients with Entry and Week 24 Data		
	Analgesic	Bone Pain	WHO PS	Analgesic	Bone Pain	WHO PS
Arimidex 1 mg (N=135)	124	124	119	53	53	53
Arimidex 10 mg (N=118)	106	106	118	52	52	52
Megace 40 mg (N=125)	114	114	116	48	48	48

- **Endocrine Assessments**

Serum estradiol concentrations were performed using a commercially available assay and were used as a measure of compliance. In both anastrozole groups, mean estradiol concentrations were suppressed over baseline levels to a similar extent. Mean estradiol levels were increased over baseline levels in patients on the megestrol acetate arm.



- **Sponsor's Conclusions on Efficacy Results**

As in Trial 0004, there was no statistical difference between anastrozole 1 or 10 mg daily and megestrol acetate 40 mg four times daily in time to disease progression, objective response rate, or time to treatment failure

The response rates in this trial were lower than those reported in the literature for megestrol acetate, due in part to the nature of the patients enrolled (having prior hormonal therapy and chemotherapy, and only one-third with soft tissue only disease) and the strict interpretation of objective responses. All treatment groups had a similar percentage of patients with a best response of stable disease of 24 or more weeks (ranging from 22-24%).

4.24 Safety Results

Drug-related events that occurred in any treatment group in at least 3% of patients are summarized below. Further detail regarding the safety profile of anastrozole is provided in reviews of the Integrated Summary of Safety and of the 4-Month Safety Update in Section 6.

Headache, pain, hot flushes, nausea, dizziness, somnolence and rash occurred in all treatment groups and were not considered serious

Weight gain was more common in patients treated with megestrol acetate (8.0%) than in patients treated with anastrozole (2.2% for 1 mg, 1.7% for 10 mg). Similarly, peripheral edema and dyspnea were more common with megestrol acetate (4.0% and 5.6%) than with anastrozole (1 mg: 0.7% and 1.5%; 10 mg: 0.9% and 0). Hypertension and vaginal hemorrhage were also observed more commonly with megestrol acetate (3.2% for each) as compared to anastrozole (1 mg: 0 and 0.7%; 10 mg: 0.9% for each)

- **Treatment Withdrawals**

Adverse events lead to treatment withdrawal in a total of 14 patients. Four patients withdrew from the 1 mg anastrozole arm: one each with vomiting, dyspnea; allergic syndrome; and obstructive jaundice. Four patients withdrew from the 10 mg anastrozole arm: one each with dyspnea; hypercalcemia and pancytopenia, fever and headache, and leg edema and rash. Six patients withdrew from the megestrol acetate arm: one each with nausea and vomiting; conjunctivitis, nausea, diarrhea, rash, bleeding gums, pain of the mouth and ears; hot flushes; dyspnea and hyperglycemia; stroke; and pulmonary embolus

- **Deaths on Study**

A total of 71 deaths were reported, including 58 from progression of breast cancer alone, and 13 from other causes. Ten of the 13 deaths from other causes were due to adverse events occurring during treatment or within the 2-week follow-up period and were due to stroke, or bowel perforation (1 mg anastrozole), to renal failure (10 mg anastrozole), and to pneumonia (4 patients), stroke, cardiac arrest, or sudden death (megestrol acetate). These adverse events were not considered by the investigators to be related to treatment

Three other patients died of causes other than breast cancer after the 2-week follow-up period, two in the 1 mg anastrozole arm, and one in the 10 mg anastrozole arm

- **Laboratory Abnormalities**

There were no significant changes from study entry in mean white blood cell count, hemoglobin, and platelet count, and mean values were similar across treatment groups. Anemia (defined as a decrease in hemoglobin of $\geq$ 3 g/dl or any value < 9.5 g/dl), was noted in 6% of patients on the 10 mg anastrozole and megestrol acetate arms, but this was not considered treatment-related. Leukopenia (defined as WBC $\leq$ 2.8 x 10^9/l) or leukocytosis (defined as WBC $\geq$ 16 x 10^9/l) was observed in 7% of patients treated with 1 mg anastrozole. In many patients, the WBC abnormality was present at baseline and there was no definite trend in leukocyte abnormalities in any treatment group.

There were no significant changes from study entry in mean values of alkaline phosphatase, AST, ALT, gamma GT, LDH, cholesterol, sodium and calcium, and mean values were similar across treatment arms. Gamma-GT and alkaline phosphatase values were elevated in some patients at entry for all groups and remained elevated during the trial. These abnormalities were believed to be universally related to breast cancer rather than treatment.

Mean body weight was similar for each group at study entry. Weight gain of 5% or more was experienced by 44 (35%) of patients on megestrol acetate; gains of 10% or more by 15 (12%) of patients on megestrol acetate. For anastrozole, weight gain of 5% or more occurred in 13% (1 mg) and 16% (10 mg), weight gain of 10% or more in only 2%. Mean blood pressure and pulse rate were similar in all groups at entry and during the trial.

4.25 Sponsor's Conclusions Regarding Trial 0005

There was no statistically significant difference between 1 mg or 10 mg anastrozole once daily or 40 mg megestrol acetate four times daily in any of the primary efficacy endpoints (time to progression, objective response rate, or time to treatment failure). The 1 mg anastrozole arm was associated with better WHO performance status scores, the 10 mg anastrozole arm with less bone pain, and the megestrol acetate arm with better psychological scores in quality of life assessments. These effects were transient however.

All three treatments were well-tolerated. The incidence of adverse events that lead to treatment withdrawal was low (3-5%), and no particular event predominated in any of the treatment groups. More patients on megestrol acetate experienced events that lead to death (pneumonia in 4/8 cases); common adverse events were dyspnea, weight gain, peripheral edema, and vaginal hemorrhage. Mild to moderate nausea was common on both anastrozole arms. Hot flushes and thromboembolic events were uncommon in all groups

The efficacy and safety of anastrozole supports its use for the treatment of advanced breast cancer in postmenopausal women who have failed tamoxifen

5. Integrated Summary of Efficacy

5.1 Clinical Pharmacology Trials

Five clinical pharmacology trials were conducted to investigate the suppression of serum estradiol concentrations produced by a range of doses of anastrozole in either healthy male volunteers (Trial 0001), healthy postmenopausal women (Trials 0002 and 0009), or postmenopausal women with breast cancer (Trials 0003 and 0007). Trial 0007, an extension of Trial 0003, was a compassionate use trial to allow continued use of anastrozole in responding patients from Trial 0003. Three additional trials (0008, 0021, and 0023) were carried out to identify the no-effect dose in healthy postmenopausal women.

Plasma anastrozole concentrations increased proportionately with dose over the 1 to 20 mg dose range; clearance and half-life were independent of dose. Anastrozole was rapidly absorbed in fasted volunteers and slowly eliminated (plasma elimination half-life in postmenopausal women of approximately 40 to 50 hours). Food delayed the absorption of anastrozole only slightly. Steady-state concentrations were achieved by the tenth dose. After multiple doses of anastrozole, there was a 3- to 4-fold accumulation of anastrozole in plasma.

A no-effect single dose of anastrozole could not be reliably determined. Anastrozole doses of 0.5 mg or higher produced > 80% suppression of serum estradiol, measured using highly sensitive assays (limit of quantitation 3.0 or 3.67 pmol/l). Daily dosing with 0.5 and 1.0 mg anastrozole demonstrated that a greater number of patients treated with 1 mg had serum estradiol levels below the assay limit of quantitation, and lower post-treatment estradiol levels, although no statistical difference between the two doses was shown (Trial 0009). There were no significant effects on adrenal steroids or gonadotrophins. Cortisol and aldosterone responses to ACTH were not impaired.

In males, dose-related estradiol suppression was observed; anastrozole doses $\geq$ 7.5 mg produced a > 80% reduction in serum estradiol levels lasting at least 24 hours. Serum LH and FSH concentrations increased, likely due to hypothalamic aromatase inhibition (an expected finding).

Additional trials in special patient populations indicated that no dose adjustments would be necessary for subjects with either hepatic (Trial 0014) or renal impairment (Trial 0018). Plasma concentrations of anastrozole were 25-30% higher in volunteers with cirrhosis than in normal control subjects, and the elimination half-life was longer (53 vs. 41 hours). In contrast, plasma concentrations of normal subjects in other trials were similar to those of the cirrhotic volunteers in Trial 0014. In addition, plasma concentrations in breast cancer patients were similar in the presence or absence of hepatic dysfunction. In subjects with renal impairment, there was a small reduction in the renal clearance of anastrozole which did not alter the oral clearance. Plasma concentrations of anastrozole in subjects with renal dysfunction were similar to those seen in normal subjects in other trials.

A separate trial to investigate the pharmacokinetics of anastrozole in the elderly was not performed since the pharmacokinetics were fully characterized in postmenopausal women, the target population. In the controlled trial 0004, plasma levels showed no age-related trends. Based on these results, no dose adjustments are recommended for elderly patients.

Taken together, these findings supported the selection of the 1 mg dose for further investigation. Because duration of maximal suppression was greater than 24 hours after single and multiple 1 mg doses, once-daily dosing was employed. Given the degree of estradiol suppression observed in the clinical pharmacology trials, phase II trials were not conducted. It was believed that anastrozole would be at least as effective as other aromatase inhibitors for the treatment of advanced breast cancer in postmenopausal women. Therefore, two controlled trials, 0004 and 0005, were conducted comparing two doses of anastrozole with megestrol acetate. Doses of anastrozole were 1 mg, the lowest dose that gave maximal reduction in estradiol levels and 10 mg, a ten-fold higher dose previously shown to be well-tolerated.

5.2 Controlled Trials: Demographic Results

A total of 764 patients from 49 centers in North America and 73 centers in Europe, Australia, and South Africa were enrolled onto Trials 0004 and 0005. Overall patient demographic characteristics are compared across treatment groups within each trial and across trials in Table 1 below. **Comment:** *Note that patients who did not receive tamoxifen therapy or for whom duration of tamoxifen therapy could not be calculated are not included in Table 1 for the calculation of % of patients with "Prior Tamoxifen", "Duration of Prior Tamoxifen", and % of patients with "PR/CR to Prior Tamoxifen for Advanced Disease". Thus, 14 patients on 1 mg anastrozole, 18 on 10 mg anastrozole, and 3 patients on megestrol acetate are excluded.*

Comparison of Baseline Patient Characteristics in Trials 0004 and 0005:

1. The median duration of tamoxifen as adjuvant treatment ranged from two to four years. For each of the treatment groups in Trial 0005, the median disease-free interval on adjuvant tamoxifen therapy was several months shorter as compared to Trial 0004: 28 vs. 34 months for the 1 mg anastrozole arms, 28 vs. 40 months for the 10 mg anastrozole arms, and 32 vs. 47 months for the megestrol arms. Note that disease-free intervals in the 10 mg anastrozole and megestrol arms differ by one year or more. These differences may reflect differences in patient selection, or other unknown factors.

2. The median duration of tamoxifen treatment for advanced disease was roughly two years in all treatment groups in both trials

3. A greater proportion of patients had objective responses to prior tamoxifen therapy for advanced disease on Trial 0005 as compared to Trial 0004: 42% vs. 19% overall. Note that data regarding best response to prior tamoxifen were unknown for 34% of patients on Trial 0004 vs. 2% on Trial 0005

4. A smaller proportion of patients had ER+ disease on Trial 0005 as compared to Trial 0004: 58% vs. 81% overall. Note that data on ER status was unknown for 37% of patients on Trial 0005 vs. 14% on Trial 0004.

5. A smaller proportion of patients had prior chemotherapy on Trial 0005 as compared to Trial 0004: 28% vs. 43% overall.

6. A larger proportion of patients on Trial 0005 had measurable disease as compared to Trial 0004: 79% vs. 63% overall. Inclusion of more patients with nonmeasurable disease would dilute the partial response rate in an intent-to-treat analysis since PRs could not be assigned to such patients. On Trial 0005, only 1% of patients had no evaluable metastatic disease as compared to 5% of patients on Trial 0004.

7. Only 12% of patients on Trial 0004 and 15% of patients on Trial 0005 had soft tissue disease only, the site most likely to show an objective response with hormonal therapy.

8. Trial 0004 had a higher proportion of patients with protocol violations than Trial 0005 (9.3% vs. 3.4%). On the other hand, Trial 0004 had a lower proportion of patients with protocol deviations (43% vs. 60%).

5.3 Controlled Trials: Efficacy Results

Efficacy results for the two controlled trials are summarized in Table 2 below. Anastrozole appears to be as efficacious as megestrol acetate in the individual trials and when results of the trials are combined.

- **Time to Disease Progression**

In the sponsor's study reports, time to disease progression, the primary endpoint in the two controlled trials, was calculated from the date of randomization to the date of first documentation of disease progression or date of death. (Note that the protocol for Trial 0004 did not specify use of the date of death for the calculation of time to disease progression; the protocol for Trial 0005 did not specify either date of progression documentation or date of death.) The median duration of follow-up was approximately 6 months, and was similar across treatment groups and across trials.

Using the Cox proportional hazards model, comparisons of the 1 mg and 10 mg anastrozole doses vs. megestrol acetate were not significantly different with respect to time to progression (see below). The individual trial results were similar (see Review Sections 4.13 and 4.23).

Comparison of Trials 0004 and 0005: Time to Progression

Treatment	# Patients	# Events	Hazard Ratio	P value
1 mg A vs. M	A: 263	A: 159	0.97	0.76
	M: 253	M: 163	(0.75 - 1.24)	
10 mg A vs. M	A: 248	A: 146	0.92	0.47
	M: 253	M: 163	(0.71 -1.19)	

The upper confidence limit for the hazard ratio in the combined analysis is less than 1.25 for each comparison, indicating that the time to progression among women treated with anastrozole is unlikely to be 25% more than megestrol acetate.

Overall, a total of 370 (48%) patients remained on study treatment after disease progression was determined by a computerized algorithm based on UICC criteria. Of these, 30% (111 patients) continued treatment for 4 weeks or more after progression. **Comment:** *The benefits of continued therapy in progressed patients is difficult to measure.*

- **Objective Response Rate**

If the results of the two controlled trials are combined, there were 6 CRs and 21 PRs on 1 mg anastrozole, for an overall response rate of 10.3%. On 10 mg anastrozole, there were 4 CRs and 18 PRs, for an overall response rate of 8.9%. On megestrol acetate, there were 5 CRs and 15 PRs, for an overall response rate of 7.9%. In the individual trials, the pattern of objective response rates was similar across treatment groups for all randomized patients, and for the subset of patients with measurable disease.

If patients who had disease stabilization for 24 weeks or more are included along with the CRs and PRs, response rates for each of the treatment arms are 35%, 32%, and 34% respectively. Disease stabilization was observed in roughly 20% of patients with measurable disease and in 40% of patients with nonmeasurable disease. Reports in the literature suggest that patients with advanced breast cancer achieving disease stabilization on hormonal therapy for 5-6 months have similar times to progression and survival as patients having complete or partial responses.

Using the logistic regression model, comparisons of the 1 mg and 10 mg anastrozole doses vs. megestrol acetate were not significantly different with respect to objective response rate (see below). The individual trial results were similar (see Review Sections 4.13 and 4.23).

Comparison of Trials 0004 and 0005: Objective Response Rate

Treatment	# Patients	# Events	Odds Ratio	P value
1 mg A vs. M	A: 263	A: 27	1.32	0.37
	M: 253	M: 20	(0.66 - 2.65)	
10 mg A vs. M	A: 248	A: 22	1.15	0.68
	M: 253	M: 20	(0.55 - 2.36)	

These results indicate that, given the 8% response rate for megestrol acetate, the response rate for anastrozole is unlikely to be less than 4%, but could be as high as 18%. This would indicate that anastrozole is clinically equivalent to megestrol acetate.

The duration of response for the two controlled trials combined was 92 to 512+ days for 1 mg anastrozole, 112 to 533 days for 10 mg anastrozole, and 111+ to 427+ days for megestrol acetate. Thus, responses were durable, with 65% of responding patients having responses lasting 6 months or more, and 15% having responses lasting 12 months. The median duration for stable disease could not be estimated for the 1 mg dose, but was 484 days for 10 mg anastrozole and 410 days for megestrol.

- **Time to Treatment Failure**

Disease progression was the primary reason for treatment failure in the two controlled trials, affecting > 85% of patients failing study treatment. Treatment failures due to adverse events or concurrent illness accounted for only 2% of patients on the anastrozole arms, and for 4% of patients on megestrol acetate. Thus, conclusions drawn regarding time to treatment failure are similar to those for time to disease progression.

- **Survival**

Combining the two controlled trials, 38 (14%) patients on 1 mg anastrozole, 32 (13%) patients on 10 mg anastrozole, and 47 (19%) patients on megestrol acetate died at the time of data cut-off. Using the Cox proportional hazards model, comparisons of the 1 mg and 10 mg anastrozole doses vs. megestrol acetate were not significantly different with respect to time to death (see below). The individual trial results were similar (see Review Sections 4.13 and 4.23).

Comparison of Trials 0004 and 0005: Time to Death

Treatment	# Patients	# Events	Hazard Ratio	P value
1 mg A vs. M	A: 263	A: 38	0.80	0.30
	M: 253	M: 47	(0.49 - 1.30)	
10 mg A vs. M	A: 248	A: 32	0.71	0.13
	M: 253	M: 47	(0.42 - 1.18)	

Clinical equivalence for this variable cannot be claimed due to the low number of deaths.

- **Quality of Life Assessments**

No consistent treatment differences were observed in the quality of life assessments performed in the controlled trials. At baseline, responding patients in both trials had better functional status and psychological scores, and a higher proportion had no bone pain and a WHO performance status of 0 relative to patients whose best response was disease progression. During treatment, evaluations performed at weeks 12 and 24 failed to show any consistent patterns of change in the two groups. These assessments may not have captured the full effects of treatment because data were not available at all timepoints for all patients (see Review Sections 4.13 and 4.23), and scores were not collected after disease progression.

5.4 Controlled Trials: Efficacy in Patient Subgroups

The sponsor evaluated efficacy results for the following patient subgroups using data from both controlled trials combined: prior tamoxifen therapy (adjuvant vs. advanced disease), presence of measurable disease (yes or no), and presence of visceral disease (yes or no).

Prior tamoxifen therapy was a prognostic factor for time to disease progression. Using the Cox proportional hazards model, the hazard ratio for adjuvant tamoxifen therapy vs. tamoxifen for advanced disease was 1.38 (CI: 1.15 - 1.66, p= 0.0005). See the Appendix for a Kaplan-Meier plot of this comparison. This suggests that prior adjuvant tamoxifen therapy was associated with a shorter time to progression. The sponsor suggests that investigators were not able to "select" patients based on their prior response to adjuvant therapy, whereas this was possible for patients who had received tamoxifen for advanced disease. Despite this, patients on all treatment arms received similar benefit from treatment whether they had adjuvant tamoxifen or tamoxifen for advanced disease (see additional Kaplan-Meier plots of 1 or 10 mg anastrozole vs. megestrol acetate for the adjuvant and advanced tamoxifen patient groups).

Comment: *Disease progression rates for each of the controlled trials also trended toward a higher progression rate among patients who received tamoxifen adjuvantly (Trial 0004: 58% vs. 52% for adjuvant vs. advanced tamoxifen patients; Trial 0005: 66% vs. 56% for adjuvant vs. advanced tamoxifen patients).*

The presence or absence of measurable disease was a prognostic factor for time to progression. Again, using the Cox proportional hazards model, the hazard ratio for measurable disease vs. no measurable disease was 1.75 (CI: 1.40 - 2.19, p= 0.0001). See the Appendix for a Kaplan-Meier plot of this comparison. The presence of measurable disease was associated with a shorter time to progression, probably because of the relative ease of detecting and quantitating progression in measurable lesions as compared to nonmeasurable lesions. Despite this finding, patients on all treatment arms received similar benefit from treatment whether they had measurable or no measurable disease (see additional Kaplan-Meier plots of 1 or 10 mg anastrozole vs. megestrol

acetate for the measurable and nonmeasurable patient groups).

The presence or absence of visceral disease was a prognostic factor for time to progression. Using the Cox proportional hazards model, the hazard ratio for visceral disease vs. no visceral disease was 1.47 (CI: 1.22 - 1.76, p= 0.0001). See the Appendix for a Kaplan-Meier plot of this comparison. The presence of visceral disease was associated with a shorter time to progression. This finding was not unexpected, since visceral lesions tend to respond less frequently to hormonal treatment than other sites of metastatic disease. Despite this finding, patients on all treatment arms received similar benefit from treatment whether they had visceral or no visceral disease (see additional Kaplan-Meier plots of 1 or 10 mg anastrozole vs. megestrol acetate for the visceral disease and no visceral disease patient groups).

Prior tamoxifen for adjuvant therapy, presence of measurable disease, and presence of visceral disease were also prognostic factors for time to treatment failure. Results of these analyses were analogous to those summarized above for time to progression.

5.5 Efficacy in Relation to Dose

No differences between the effects of anastrozole, at doses of 1 or 10 mg once daily, and megestrol acetate were observed for the efficacy endpoints of time to disease progression, objective response rate, and time to treatment failure. The data are not sufficiently mature to allow inferences on survival. Differences between treatments for quality of life assessments were not of sufficient magnitude to be clinically meaningful. Although direct comparisons between the two doses of anastrozole were not made, it is unlikely that meaningful differences exist, given the lack of difference between either dose and megestrol acetate. Thus, the sponsor recommends the 1 mg dose of anastrozole once daily as optimal treatment for advanced breast cancer.

5.6 Sponsor's Conclusions Regarding Efficacy

Anastrozole is a potent inhibitor of serum estradiol concentrations; this effect is believed to be the mechanism by which anastrozole produces clinical benefit. Other aromatase inhibitors (aminoglutethimide, formestane, and fadrozole) do not suppress estradiol to the limit of quantitation of the assay as does anastrozole.

The selectivity of anastrozole for the aromatase enzyme, rather than other cytochrome P450 enzymes controlling glucocorticoid and mineralocorticoid synthesis in the adrenal gland has been demonstrated. Glucocorticoid or mineralocorticoid replacement therapy is not required with anastrozole.

The clinical efficacy results of two controlled trials support the use of anastrozole as an alternative to megestrol acetate for the treatment of advanced breast cancer in postmenopausal women.

Table 1 Comparison of Baseline Demographics: Controlled Trials of Arimidex

Patient Characteristic (% of Patients)	Trial 0004 N=386			Trial 0005 N=378		
Mean Age (yrs)						
A 1 mg:	65 (29-93)			65 (38-97)		
A 10 mg:	66 (41-91)			66 (44-87)		
M:	66 (39-90)			64 (40-84)		
Prior Tamoxifen	Adjuvant	Advanced		Adjuvant	Advanced	
A 1 mg:	45%	47%		47%	50%	
A 10 mg:	36%	53%		38%	58%	
M:	39%	59%		42%	58%	
Duration of Prior Tamoxifen	Adjuvant	Advanced		Adjuvant	Advanced	
A 1 mg:	34 mos	25 mos		28 mos	22 mos	
A 10 mg:	40 mos	26 mos		28 mos	23 mos	
M:	47 mos	22 mos		32 mos	23 mos	
PR/CR to Prior Tamoxifen for Advanced Disease						
A 1 mg:	13%			36%		
A 10 mg:	17%			51%		
M:	24%			37%		
ER+ Status						
A 1 mg:	85%			62%		
A 10 mg:	75%			54%		
M:	79%			58%		
Prior Chemotherapy						
A 1 mg:	45%			30%		
A 10 mg:	45%			28%		
M:	44%			26%		
Extent of Measurable Disease						
A 1 mg:	64%			81%		
A 10 mg:	61%			75%		
M:	63%			79%		
Metastatic Sites at Entry	ST	Bone	Visc	ST	Bone	Visc
A 1 mg:	13%	35%	11%	11%	22%	21%
A 10 mg:	11%	29%	12%	19%	25%	16%
M:	13%	32%	17%	20%	29%	13%

Table 2 Comparison of Efficacy Endpoints: Controlled Trials of Arimidex

Endpoint	Trial 0004 N=386	Trial 0005 N=378
Time to Progression		
A 1 mg:	5.7 mos (3.4 - 8.7 mos)	4.4 mos
A 10 mg:	4.8 mos (3.3 - 7.4 mos)	5.2 mos
M:	5.0 mos (3.2 - 6.8 mos)	4.0 mos
% Patients w/ Dis Prog*		
A 1 mg:	54%	67%
A 10 mg:	58%	60%
M:	61%	68%
Objective Response Rate		
A 1 mg:	10.2%	10.4%
A 10 mg:	5.4%	12.7%
M:	5.5%	10.4%
Response Duration		
A 1 mg:	(3.1 - 17.1 mos)	8.7 mos (3.5 - >15.3 mos)
A 10 mg:	(3.7 - 17.8 mos)	- (4.3 - >14.2 mos)
M:	(3.7 - 12.3 mos)	8.6 mos (3.9 - >14.2 mos)
Time to Treatment Failure		
A 1 mg:	5.6 mos (3.2 - 6.5 mos)	4.0 mos
A 10 mg:	4.4 mos (3.1 - 5.7 mos)	4.3 mos
M:	4.2 mos (3.0 - 6.1 mos)	3.8 mos
% Patients w/ Tx Failure		
A 1 mg:	58%	70%
A 10 mg:	63%	66%
M:	66%	71%
Time to Death		
A 1 mg:	NC	NC
A 10 mg:	NC	14.7 mos
M:	NC	NC
% Patients dying: all causes		
A 1 mg:	13%	16%
A 10 mg:	8%	19%
M:	15%	22%

*Includes patients who died before progression
NC - Not Calculable

6. Integrated Summary of Safety

6.1 Background

At the time of data cut-off (9/15/94), 1005 subjects had participated in the clinical trial program. This included the 761 women with advanced breast cancer in the two controlled trials (262 on anastrozole 1 mg, 246 on anastrozole 10 mg, and 253 on megestrol acetate). In addition, 19 women with advanced breast cancer received anastrozole 5 mg daily for 14 days followed by anastrozole 10 mg daily for 14 days. Seventeen of these women were allowed to continue therapy with 10 mg daily for up to 729 days (i.e., up to disease progression). There were also 133 healthy postmenopausal women treated in clinical pharmacology trials: some receiving single doses of anastrozole ranging from 0.000005 mg to 20 mg, others receiving multiple doses daily ranging from 0.00005 to 10 mg for 10-13 days. There were 77 healthy male volunteers who received single doses of anastrozole up to 60 mg. A single dose of 10 mg was also administered to 8 subjects with hepatic impairment and to 7 subjects with renal impairment. For an overview of the pharmacokinetic profile of anastrozole in humans, see Review Section 5.1.

- **Demographics**

Women with breast cancer in controlled trials combined: The mean age was approximately 65 years, the majority were Caucasian, and 85% had a WHO performance status of 0 or 1 at entry. Only 6 patients had a WHO performance status of 3 or 4; these represented protocol violations. Mean weight was roughly 68 kg. Liver metastases were present in about 16% of all randomized patients. At entry, 66 evaluable patients had abnormal hepatic enzymes defined as any of the following: total bilirubin $\geq$ 2 x ULN, albumin below the LLN, alkaline phosphatase, AST, ALT, or gamma GT $\geq$ 3 x ULN. These patients represent 8-9% of all patients on each of the three treatment arms. At entry, there were 14 evaluable patients with renal impairment, defined as a serum creatinine above the ULN. These patients represent 0.4 - 3.2% of patients on each of the treatment arms. Note that baseline data on hepatic enzymes and serum creatinine were missing in 2-5% of patients on each arm. For additional demographic information, refer to Review Sections 4.12 and 4.22.

Other groups: The median age of the 19 women with advanced breast cancer in the clinical pharmacology trials was 60 years, of postmenopausal women and subjects with hepatic impairment 58 years, of subjects with renal impairment 55 years, and of healthy males 36 years. Most participants were Caucasian. Mean weights ranged from 66 kg (postmenopausal women) to 76 kg (healthy males). **Comment:** *Compared to the other groups evaluated, women with breast cancer on the controlled trials had the lowest and highest weights recorded at entry (31 and 130 kg, respectively), representing both cachectic and frankly obese individuals.*

- **Exposure**

The majority of patients in the clinical program received oral ARIMIDEX ™ tablets. In five

pharmacology trials (0001, 0008, 011, 021, 0023), some subjects received an oral solution to allow administration of non-standard doses. The rate and extent of absorption of the anastrozole solution was similar to that of ARIMIDEX ™ tablets. In studies of anastrozole metabolism, ^{14}C-radiolabeled anastrozole was administered (Trial 0010; 0020). The maximum exposure to anastrozole among patients taking the 10 mg dose was 5340 mg, a total dose far exceeding the expected exposure to the recommended clinical dose of 1 mg. The majority of patients received treatment for more than 12 but less than 48 weeks. More than 6% of patients on each of the treatment arms in the controlled trials received study drug for > 48 weeks. In the entire clinical program, total exposure to anastrozole was estimated to be 238 subject-years at the cut-off date.

- **Recording of Adverse Events**

Recall that the protocols for the two controlled trials were amended so that only adverse events that occurred during treatment or within 2 weeks after stopping treatment were recorded. Since the half-life of anastrozole is roughly 50 hours, a 2-week monitoring period was deemed adequate to identify adverse events related to anastrozole. In addition, a longer monitoring period might be confounded by the initiation of new therapies after study withdrawal.

Disease progression was not considered an adverse event. If an adverse event of unclear etiology was recorded as such, and then later considered to be due to disease progression, the investigator was permitted to amend the case report form.

This Integrated Summary of Safety does not include the small number of subjects who were never treated; those who were given the incorrect treatment were included according to the treatment actually received.

Patient deaths occurring during treatment or within 2 weeks of stopping treatment due to causes other than breast cancer are considered relevant to the safety profile of anastrozole and are discussed in this Integrated Summary of Safety. Deaths due to breast cancer alone, and/or occurring after the 2 week monitoring period up to the cut-off date are discussed in the Integrated Summary of Efficacy.

6.2 Anticipated Adverse Events

For the two controlled trials, planned statistical analyses were carried out on the incidence of six anticipated events, expected to occur on the basis of the pharmacology of anastrozole and megestrol acetate: weight gain, edema, thromboembolic disease, gastrointestinal disturbances, hot flushes, and vaginal dryness. Any patient who experienced one or more of these events was included in this analysis. The incidence of these events was compared between patients treated with 1 or 10 mg anastrozole and megestrol acetate, using Fisher's exact test. Separate tests were carried out for the two comparisons and the two-tailed p-values obtained were compared against a critical p-value= 0.01

Anastrozole 1 mg versus Megestrol Acetate

Adverse Event	Number of Patients (%)	P-value
Weight gain	A: 4 (1.5%) M: 30 (12%)	<0.0001
Edema	A: 19 (7%) M: 35 (14%)	0.02
Thromboembolic disease	A: 9 (3%) M: 12 (5%)	0.51
GI disturbance	A: 77 (29%) M: 54 (21%)	0.04
Hot flushes	A: 33 (13%) M: 35 (14%)	0.70
Vaginal dryness	A: 5 (2%) M: 2 (1%)	0.45

Anastrozole 10 mg versus Megestrol Acetate

Adverse Event	Number of Patients (%)	P-value
Weight gain	A: 10 (4%) M: 30 (12%)	0.002
Edema	A: 28 (11%) M: 35 (14%)	0.42
Thromboembolic disease	A: 4 (1.6%) M: 12 (5%)	0.07
GI disturbance	A: 81 (33%) M: 54 (21%)	0.005
Hot flushes	A: 29 (12%) M: 35 (14%)	0.51
Vaginal dryness	A: 3 (1%) M: 2 (1%)	0.68

Thus, both the 1 mg and 10 mg anastrozole doses were associated with a lower incidence of weight gain. **Comment:** *In the analysis above, no definition of "weight gain" is given and the*

source(s) of information on weights is not provided. In a different analysis of weight gain performed by the sponsor, weights are measured objectively and compared to baseline. In this case, the numbers of patients with a ≥ 5% weight gain in each of the three treatment arms were 33, 34, and 87, respectively. The numbers of patients in the subset with a ≥ 10% weight gain were 6, 8, and 27 in each of the arms, respectively. These numbers suggest a higher incidence of weight gain in all treatment arms that is not accounted for in the analysis presented above.

Gastrointestinal disturbance was more common in patients treated with anastrozole than with megestrol acetate, particularly at the 10 mg dose. These events were primarily nausea, vomiting, change in bowel habits, and anorexia, of mild to moderate severity. Only one patient withdrew due to vomiting: patient on anastrozole 1 mg on Trial 0005. The majority of patients reporting nausea or vomiting (112 of 137) in all treatment groups were also taking narcotics and other analgesics which may have contributed to these events.

6.3 Drug-Related Adverse Events

Drug-related events were defined as all adverse events that were considered by the investigator to be probably or definitely related to trial treatment and those for which causality was recorded as "undetermined". Table 1 below summarizes the most common drug-related events occurring during or within 2 weeks of treatment with anastrozole or megestrol acetate in the two controlled trials. The source documents used to create this table were Table 34, vol 1.74 for Trial 0004, and Tables 30, vol 1.90, and T9.4, vol 1.91 for Trial 0005. See Appendix for additional detailed adverse event tables provided by the sponsor.

- **Anastrozole (Controlled Trials)**

In the anastrozole 1 mg arm, the mean dose mg/kg/day (range in the anastrozole 10 mg arm, the mean dose g/day (range The most common drug-related events in patients receiving anastrozole were hot flushes, headache, nausea, asthenia and non-specific pain.

Hot flushing is an anticipated pharmacologic withdrawal and was mild in most cases. Hot flushes were reported early in lead to treatment withdrawal.

The incidence of headache was possibly related dose, however, in clinical pharmacology trials the incidence of drug-related among postmenopausal women given placebo was 9%. This suggests that the incidence related headache was comparable to the background incidence of headache in this age group.

Nausea was the only adverse event for which there was evidence of a relationship to dose. The incidence of nausea was slightly higher in patients receiving > 0.075 mg/kg/day as compared to those receiving less than this dose (20% vs 15%). In both the 1 and 10 mg anastrozole groups, the onset of nausea occurred most frequently during the first 12 weeks of treatment, after which

Table 1: Comparison of Drug-Related Adverse Events in Controlled Trials of Arimidex

Endpoint	Trial 0004 N=386	Trial 0005 N=378
Hot Flushes		
A 1 mg:	18.8%	3.0%
A 10 mg:	14.7%	5.1%
M:	8.6%	4.8%
Headache		
A 1 mg:	8.6%	2.2%
A 10 mg:	15.5%	5.1%
M:	4.7%	4.0%
Nausea		
A 1 mg:	3.9%	4.5%
A 10 mg:	7.8%	3.4%
M:	7.0%	1.6%
Asthenia		
A 1 mg:	9.4%	1.5%
A 10 mg:	6.2%	0
M:	10.2%	2.4%
Pain		
A 1 mg:	5.5%	1.5%
A 10 mg:	5.4%	0
M:	3.9%	3.2%
Weight Gain		
A 1 mg:	0.8%	2.2%
A 10 mg:	4.7%	1.7%
M:	15.6%	8.0%
Dyspnea		
A 1 mg:	3.1%	1.5%
A 10 mg:	3.1%	0
M:	8.6%	5.6%
Peripheral Edema		
A 1 mg:	2.3%	0.7%
A 10 mg:	4.7%	0.9%
M:	3.9%	4.0%
Increased Appetite		
A 1 mg:	0	0
A 10 mg:	1.8%	0
M:	7.8%	0.8%
Vaginal Hemorrhage		
A 1 mg:	3.1%	0.7%
A 10 mg:	1.6%	0.9%
M:	5.5%	3.2%

- **Abnormal Hepatic Biochemistry**

Abnormal hepatic biochemistry was defined as any of the following: bilirubin $\geq$ 2 x ULN, ALT, AST, gamma GT or AP $\geq$ 3 x ULN, or albumin below the LLN. No relationship between abnormal hepatic biochemistry and the incidence of adverse events were noted, with the exception of gastrointestinal events.

In the anastrozole 1 mg and megestrol acetate arms, nausea and vomiting were reported with a roughly 2-fold higher incidence in patients with abnormal hepatic biochemistry as compared to those without (anastrozole patients with abnormal vs. normal biochemistry: 27% vs. 15% for nausea, and 23% vs. 8% for vomiting; megestrol patients with abnormal vs. normal biochemistry: 22% vs. 10% for nausea, and 9% vs. 6% for vomiting). These differences were not observed among patients treated with anastrozole 10 mg, however. Note that the number of patients per arm with abnormal hepatic biochemistry was roughly 20 as compared to over 200 patients per arm with normal studies.

Constipation occurred more frequently among patients on the megestrol acetate arm with abnormal hepatic biochemistry as compared to those with normal studies (22% vs. 7%).

- **Clinical Pharmacology Trials**

Among 19 patients with advanced breast cancer in clinical pharmacology trials (0003 and 0007), the incidence of the most common drug-related adverse events was: headache (32%), asthenia (32%), hot flushes (32%), and dizziness (21%). Recall that dosing in this group was 5 mg anastrozole daily for 14 days, followed by 10 mg daily for 14 days; 17 of these patients continued on 10 mg daily until disease progression.

A total of 133 healthy postmenopausal women were enrolled in clinical pharmacology trials. Of these, 120 subjects were evaluable for adverse events on anastrozole (broad range of single or multiple doses), and 58 were evaluable for adverse events on placebo (note that 45 subjects were enrolled in cross-over trials and were exposed to both anastrozole and placebo). The most frequent drug-related adverse event was headache which occurred with similar incidence in the anastrozole and placebo groups (8.3% vs. 8.6%). Hot flushes and dizziness were more common on the placebo group, with an incidence of 5% each. Leukopenia was observed in both groups with similar frequency (2.5% for anastrozole and 3.4% for placebo).

A total of 77 healthy males were enrolled in clinical pharmacology trials. Of these, 60 subjects were evaluable for adverse events on anastrozole (broad range of single doses as high as 60 mg), and 19 were evaluable for adverse events on placebo. Two subjects on anastrozole experienced drug-related events: increased libido and rash in 1 subject each. Three subjects on placebo experienced drug-related events: headache in 1 and postural hypotension in 2.

None of the 8 subjects with renal impairment had drug-related events (Trial 0018), while 3/7

subjects with hepatic impairment suffered drug-related headache (Trial 0014). Recall that these individuals received a single dose of 10 mg anastrozole. A total of fifteen matched healthy subject controls, also given a single dose of 10 mg anastrozole, were enrolled in these two trials and experienced two drug-related events: headache in 1 subject and somnolence in 1.

6.4 Serious Adverse Events

Serious adverse events were defined as fatal, life-threatening, disabling or permanently incapacitating events, or any event that resulted in hospitalization, or withdrawal from treatment due to any reason other than disease progression. These events would have occurred during or within 2 weeks of stopping treatment.

- **Anastrozole (Controlled Trials)**

On the 1 mg anastrozole dose, 17% (45/262) of patients experienced serious adverse events. Of these, 37 patients required hospitalization, 7 patients withdrew treatment and 5 patients died. Serious events that occurred with an incidence of 1% or more were: dyspnea (6 patients), thrombophlebitis, asthenia, and aggravation reaction (4 patients each), and nausea, vomiting and somnolence (3 patients each). Note that an aggravation reaction in these cases was a worsening of a pre-existing condition, namely cholelithiasis, hyponatremia, chronic obstructive pulmonary disease, and pain.

Serious drug-related events occurred in 15 patients on 1 mg anastrozole and lead to treatment withdrawal in 4. There were no deaths attributable to a serious drug-related event. The most frequent events were somnolence (3 patients) and dyspnea (2 patients).

On the 10 mg anastrozole dose, 21% (51/246) of patients experienced serious adverse events. Of these, 39 patients required hospitalization, 8 patients withdrew treatment and 2 patients suffered a treatment-related death. Serious events that occurred with an incidence of 1% or more were: dyspnea (9 patients), vomiting (6 patients), nausea (5 patients), pathologic fracture (4 patients), and asthenia, pain, bone pain, pleural effusion, pneumothorax, and anemia (3 patients each).

There was no relationship between dose of anastrozole per kg body weight, duration of treatment, or patient age and the incidence of serious adverse events.

Serious drug-related events occurred in 12 patients on 10 mg anastrozole and lead to treatment withdrawal in 7. There were no deaths attributable to a serious drug-related event. The most frequent events were headache and hypercalcemia (2 patients each).

- **Megestrol Acetate (Controlled Trials)**

On megestrol acetate, 26% (65/253) of patients experienced serious adverse events. Of these, 46 patients required hospitalization, 10 patients withdrew treatment and 9 patients suffered a

treatment-related death. Serious events that occurred with an incidence of 1% or more were: dyspnea (19 patients), nausea (7 patients), vomiting (6 patients), asthenia and pneumonia (5 patients each), pulmonary embolism, increased cough, dehydration, and pathologic fracture (4 patients each), and pleural effusion, anemia, pain, and reaction unevaluable (3 patients each). The unevaluable events involved rod and screw replacements to the left femur, revision of hip arthroplasty, and inferior vena cava obstruction.

The incidence of serious dyspnea appeared to be related to drug exposure, with 14% of patients receiving > 3 mg/kg/day developing dyspnea as compared to 7% of patients receiving ≤ 3 mg/kg/day. In addition, the onset of serious adverse events increased with time, particularly after week 48. Patients in the 65-80 year old age group had the highest incidence of serious adverse events, primarily due to the higher incidence of severe dyspnea in this group.

Serious drug-related events occurred in 21 patients on megestrol acetate and lead to treatment withdrawal in 8. There was one death attributable to a serious drug-related event. The most frequent events were dyspnea (8 patients), pulmonary embolism (4 patients), and asthenia, pain and nausea (2 patients each).

Overall, treatment with anastrozole was associated with fewer serious adverse events than megestrol acetate, however, the incidence of serious drug-related events was comparable in all three treatment groups. There were no trends in the incidence of serious adverse events on any treatment arm related to renal impairment or hepatic impairment at entry, or to hepatic function during treatment.

- **Clinical Pharmacology Trials**

Three of the 19 advanced breast cancer patients on Trials 0003/0007 experienced a total of 9 serious adverse events; one patient withdrew treatment. None of these events were considered drug-related.

Three of the 120 healthy postmenopausal women on anastrozole and 2 of the 58 women on placebo experienced serious adverse events. Three women withdrew treatment. One of these events was considered drug-related: pruritic rash in a woman on placebo.

There were no serious adverse events in healthy men, subjects with hepatic or renal impairment or healthy control subjects after exposure to anastrozole or placebo.

6.5 Adverse Events Leading to Treatment Withdrawal

- **Anastrozole**

In the entire clinical program, 19 of 737 (2.6%) subjects receiving anastrozole experienced adverse events leading to treatment withdrawal. No single event predominated, involving 1 or 2

patients at the most.

In the controlled trials, 7 of 262 (2.7%) patients on 1 mg anastrozole and 8 of 246 (3.3%) patients on 10 mg anastrozole withdrew from treatment. In 4 patients on 1 mg anastrozole and in 7 patients on 10 mg anastrozole, these events were considered drug-related. Of n

Two patients were withdrawn for hypercalcemia on the 10 mg anastrozole arm. In one patient this event was considered to be the result of tumor flare following anastrozole and was considered drug-related. In the second patient hypercalcemia developed in the setting of multiple bone metastases and was of undetermined relationship to anastrozole.

One patient was withdrawn from the 1 mg anastrozole arm because of an allergic reaction that included laryngeal edema and pruritic rash after 3 days of treatment. A concomitant medication begun 5 days before study entry, ketorolac, may have contributed to this reaction.

One patient was withdrawn from the 10 mg anastrozole arm because of exacerbation of a pre-existing staphylococcal skin infection which flared on re-challenge with anastrozole.

One patient was withdrawn from the 1 mg anastrozole arm due to peripheral neuropathy of undetermined etiology.

One patient on the 1 mg anastrozole arm, with abnormal hepatic biochemistry at entry, was withdrawn because of vomiting

- **Megestrol Acetate**

In the controlled trials, 10 of 253 (4%) patients withdrew from treatment on megestrol acetate. In eight patients, the events were considered drug-related Three patients withdrew for nausea and one for vomiting. Five patients with pre-existing cardiopulmonary conditions withdrew for events related to cardiovascular/pulmonary systems, namely cerebrovascular accident, dyspnea, palpitations, and dizziness. One patient may have had an allergic reaction, developing reddened palms, conjunctivitis, nausea and diarrhea One patient with diabetes mellitus was withdrawn for hyperglycemia.

Overall, there were more cardiovascular, respiratory and gastrointestinal adverse events leading to withdrawal of megestrol acetate treatment as compared to either anastrozole dose.

- **Clinical Pharmacology Trials**

One breast cancer patient of the 19 enrolled on Trial 0003/0007 was withdrawn for

thrombocytopenia. This was considered to be related to bone marrow involvement by disease rather than to anastrozole.

Among healthy postmenopausal subjects, 3 of 120 (2.5%) subjects on anastrozole and 2 of 58 (3.4%) of subjects on placebo withdrew from treatment. Of note were two cases of myocardial ischemia/infarction among women on anastrozole. Only one case was considered drug-related, that of pruritic rash in a woman on placebo.

There were no adverse events leading to withdrawal among healthy male volunteers, subjects with hepatic or renal dysfunction, or healthy control subjects.

Treatment Withdrawal Rates by Compliance in Trial 0004:
Recall that non-compliance in Trial 0004 has been defined as "patients returning > 20% of pills" at an office visit (see Review Section 4.13). One of 24 (4.2%) "non-compliant" patients on 1 mg anastrozole, 3 of 29 (10.3%) "non-compliant" patients on 10 mg anastrozole, and 2 of 24 (8.3%) "non-compliant" patients on megestrol withdrew from treatment due to adverse events. These withdrawal rates are higher than those for "compliant" patients: 1.9% (2/104) for 1 mg anastrozole, 1% (1/100) for 10 mg anastrozole, and 1.9% (2/104) for megestrol.

Review of the incidence of all adverse events occurring among patients on the 10 mg anastrozole arm revealed an increased overall reporting among "non-compliant" patients, with 28/29 (97%) of "non-compliant" patients reporting vs. 100/129 (87%) of "compliant" patients. Whereas, "non-compliant" patients accounted for 22% of all patients on this treatment arm, they accounted for 29% of asthenia reports, 32% of bone pain reports, 33% of anorexia reports, 38% of nausea reports, 41% of vomiting reports, and 35% of hot flushing reports. In contrast, among patients on the 1 mg anastrozole and megestrol arms, adverse event reporting was similar among "compliant" and "non-compliant" patients. This suggests that while anastrozole 10 mg was well-tolerated by the majority of patients, a subset of patients (roughly 1 in 5) will tolerate treatment less well and possibly interrupt dosing between office visits to ameliorate their symptoms.

6.6 Deaths

Patient deaths that occurred during treatment or within 2 weeks of stopping treatment were reviewed by a ZENECA-nominated physician who was blinded regarding the treatment the patient had received. There were no deaths reported on the clinical pharmacology trials. The table below summarizes patient deaths in the controlled trials.

	Anastrozole 1 mg (N=262)	Anastrozole 10 mg (N=246)	Megestrol Acetate (N=253)
Patients who died			
-breast cancer alone	10 (3.8%)	6 (2.4%)	7 (2.8%)
-other causes	5 (1.9%)	2 (0.8%)	9 (3.6%)

Among the patients treated with 1 mg anastrozole, causes of death other than breast cancer were two deaths due to gastrointestinal events (intestinal perforation and small bowel infarction) two due to cardiovascular events (cerebrovascular accident and internal carotid artery aneurysm), and one respiratory death.

Among the patients treated with 10 mg anastrozole, causes of death other than breast cancer were one death due to cardiac arrest and one to kidney failure.

Among the patients treated with megestrol, causes of death other than breast cancer were four deaths due to pneumonia, and four cardiovascular deaths (two with cardiac arrest, one cerebrovascular accident, and one pulmonary embolus). The case of pulmonary embolus occurred in a 72 year-old woman on megestrol for over 4 weeks, and was considered drug-related A ninth patient died of unknown causes.

There was no relationship between the incidence of deaths due to causes other than breast cancer and duration of treatment, patient age, or clinical features on any treatment arm.

6.7 Clinical Laboratory Data

- **Hematology**

In the controlled trials, there were no clinically significant trends in mean hematology laboratory results during treatment with anastrozole 1 or 10 mg, or megestrol acetate. Three patients had grade 3 leukopenia, but in each case, grade 2-3 neutropenia was present at baseline and could be attributed to underlying disease or prior treatment. Anemia was reported as a serious adverse event in 3 patients on anastrozole 10 mg and in 3 on megestrol acetate. These events were attributed to disease progression and did not lead to treatment withdrawal. Most cases of thrombocytopenia were either present at entry or occurred intermittently on study and were considered related to disease progression, with one exception. Patient had a history or temporal arteritis and a normal platelet count at entry which declined after week 24 to 71,000. This was associated with an upper respiratory infection that was treated with a cephalosporin and fluconazole.

In the clinical pharmacology trials, the 19 women with breast cancer on Trials 0003/0007 had

similar hematology results as did women on anastrozole in the controlled trials. Among healthy postmenopausal women, adverse events of anemia occurred with equal frequency in subjects exposed to anastrozole or to placebo, possibly due to the frequent blood draws that were performed. Not unexpectedly, two of the seven subjects with renal impairment were found to have anemia.

- **Hepatic Biochemistry**

In the controlled trials, there were no significant alterations in mean albumin, AST, ALT and bilirubin from baseline among patients on anastrozole 1 or 10 mg, or megestrol acetate. Mean gamma GT at entry was elevated above the ULN and increased dramatically after treatment discontinuation (2- to 3-fold for anastrozole, 1.7-fold for megestrol). This was considered to be most likely due to disease progression in the liver. Mean alkaline phosphatase levels rose slightly from baseline during the trials, and to a greater extent after treatment withdrawal. Since specific iso-enzymes were not measured, the elevations in alkaline phosphatase may have been due to either bone or hepatic disease.

In the clinical pharmacology trials, elevation of ALT $\geq$ 2 x ULN was noted sporadically: in one patient with breast cancer, in two postmenopausal women (one on anastrozole and one on placebo), in one healthy male on anastrozole and in one subject with hepatic dysfunction. Elevation of bilirubin to $\geq$ 2 x ULN was observed in one breast cancer patient, and elevation of alkaline phosphatase to $\geq$ 2 x ULN in two patients.

Reviewer's Assessment of Hepatic Biochemistry Alterations:
The contribution of liver metastases at study entry to the elevations noted in hepatic biochemistry studies was assessed. The most dramatic changes occurred in gamma GT levels (drawn only in Trial 0005) and are summarized below. A total of 66 patients had gamma GT levels measured at baseline and at withdrawal on the 1 mg anastrozole arm, 49 patients on the 10 mg anastrozole arm, and 68 patients on the megestrol arm. The normal range for gamma GT was 7-43 U/L.

Serum Gamma GT Levels: Pretreatment vs. Time of Withdrawal

	All Patients			No Liver Mets			Liver Mets		
	N	Pre-tx mean	WD mean	N	Pre-tx mean	WD mean	N	Pre-tx mean	WD mean
Anastrozole 1 mg	66	72	150	49	50	59	17	134	411
Anastrozole 10 mg	49	80	195	36	82	182	13	76	230
Megestrol Acetate	68	63	109	52	46	65	16	118	254

Patients without liver metastases had mean gamma GT levels that were < 2 x ULN at entry;

levels rose 1.2-, 2.2- and 1.4-fold, respectively, at the time of study withdrawal. Mean total bilirubin, AST, and ALT levels in patients without liver metastases were WNL at entry and at withdrawal. Mean alkaline phosphatase levels in these patients were < 2 x ULN at entry; levels rose 1.2-, 1.6- and 1.2-fold, respectively, at the time of withdrawal. These changes could represent the development of liver metastases on study. The contribution of bone metastases in these patients is not known.

In contrast, patients with liver metastases had mean gamma GT levels that were 2-3 x ULN at entry; levels rose 3.1-, 3-, and 2.2-fold, respectively, at withdrawal. Mean total bilirubin, AST and ALT levels in patients with liver metastases were WNL at entry and at withdrawal, except for patients on the 1 mg anastrozole arm who experienced a 1.7-fold rise in AST and a 3.3-fold rise in ALT. A similar trend was not noted among patients receiving the 10 mg anastrozole dose. Mean alkaline phosphatase levels were ≥ 2 x ULN at entry; levels rose 1.9-, 1.5-, and 1.5-fold, respectively, at withdrawal. These changes are likely related to the progression of liver metastases on study, although other contributing factors cannot be ruled out.

- **Renal Function**

In the controlled trials, there was no clinically significant difference between mean serum creatinine before treatment and at withdrawal for patients on the 1 or 10 mg anastrozole arms. In the megestrol acetate arm, there was a slight rise (10%) in mean values during the trials and at withdrawal. In the clinical pharmacology trials, there were no observed differences between baseline and withdrawal mean serum creatinine levels among breast cancer patients. Two of the subjects with renal impairment had serum creatinine levels ≥ 1.5 x ULN.

- **Cholesterol**

In the controlled trials, mean serum cholesterol levels increased by 0.5 mmol/l after treatment with anastrozole 1 or 10 mg, and the proportion of patients with cholesterol above the normal range increased. This was not observed on the megestrol arm. Studies of apoprotein A (associated with HDL cholesterol) and of apoprotein B (associated with LDL cholesterol) were performed in Trial 0005. There was an equal rise in LDL concentrations in all three treatment groups, but no change in HDL levels in anastrozole-treated patients and decreased HDL levels in megestrol-treated patients.

The clinical significance of these findings is unknown. Elevations of serum total cholesterol and of LDL cholesterol are also expected to occur with withdrawal of tamoxifen and with the onset of menopause, as a result of estrogen deprivation. In addition, aminoglutethimide, another aromatase inhibitor, causes a rise in both serum total cholesterol and of LDL cholesterol. The potential increase in cardiovascular risk is balanced by the poor prognosis of women diagnosed with metastatic breast cancer. Note, however, that a decrease in total cholesterol of 0.6 mmol/l is associated with a 7% reduction in risk of coronary death over a two year period. At present there does not appear to be an increase in cardiovascular mortality in the anastrozole groups,

although median follow-up is only six months.

6.8 Drug-Drug Interactions

In vitro, anastrozole was at least 1000-fold less potent than ketoconazole as an inhibitor of human $P_{450\,3A4}$ (Ki = 0.02 μM). In clinical pharmacology trials, a single dose of anastrozole 30 mg or twelve daily doses of 10 mg had no significant effect on antipyrine pharmacokinetics. Another trial in which subjects had received cimetidine 300 mg qid x 17 doses in conjunction with anastrozole showed no alteration of anastrozole pharmacokinetics. These data suggest that anastrozole is unlikely to cause drug interactions by inhibition or induction of cytochrome P_{450}.

The adverse event database for the two controlled trials combined was searched for potential interactions between anastrozole and 19 different classes of drugs. Of particular concern were drugs that are highly protein bound (aspirin and warfarin), drugs with a narrow therapeutic dosing window (digoxin, oral hypoglycemic agents), and drugs that are frequently used in this patient population.

Concurrent use of warfarin or other oral anticoagulants with anastrozole was not associated with excessive hemorrhagic or thromboembolic phenomena as compared to concurrent use with megestrol acetate. In vitro, anastrozole has moderate protein binding (40%), so that interactions with warfarin would be unlikely.

6.9 *Endocrine Effects*

The maximally effective dose of anastrozole for selective aromatase inhibition (10 mg/kg) is 100-fold less than non-selective doses which could interfere with adrenal glucocorticoid or mineralocorticoic production or thyroid function.

In 8 healthy postmenopausal women (Trial 0002), pre- and post-dose assessment of adrenal hormones (cortisol, aldosterone, dehydroepiandrosterone sulphate [DHEA-S], 17-hydroxyprogesterone [17-HP], and androstenedione) showed that these were not significantly different. ACTH stimulation tests showed normal cortisol, 17-HP, and aldosterone responses 30 and 60 minutes after challenge with 250 mg of synthetic ACTH on day 10, following a ten day course of 3 mg/day anastrozole. After a washout period, subjects were crossed over to placebo. Analogous hormonal studies performed on day 10 of a ten day placebo course showed similar findings. There were no detectable changes in LH, FSH, ACTH or sex hormone binding globulin.

In 19 women with advanced breast cancer (Trial 0003), patients were given a 14-day course of 5 mg anastrozole, immediately followed by a 14-day course of 10 mg anastrozole. ACTH stimulation tests performed at baseline, day 14 and day 28 showed no differences in cortisol and aldosterone responses. There were also no alterations in LH, FSH, ACTH or TSH on days 14 or 28 as compared to baseline. Seventeen of these patients continued on 10 mg daily in Trial 0007. ACTH stimulation tests performed on days 59 and 115 also showed normal responses.

These findings suggest that anastrozole does not alter any of the major pathways of adrenal steroidogenesis in postmenopausal women and does not disturb thyroid function. In addition, anastrozole does not possess estrogenic, progestational or androgenic activity in this population.

In Trial 0001, 29 healthy male volunteers were evaluated after anastrozole treatment (doses ranging from 0.1 mg to 60 mg) and placebo. There were no consistent, dose-related changes in cortisol, aldosterone, ACTH, or DHEA-S demonstrating that anastrozole doses up to 60 mg have no significant effect on adrenal steroidogenesis. In addition, there were no consistent dose-related changes in either androstenedione or testosterone levels indicating that anastrozole does not significantly impair the function of either of the key enzymes (17-hydroxylase and 17,20-desmolase) involved in the final stage of androgen biosynthesis

Hypothalamic aromatization of testosterone is known to contribute to its negative feedback on pituitary gonadotrophin secretion in man. There were statistically significant increases in LH and FSH levels almost certainly due to inhibition of hypothalamic aromatase activity, i.e., the pharmacological action of anastrozole.

In the two controlled trials, there was no apparent clinical evidence for adrenocorticoid insufficiency.

6.10 Sponsor's Conclusions Regarding Safety

Anastrozole is a selective aromatase inhibitor that does not affect the pituitary-adrenal axis Concomitant adrenocorticoid supplementation is not required

Anastrozole 1 mg was generally well-tolerated and was associated with few adverse events that required discontinuation of treatment. The anticipated pharmacologic action of anastrozole may give rise to certain effects, such as hot flushes, vaginal dryness, and hair thinning. Other effects that may occur include gastrointestinal disturbances (anorexia, nausea, vomiting, and diarrhea), somnolence, headache and rash. Mild increases in serum cholesterol levels have been documented.

No adjustment in dose is recommended in the elderly, or in patients with hepatic or renal impairment. Anastrozole has not been studied in patients with severe hepatic or renal impairment.

The safety profile of anastrozole 1 mg daily is satisfactory and supports its use in the treatment of advanced breast cancer in postmenopausal women

7. 4-Month Safety Update

7.1 Background

In this safety update, a cut-off date of 3/31/95 has been applied; safety results occurring on or before that date in a total of 1017 subjects are presented. The bulk of additional data is derived from the continued exposure of 761 patients with advanced breast cancer on the two controlled trials (0004 and 0005) and of 17 patients on the clinical pharmacology trial (0003/0007). Data on 12 additional breast cancer patients (Trial 0022) exposed to anastrozole are also included. Overall, this safety update represents 346 patient-years of exposure, a 45% increase in patient-years above that reported in the Integrated Summary of Safety (ISS).

Trial 0022 was conducted in two phases. In Phase I, 12 postmenopausal women with advanced breast cancer were randomized to receive either 1 or 10 mg anastrozole once daily for 28 days, then crossed over to receive the alternative dose for 28 days. This phase has been completed. Phase II, still ongoing, allows treatment with 10 mg daily until disease progression.

- **Demographics**

Patient demographics for the two controlled trials was reviewed in Sections 4.12, 4.22, and 6.1. Demographics for other patient/subject groups were included in Section 6.1. The age, weight, and ethnic origin of the 12 patients on Trial 0022 were similar to those of other patients with breast cancer in clinical pharmacology trials (0003/0007).

- **Exposure**

In the controlled trials, 262 patients received 1 mg anastrozole for a median of 175 days (range 5-659 days), and 246 patients received 10 mg anastrozole for a median of 203 days (range days) as of the new cut-off date. Nearly 50% of patients in each group had received treatment for 12-48 weeks, while 25% had received treatment for > 48 weeks.

In the clinical pharmacology trial 0003/0007, seventeen patients have been treated with 10 mg anastrozole from 9 to 926 days as of 3/31/95.

7.2 Drug-Related Adverse Events

Drug-related events were defined as all adverse events that were considered by the investigator to be probably or definitely related to trial treatment and those for which causality was recorded as "undetermined". See Appendix for sponsor's detailed adverse event tables.

In the controlled trials, for the period between the ISS and this update, 6 patients treated with anastrozole (4 on the 1 mg arm and 2 on the 10 mg arm) and 6 patients treated with megestrol acetate have reported drug-related events. The pattern of drug-related events in all treatment

groups was similar to that reported in the ISS and does not suggest any new or unsuspected toxicity occurring after prolonged anastrozole treatment.

Since the cut-off date for the ISS, one drug-related adverse event was reported in clinical pharmacology trials (0003/0007 and 0022): angina pectoris.

7.3 Serious Adverse Events

In the interval between the ISS and this update, 45 new serious adverse events were reported by 29 patients in the controlled trials (7 patients each on the 1 mg anastrozole and megestrol arms, and 15 patients on the 10 mg anastrozole arm). These included two reports each of nausea and vomiting on the 10 mg anastrozole arm, and four reports of dyspnea (1 each for the two anastrozole arms and two for megestrol). One patient suffered a cerebral infarct and thrombophlebitis on 10 mg anastrozole, and two patients on megestrol experienced cerebral infarct or ischemia.

Serious adverse events that were considered drug-related occurred in 3 patients: elevation of serum gamma GT in 1 patient on 1 mg anastrozole; cerebral ischemia/dementia and heart failure/lung edema in 1 patient each on megestrol acetate. No serious adverse event other than dyspnea had an incidence above 3.5% in any treatment group. The distribution of serious adverse events in this updated report resembles that reported in the ISS.

In the ongoing clinical pharmacology trials, four reports of serious adverse events occurred in the interval between the ISS and this update: none were considered to be drug-related.

7.4 Adverse Events Leading to Treatment Withdrawal

In the controlled trials, for the interval between the ISS and this update, one patient was withdrawn from the 1 mg anastrozole arm (patient 0005/0010 with elevation of serum gamma GT) and three patients were withdrawn from the megestrol acetate arm (patient with a cerebral infarct, patient with cerebral ischemia/dementia, and patient with heart failure/lung edema).

Overall, the proportion of patients withdrawn from treatment for an adverse event in each arm was: 3.1% (8/262) for 1 mg anastrozole, 3.3% (8/246) for 10 mg anastrozole, and 5.1% (13/253) for megestrol acetate. The proportion of patients withdrawn from treatment for a drug-related adverse event in each arm was: 1.9% (5/262) for 1 mg anastrozole, 2.8% (7/246) for 10 mg anastrozole, and 4% (10/253) for megestrol acetate.

No patients have been withdrawn from clinical pharmacology trials due to adverse events during this period.

7.5 Deaths

Patient deaths that occurred during treatment or within 2 weeks of stopping treatment were reviewed by a ZENECA-nominated physician who was blinded regarding the treatment the patient had received.

Since the cut-off date for the ISS, there have been 9 patient deaths in the two controlled trials. These were due to breast cancer in 7: 2 patients on 1 mg anastrozole, 3 patients on 10 mg anastrozole, and 2 patients on megestrol. Deaths due to other causes occurred in 1 patient on 10 mg anastrozole (myocardial infarction), and 1 patient on megestrol acetate (cerebral ischemia/dementia).

There have been no deaths during or within 2 weeks after stopping treatment in women with breast cancer in the clinical pharmacology trials.

At the cut-off date for this update, the incidence of patient deaths due to causes other than breast cancer in the controlled trials was: 1.9% (5/262) for 1 mg anastrozole, 1.2% (3/246) for 10 mg anastrozole, and 4% (10/253) for megestrol acetate. The causes of death were generally those expected in a population of middle-aged and elderly women with advanced breast cancer, namely ischemic heart disease and cerebrovascular disease.

7.6 Clinical Laboratory Data

- **Hematology**

At the cut-off date for this update, there have been no clinically significant trends in mean hematology results in women with breast cancer in the controlled trials or in the clinical pharmacology trials.

- **Hepatic Biochemistry**

As noted in the ISS, the most prominent alterations in mean hepatic biochemistry results consisted of increases in gamma GT from baseline at the time of study withdrawal: 2.2-fold in the 1 mg anastrozole arm, 2.7-fold in the 10 mg anastrozole arm, and 1.7-fold in the megestrol arm. Since the ISS, there have been 7 patients with gamma GT elevations $\geq 3 \times$ ULN: 3 on 1 mg anastrozole and 2 on each of the other arms. In four of these cases, disease progression was noted close to the time of the laboratory abnormality; the remaining 3 patients (one in each arm) remain on study with stable disease. Since the ISS, there have been two patients with alkaline phosphatase elevations $\geq 3 \times$ ULN: one each on the 1 mg anastrozole and megestrol arms. Mean concentrations of total bilirubin, albumin, AST and ALT did not change appreciably in any of the treatment arms. Since the ISS, there have been no new patients in clinical pharmacology trials with significant abnormalities in hepatic biochemistry.

- **Renal Function**

In the controlled trials, there was no clinically significant difference between mean serum creatinine before treatment and at withdrawal for patients on the 1 or 10 mg anastrozole arms. Since the ISS, there have been no reports of creatinine elevations in these patients. In the clinical pharmacology trials, there were no observed differences between baseline and withdrawal mean serum creatinine levels among breast cancer patients.

- **Cholesterol**

In the controlled trials, mean serum cholesterol levels increased by 0.5 mmol/l after treatment with anastrozole 1 or 10 mg. Since the ISS, cholesterol elevations have been reported for 13 patients (7 in the 1 mg anastrozole arm, 4 in the 10 mg anastrozole arm, and 2 in the megestrol arm). In this update, changes in apoprotein A and B levels resembled those reported in the ISS in magnitude and direction for each of the treatment groups (see Review Section 6.7). Patients on the clinical pharmacology trials showed a smaller rise in serum cholesterol with anastrozole treatment and no additional patients developed cholesterol elevations.

7.7 Sponsor's Conclusions Regarding Safety Update

This 4-month Safety Update has reviewed all safety data related to anastrozole collected up to March 31, 1995. No new categories of adverse events have been identified that were not discussed in the ISS. This review supports the overall conclusions of the ISS, namely, that the safety profile of anastrozole is acceptable, and that 1 mg be the recommended dose in the treatment of advanced breast cancer in postmenopausal women.

8. Reviewer's Conclusions

The major source of estrogen in the postmenopausal woman is derived from androstenedione, which is produced in the adrenal. Androstenedione is then converted by an aromatase reaction in peripheral tissues to estrone and estradiol. The aromatase cytochrome P-450 enzyme complex is present in several tissues, including adipose tissue, and normal and neoplastic breast tissue. Aromatase activity is detectable in 50-60% of breast tumors. The contribution that tumor/adipose aromatase makes to estrogen concentrations within breast tumors, and whether the estrogen formed is biologically important remain controversial issues. Nevertheless, one approach to the treatment of hormone-dependent breast cancer has been the inhibition of estrogen biosynthesis.

Aminoglutethimide is the pioneer of the reversible competitive nonsteroidal aromatase inhibitors. However, aminoglutethimide is a nonselective inhibitor, causes adrenal suppression, and is associated with lethargy, pruritic rash, and orthostatic dizziness. Further studies have led to the discovery of a new generation of more specific and potent aromatase inhibitors, including three triazole derivatives: anastrozole, vorazole, and letrozole.

Anastrozole suppresses serum estradiol concentrations to undetectable levels in healthy postmenopausal women and in postmenopausal patients with advanced breast cancer. The recommended dose of 1 mg is the lowest dose that appears to reliably suppress estradiol when highly sensitive assays are utilized. Anastrozole's long plasma elimination half-life (40-50 hours), and good oral bioavailability allow for convenient, once-daily, oral dosing.

Unlike aminoglutethimide, anastrozole does not inhibit any of the major pathways of adrenal steroidogenesis. In clinical pharmacology studies involving healthy postmenopausal women and male volunteers, pre- and post-anastrozole dosing evaluation of adrenal hormones showed no significant differences. Cortisol and aldosterone responses after ACTH challenge were normal in these subjects, and among postmenopausal breast cancer patients after 115 days of continuous anastrozole therapy (10 mg). In the two controlled trials, there were no apparent signs of adrenal insufficiency among the 508 advanced breast cancer patients treated with anastrozole. Thus, glucocorticoid or mineralocorticoid replacement therapy with anastrozole does not appear necessary.

Anastrozole does not appear to disturb thyroid function in postmenopausal women with breast cancer after 28 days of continuous dosing with 10 mg anastrozole.

No dose adjustment of anastrozole appears necessary in the setting of renal insufficiency, although only a small number of renally-impaired individuals were evaluated in the entire clinical program. Recall that renally-impaired subjects in clinical pharmacology trials received only one dose of anastrozole.

No dose adjustment of anastrozole appears necessary in the setting of mild to moderate hepatic impairment. Again, recall that cirrhotic subjects in clinical pharmacology trials received only one

dose of anastrozole. In the controlled trials, the elevations noted in mean serum gamma GT levels, particularly among patients with liver metastases at the time of treatment withdrawal, did not appear to have major clinical significance, except as a harbinger of progression of disease within the liver. However, in the event that persistent elevations in serum gamma GT levels become detectable in the absence of liver metastases, further evaluation would be warranted. Anastrozole dosing in the setting of severe hepatic impairment has not been evaluated.

Anastrozole has moderate protein binding (40%), so significant drug-drug interactions with other drugs, such as warfarin, appear unlikely.

The clinical significance of the anastrozole-related elevations in serum total cholesterol (0.5 mmol/l) and in LDL cholesterol in postmenopausal women with advanced breast cancer is unknown.

Anastrozole has not been studied in premenopausal women; its use in this population is not recommended given the anticipated pharmacologic effects of anastrozole. Interruption of estrogen biosynthesis in premenopausal women would result in reflex increments in FSH and LH, with production of new aromatase enzyme and enhanced ovarian steroidogenesis. (The combination of anastrozole with GnRH agonists may overcome these concerns in premenopausal women.) Anastrozole is contraindicated in pregnant women, and its safety in children has not been established.

- **Efficacy Concerns**

Treatment with anastrozole 1 or 10 mg produced few objective responses, on the order of 10%. These were primarily in soft tissue sites, and occasionally in bone. Responses were fairly durable, however, with approximately 65% of responses lasting six months or more. There were three complete and three partial responses lasting one year or more. As would be predicted, response to anastrozole was associated with ER+ status, soft tissue involvement, and prior response to tamoxifen. PR+ status and reason for prior hormonal treatment (adjuvant vs. advanced disease) did not appear to impact on response rate. Patients with ER- status, or whose best previous response to tamoxifen for advanced disease had been disease progression, rarely responded to anastrozole in the controlled trials.

The 8% objective response rate for megestrol acetate in this clinical program clearly fell at the low end of the spectrum of response rates reported in the literature. Phase II trials in advanced breast cancer patients with or without prior hormonal therapy reported response rates in the range of 4 to 56%. A response rate of only 5% (2/38) was reported in a group of patients crossed over to megestrol acetate after failing tamoxifen in a randomized comparison of these two agents; survival after crossover was 3 to 4 months (Muss et al., JCO, 1988). The low response rates noted in this clinical program could be due to a host of factors related to patient selection (e.g., proportion of women with ER+ status, measurable disease, soft tissue vs. visceral involvement, prior response to tamoxifen), and response criteria applied (e.g., partial responses could not be assigned to

could not be assigned to patients with nonmeasurable disease).

The protocols for the pivotal trials, 0004 and 0005, did not specify a period of withdrawal after progression on tamoxifen before beginning study treatment. The median time to first response for Trial 0004 was 62 days (range days); and 72 days for Trial 0005 (range days). In Trial 0004, 8/27 objective responses were first noted at 4 weeks (3 on anastrozole 1 mg, 2 on anastrozole 10 mg, and 3 on megestrol acetate). In Trial 0005, 9/42 responses were first noted at 4 weeks (4 each on anastrozole 1 and 10 mg, 1 on megestrol acetate). Given, the long half-life of tamoxifen, the possibility exists that some of the responses observed in these trials, both objective and disease stabilization, may have been withdrawal responses.

Median times to progression and to treatment failure with anastrozole therapy in the controlled trials were comparable due to the large proportion of patients who discontinued treatment because of disease progression. These endpoint durations ranged from 4 to 6 months, suggesting that use of anastrozole for advanced breast cancer following tamoxifen failure represents a short-lived treatment option. Despite this, survival rates in these trials may prove to be quite favorable. Survival on anastrozole is not yet calculable for the recommended 1 mg dose, but was reported to be 442 days for the 10 mg anastrozole arm in Trial 0005. Possible reasons for this outcome include, the clinical benefit derived from anastrozole-induced disease stabilization in these patients, or the contribution of subsequent antitumor treatments.

Although the controlled trials were designed to show anastrozole's superiority to the megestrol acetate comparator, comparability in efficacy endpoints has been demonstrated. Given the sample sizes of these trials at the time of study termination, equivalence of 3 weeks in time to disease progression between anastrozole and megestrol acetate would be statistically detectable with only 22-24% power. This assumes an accrual period of 15 months, a follow-up period of 12 months, a median time to progression for megestrol acetate of 4.5 months, and a 5% type I error rate. (See Statistical Review for further details.)

Is comparability to megestrol acetate as demonstrated in the two controlled trials truly an unexpected finding? Perhaps not. Three randomized trials have shown megestrol acetate to be as effective as aminoglutethimide for second line therapy of advanced breast cancer. Recently, a randomized trial demonstrated that using half (500 mg) of the conventional dose of aminoglutethimide, without hydrocortisone, did not significantly lower efficacy (the incidence of adverse events was reduced). Thus, while anastrozole is a more potent and selective aromatase inhibitor than aminoglutethimide, it remains to be shown whether complete suppression of estrogen production and action will result in enhanced tumor regression with anastrozole.

- **Safety Concerns**

The most common drug-related adverse events with anastrozole were hot flushes, headache, nausea, asthenia, and non-specific pain. Patients discontinued treatment with anastrozole infrequently because of adverse events. In particular, for the events listed above, headache and

vomiting (not nausea) resulted in two patient withdrawals each in the controlled trials (as of the most recent cut-off date). There were no overt clinical signs or laboratory abnormalities indicative of adrenal suppression with anastrozole.

There was some evidence for a relationship between anastrozole dose and gastrointestinal disturbances. This was suggested in the sponsor's analysis of anticipated adverse events. In addition, patients on the 10 mg anastrozole dose who were non-compliant with dosing reported nausea and vomiting more frequently than patients who were compliant with dosing.

The most common drug-related adverse events with megestrol acetate were weight gain, dyspnea, edema, hot flushes, asthenia, non-specific pain, nausea, increased appetite, and vaginal hemorrhage. Treatment withdrawals due to these events occurred in two patients each with dyspnea and nausea, and in one patient each with lung edema, asthenia, non-specific pain, and hot flushes. Interestingly, no patient withdrew due to weight gain. Review of serious adverse events and deaths suggests a less favorable profile of cardiopulmonary events with megestrol acetate as compared to anastrozole.

- **Benefit/Risk Assessment**

Based on the results of the two controlled clinical trials, and on inferences from the literature, anastrozole appears to be as effective as other currently available hormonal agents for the treatment of patients with advanced breast cancer who have progressed on tamoxifen. Anastrozole's safety profile appears to be favorable compared to the anticipated events noted for megestrol acetate (cardiopulmonary events) and for aminoglutethimide (lethargy, rash, and orthostatic dizziness).

Strictly speaking, two breast cancer populations have been studied in this clinical program: those progressing on tamoxifen given for advanced disease, and those progressing on tamoxifen given in the adjuvant setting. In the first case, life expectancy is generally considered to be limited and the goal of treatment is palliation with minimal toxicity: anastrozole represents a reasonable alternative in this setting. For women who have progressed on tamoxifen as adjuvant therapy and who are candidates for continued hormonal therapy, anastrozole also represents a reasonable treatment alternative. In either instance, patients with soft tissue metastases are most likely to respond to anastrozole treatment

9. Updated Survival Analysis: Controlled Trials

On October 4, 1995, ZENECA submitted an updated survival analysis for the 764 patients enrolled on the two controlled trials. Follow-up was extended to March 31, 1995, allowing for a median follow-up of 12 months for Trial 0004, 11 months for Trial 0005, and 12 months overall.

Altogether, 74 (28%) patients on anastrozole 1 mg, 62 (25%) patients on anastrozole 10 mg, and 84 (33%) patients on megestrol acetate died as of the new cut-off date. For Trial 0004, the median time to death on anastrozole 1 mg was 21 months, and 24 months on anastrozole 10 mg. The median time to death was not calculable for patients on megestrol acetate in Trial 0004, or for patients on any treatment arm on Trial 0005.

Using the Cox proportional hazards model, comparisons of anastrozole 1 and 10 mg with megestrol acetate were not statistically different with respect to time to death (see below).

Comparison of Trials 0004 and 0005: Time to Death

Trial 0004	**# Patients**	**# Events**	**Hazard Ratio**	**P value**
1 mg A vs. M	A: 128 M: 128	A: 31 M: 41	0.83 (0.48 - 1.42)	0.43
10 mg A vs. M	A: 130 M: 128	A: 27 M: 41	0.62 (0.35 - 1.10)	0.06
Trial 0005	**# Patients**	**# Events**	**Hazard Ratio**	**P value**
1 mg A vs. M	A: 135 M: 125	A: 43 M: 43	0.89 (0.55 - 1.44)	0.58
10 mg A vs. M	A: 118 M: 125	A: 35 M: 43	0.84 (0.50 - 1.41)	0.45
0004 and 0005	**# Patients**	**# Events**	**Hazard Ratio**	**P value**
1 mg A vs. M	A: 263 M: 253	A: 74 M: 84	0.86 (0.60 - 1.23)	0.33
10 mg A vs. M	A: 248 M: 253	A: 62 M: 84	0.73 (0.50 - 1.07)	0.06

Thus, for the two trials combined, the death rate for patients on anastrozole 1 mg could be about 60% of that for megestrol acetate, or 123% of the rate for megestrol acetate. The death rate for patients on anastrozole 10 mg could be 50% of that for megestrol acetate, or 107% of the rate for megestrol acetate. These findings are similar to those given in the Integrated Summary of Efficacy, Section 5.

10. Response to FDA Regarding Withdrawal Interval

Since the effect of tamoxifen may persist for several weeks after its withdrawal, FDA was concerned that some of the responses observed in the controlled trials might be withdrawal responses. On September 15, 1995, FDA requested information regarding the length of the withdrawal interval for patients enrolled on Trials 0004 and 0005 (that is, the time between stopping prior tamoxifen therapy and beginning study treatment).

On October 11, 1995, ZENECA submitted analyses of withdrawal interval by best tumor response for patients on each controlled trial and for the trials combined. Individual patient data were also provided. A summary of these findings is shown below.

Withdrawal Interval by Best Response

Withdrawal Interval	Objective Response (CR + PR)	Disease Stabilization	Disease Progression
Anastrozole 1 mg			
$\leq$ 2 weeks	67% (18/27)	64% (59/92)	70% (97/139)
> 2 weeks	33% (9/27)	36% (33/92)	30% (42/139)
Anastrozole 1 mg			
$\leq$ 2 weeks	68% (15/22)	62% (61/99)	65% (77/119)
> 2 weeks	32% (7/22)	38% (38/99)	35% (42/119)
Megestrol Acetate			
$\leq$ 2 weeks	60% (12/20)	62% (61/99)	70% (88/125)
> 2 weeks	40% (8/20)	38% (38/99)	30% (37/125)

Overall, 60-70% of patients on each treatment arm had a withdrawal interval of $\leq$ 2 weeks. Withdrawal intervals were similar for patients in each major response category. Thus, it is not possible to exclude the presence of some withdrawal responses in each of the treatment arms.

11. ODAC, October 16, 1995

Question 1. Are Trials 0004 and 0005 adequate and well-controlled?

There was some discussion regarding whether megestrol acetate was an appropriate control for anastrozole, with Dr. Krook favoring aminoglutethimide. Dr. Forrestiere disagreed, stating that megestrol acetate was a reasonable choice. The vote was yes 9, no 1.

Question 2. There was no statistical difference between anastrozole 1 mg/day and megestrol acetate 160 mg/day in the two controlled trials with respect to any of the efficacy endpoints. However, the trials were not designed or powered to demonstrate equivalence. Is there sufficient

evidence to conclude that anastrozole is comparable to megestrol acetate as hormonal therapy for advanced breast cancer following tamoxifen failure?

The committee was reluctant to state that the two agents were comparable since this might imply statistical equivalence. No vote was actually taken, however, Dr. Krook and other committee members did believe that anastrozole was efficacious as hormonal therapy for advanced breast cancer following tamoxifen failure.

Question 3. The basis of approval for minimally toxic hormonal agents for the treatment of advanced breast cancer has generally been objective response rate. Is anastrozole 1 mg/day approvable for the treatment of postmenopausal women with advanced breast cancer following tamoxifen failure?

The vote was unanimous: yes 10, no 0. Committee members did point out that in clinical practice anastrozole might not be used in place of megestrol acetate, but rather, following failure of megestrol acetate (i.e., as third line hormonal therapy).

Question 4. Given that median response duration and survival have not been reached for all treatment arms in the two controlled trials, does ODAC wish to consider updated information on these study parameters when it becomes available?

Follow-up data should be submitted to the FDA as a phase 4 commitment, but if the results are consistent with what has been reported thus far, ODAC does not need to review them.

12. Recommended Regulatory Action, October 25, 1995

On October 16, 1995, the Oncologic Drugs Advisory Committee unanimously recommended approval of anastrozole. This decision was based on an objective response rate of 10.3%, including 14 durable responses lasting six months or more, and a median time to disease progression of 4.7 months. The median survival was 21 months on Trial 0004 but could not be calculated for the second trial due to the low number of deaths. Follow-up survival data should be submitted to the Agency when it becomes available. The safety profile of anastrozole was favorable, with only 3% of patients withdrawing treatment due to adverse events. Anastrozole does not appear to inhibit adrenal steroidogenesis or thyroid function in postmenopausal women. No dose adjustment appears to be required in the elderly or in patients with renal impairment or mild to moderate hepatic impairment. ARIMIDEX® has not been studied in patients with severe hepatic impairment, in premenopausal women with advanced breast cancer, or in pediatric patients.

Thus, ARIMIDEX® (Anastrozole) 1 mg administered orally once daily should be approved for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

13. Deficiency List

There are no deficiencies.

14. Post-Approval Studies and Analyses

We note that the sponsor has committed verbally to us and before the Oncologic Drugs Advisory Committee to the completion of two ongoing studies. The sponsor should provide a letter documenting its intent to complete and submit results of the following studies as soon as possible after marketing:

a) For Trials 0004 and 0005, the median response duration and median survival for patients on all treatment arms when this data becomes available; and

b) Ongoing phase 3 trials in advanced breast cancer comparing anastrozole 1 mg daily with tamoxifen 20 mg daily, and with fonnestane administered IM every two weeks.

15. Product Labeling Comments

Zeneca's proposed product labeling (Rev A-4, 03/95) has been reviewed. Please convey the following comments regarding product labeling to the sponsor:

CLINICAL PHARMACOLOGY (See Biopharm reviewer's comments for additional details.)

Mechanism of Action: Insert "some" in the third line to read, "produces a beneficial effect in some women with breast cancer".

Pharmacokinetics and Metabolism: Please clarify whether metabolic studies listed in the first paragraph of page 4 were conducted in postmenopausal women only or in other populations as well.

Pharmacodynamic Effect: Please include information on thyroid function in postmenopausal women receiving ARIMIDEX®

CLINICAL STUDIES

In the first paragraph, change "All patients had progressed following tamoxifen therapy" to "All patients had disease progression following tamoxifen therapy". Please make it clear that the double-blind applied only to the ARIMIDEX arms

In the second paragraph, after "Demographics were similar among treatment groups for each trial" insert the following: "However, 20% of patients on Trial 0004 and 40% in Trial 0005 had responded to prior tamoxifen therapy for advanced disease. In Trial 0004, 81% of patients were

ER-positive, 13% were ER-unknown, and 6% were ER-negative. In Trial 0005, 58% of patients were ER-positive, 37% were ER-unknown, and 5% were ER-negative. In Trial 0004, 60% of patients had measurable disease compared to 80% in Trial 0005. Then continue with "The sites of metastatic disease ...".

In the first paragraph below the table of efficacy results (page 6) delete: "In patients who had an objective response, the duration of this response was significant for all treatment groups."

In the second paragraph below the table of efficacy results (page 6), in the discussion of time to progression, change: "ARIMIDEX 1 mg and ARIMIDEX 10 mg were equivalent in efficacy to the comparator" to "ARIMIDEX 1 mg and ARIMIDEX 10 mg were similar in efficacy to the comparator".

Following the discussion of time to progression insert the following, "The odds ratio and confidence intervals of the comparison between each dose of ARIMIDEX and megestrol acetate for objective response rate demonstrate that both ARIMIDEX 1 mg and ARIMIDEX 10 mg were similar in efficacy to the comparator. For the ARIMIDEX 1 mg comparison to megestrol acetate, the odds ratio was 1.32 [0.66, 2.65] (p=0.37); for ARIMIDEX 10 mg compared to megestrol acetate, the odds ratio was 1.15 [0.55, 2.36] (p=0.68).

At the conclusion of the second paragraph, insert "These trials were not designed or powered to demonstrate equivalence."

INDICATIONS AND USAGE

Change "postmenopausal women who have progressed following tamoxifen therapy" to "postmenopausal women with disease progression following tamoxifen therapy".

Add the statement, "Patients with ER-negative disease, and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX.

CONTRAINDICATIONS

Delete the paragraph that is currently listed on page 7 and state "None known" here.

Begin a new WARNINGS section that incorporates the pharm/tox reviewer's comments.

PRECAUTIONS

General: Include the statement "ARIMIDEX should be administered under the supervision of a qualified physician experienced in the use of anticancer agents." Delete "see CONTRAINDICATIONS".

Laboratory Tests: Add a "**Laboratory Tests**" subsection which states the following: "Three-fold elevations of mean serum gamma GT levels have been observed among patients with liver metastases receiving ARIMIDEX. These changes were likely related to the progression of liver metastases in these patients, although other contributing factors could not be ruled out. Therefore, periodic monitoring of liver function tests should be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See pharm/tox reviewer's comments.

Pregnancy: Change to Pregnancy Category D (see WARNINGS)

Teratogenic Effects, Nonteratogenic Effects: See pharm/tox reviewer's comments.

Nursing Mothers, Pediatric Use: See pharm/tox reviewer's comments.

ADVERSE REACTIONS

The table of adverse events on page 10 should list events in order of frequency.

Digestive: Delete this section. Incorporate statements on gamma GT, SGOT, and SGPT under a new section labeled **Hepatic**

Hemic and Lymphatic System: Change to "**Hematologic**".

Metabolic and Nutritional: Delete statements on SGOT and SGPT, and add the following, "Mean serum total cholesterol levels increased by 0.5 mmol/l among patients receiving ARIMIDEX. Increases in LDL cholesterol have been shown to contribute to these changes.

The table of adverse events on page 12 should list events in order of frequency.

The data presented in the second paragraph on page 12 suggest a greater number of patients on all treatment arms ha ' weight gain than is shown in the preceding table. For example, for anastrozole 1 mg, 34 patients (13% of 26.) would have weight gain of 5% or more vs 4 patients listed in the table. Please clarify this apparent discrepancy.

Insert at e end of the second paragraph, page 12, "No patient on ARIMIDEX or megestrol acetate discontinued treatment due to drug-related weight gain."

Abnormal Laboratory Test Values: Delete this section.

DOSAGE AND ADMINISTRATION

Insert the statement, "Patients treated with ARIMIDEX do not require glucocorticoid or mineralocorticoid replacement therapy."

Patients with Hepatic Impairment: Change the last sentence to: "ARIMIDEX has not been studied in patients with severe hepatic impairment and these patients should be monitored with periodic liver function tests.

Julie Beitz MD 11-30-95
Julie Beitz, MD Date

Robert Justice MD 11/30/95
Robert Justice, MD Date

cc:
NDA # 20-541
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ L. Vaccari

4-MONTH SAFETY UPDATE

TABLE 5 Number of subjects with different categories of adverse events during or after exposure to anastrozole (ZD1033) in each category of trial in the entire clinical program

Category*	Controlled trials in women with breast cancer#					Clinical pharmacology trials in women with breast cancer					Other clinical pharmacology trials+		Total			
	At cut-off for ISS (n=508)		At cut-off for 4MSU (n=508)		Difference	At cut-off for ISS (n=19)		At cut-off for 4MSU (n=31)		Difference	At cut-off for ISS (n=210)		At cut-off for ISS (n=737)		At cut-off for 4MSU (n=749)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	n	(%)	
All adverse events	406	(79.9)	429	(84.4)	23	16	(84.2)	22	(71.0)	6	125	(59.5)	547	(74.2)	576	(76.9)	29
Serious adverse events	96	(18.9)	111	(21.9)	15	3	(15.8)	7	(22.6)	4	3	(1.4)	102	(13.8)	121	(16.2)	19
Withdrawals																	
due to adverse event	15	(3.0)	16	(3.1)	1	1	(5.3)	1	(3.2)	0	3	(1.4)	19	(2.6)	20	(2.7)	1
not due to adverse event**	249	(49.0)	332	(65.4)	83	15	(78.9)	20	(64.5)	5	5	(2.4)	269	(36.5)	357	(47.7)	88
Deaths																	
due to breast cancer alone	16	(3.1)	21	(4.1)	5	0	(0)	0	(0)	0	0	(0)	16	(2.2)	21	(2.8)	5
other causes	7	(1.4)	8	(1.6)	1	0	(0)	0	(0)	0	0	(0)	7	(0.9)	8	(1.1)	1

* These categories are not mutually exclusive

\# Includes only adverse events which first occurred during or within 2 weeks after stopping treatment

\+ Totals for all clinical pharmacology trials that were completed by the cut-off date for the ISS; there has been no change to the data since then

** This includes disease progression, withdrawal of consent and lost to follow-up.

TABLE 10 Drug-related adverse events with an incidence of at least 2% during or within 2 weeks after treatment with anastrozole (ZD1033) or megestrol acetate in women with breast cancer in the controlled clinical trials

Body system/adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Body as a whole															
Asthenia	14	(5.3)	17	(6.5)	3	8	(3.3)	10	(4.1)	2	16	(6.3)	17	(6.7)	1
Back pain	3	(1.1)	4	(1.5)	1	6	(2.4)	6	(2.4)	0	3	(1.2)	3	(1.2)	0
Generalised edema	0	(0)	0	(0)	0	3	(1.2)	3	(1.2)	0	5	(2.0)	5	(2.0)	0
Headache	14	(5.3)	16	(6.1)	2	26	(10.6)	27	(11.0)	1	11	(4.3)	11	(4.3)	0
Pain	9	(3.4)	11	(4.2)	2	7	(2.8)	8	(3.3)	1	9	(3.6)	10	(4.0)	1
Cardiovascular system															
Hot flushes	28	(10.7)	29	(11.1)	1	25	(10.2)	25	(10.2)	0	17	(6.7)	17	(6.7)	0
Hypertension#	1	(0.4)	2	(0.8)	1	2	(0.8)	2	(0.8)	0	5	(2.0)	6	(2.4)	1
Digestive system															
Constipation	1	(0.4)	1	(0.4)	0	6	(2.4)	6	(2.4)	0	4	(1.6)	4	(1.6)	0
Diarrhea	6	(2.3)	6	(2.3)	0	5	(2.0)	5	(2.0)	0	1	(0.4)	1	(0.4)	0
Dry mouth	5	(1.9)	6	(2.3)	1	8	(3.3)	8	(3.3)	0	5	(2.0)	5	(2.0)	0
Increased appetite	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	11	(4.3)	11	(4.3)	0
Nausea	11	(4.2)	11	(4.2)	0	14	(5.7)	14	(5.7)	0	11	(4.3)	13	(5.1)	2
Metabolic and nutritional disorders															
Peripheral edema	4	(1.5)	4	(1.5)	0	7	(2.8)	8	(3.3)	1	10	(4.0)	11	(4.3)	1
Weight gain	4	(1.5)	5	(1.9)	1	8	(3.3)	8	(3.3)	0	30	(11.9)	34	(13.4)	4
Musculoskeletal system															
Bone pain	2	(0.8)	3	(1.1)	1	5	(2.0)	5	(2.0)	0	2	(0.8)	2	(0.8)	0
Nervous system															
Dizziness	7	(2.7)	7	(2.7)	0	0	(0)	0	(0)	0	5	(2.0)	5	(2.0)	0
Paresthesia	1	(0.4)	1	(0.4)	0	6	(2.4)	7	(2.8)	1	4	(1.6)	6	(2.4)	2
Tremor	1	(0.4)	1	(0.4)	0	0	(0)	1	(0.4)	1	5	(2.0)	5	(2.0)	0
Respiratory system															
Dyspnea	6	(2.3)	6	(2.3)	0	4	(1.6)	4	(1.6)	0	18	(7.1)	18	(7.1)	0
Skin and appendages															
Alopecia	7	(2.7)	7	(2.7)	0	9	(3.7)	9	(3.7)	0	1	(0.4)	1	(0.4)	0
Sweating	4	(1.5)	4	(1.5)	0	2	(0.8)	2	(0.8)	0	11	(4.3)	11	(4.3)	0
Urogenital system															
Leukorrhea	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	8	(3.2)	8	(3.2)	0
Vaginal hemorrhage	5	(1.9)	6	(2.3)	1	3	(1.2)	3	(1.2)	0	11	(4.3)	13	(5.1)	2

* A patient may have more than one adverse event

\# This event was not listed in the corresponding table in the ISS as the incidence was not >2%.

TABLE 14 List of all patients who have had a serious adverse event since the cut-off date for the ISS

Treatment/trial	Centre/Patient	Serious adverse event
Controlled clinical trials		
ZD1033 1 mg		
Trial 0004	0005,	Gamma-glutamyl transpeptidase increased
	0006,	Abdomen enlarged Abdominal pain
	0013,	Pathological fracture
	0015,	Heart failure
Trial 0005	0027,	Peripheral edema
	0045,	Dyspnea
	0062,	Paresthesia
ZD1033 10 mg		
Trial 0004	0001,	Syncope
	0008,	Apnea
	0012,	Heart arrest Myocardial infarct
	0021,	Nausea Vomiting
	0030,	Nausea Vomiting Leukopenia
	0042,	Dyspnea
	0044,	Headache Bone pain Dizziness Paresthesia Sweating
	0045/	Gastrointestinal hemorrhage
Trial 0005	0006/	Diarrhea
	0021,	Pelvic pain
	0023,	Renal hypertension
	0028,	Cerebral infarct Thrombophlebitis
	0051,	Shock
	0097	Asthenia Neoplasm Convulsion
	0136,	Fever

* Patient also reported a serious adverse event before the cut-off date for the ISS
\# Dyspnea was also the serious adverse event reported by this patient before the cut-off date for the ISS
\+ Elective surgery

(continued)

TABLE 14 List of all patients who have had a serious adverse event since the cut-off date for the ISS (continued)

Treatment/trial	Centre/Patient	Serious adverse event
Megestrol acetate		
Trial 0004	0012	Dyspnea
	0015	Cerebral infarct
	0031	Depression
	0070	Back pain Cerebral ischemia Dementia
Trial 0005	0004	Heart failure Lung edema
	0026	Pneumonia
	0135	Back pain Dyspnea
Clinical pharmacology trials		
ZD1033 10 mg		
Trial 0022	0002	Pathological fracture
	0002	Syncope
	0002	Reaction unevaluable+
	0003	Fever

* Patient also reported a serious adverse event before the cut-off date for the ISS
\# Dyspnea was also the serious adverse event reported by this patient before the cut-off date for the ISS
\+ Elective surgery

6.2 Serious adverse events in the controlled clinical trials in women with breast cancer

Appendix F: *Serious adverse events in controlled clinical trials, T52.1; Serious adverse events by body system, T53*

Table 15 shows the number of patients in each treatment group in the controlled clinical trials who had a serious adverse event during or within 2 weeks after stopping treatment. Table 16 summarizes all serious adverse events in the controlled clinical trials by body system and COSTART preferred term.

TABLE 19 Serious drug-related adverse events during or within 2 weeks after treatment with anastrozole (ZD1033) or megestrol acetate in women with breast cancer in the controlled clinical trials

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Body as a whole															
Abdominal pain	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Aggravation reaction	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Ascites	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Asthenia	1	(0.4)	1	(0.4)	0	1	(0.4)	0	(0)	-1+	2	(0.8)	2	(0.8)	0
Face edema	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Fever	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Headache	1	(0.4)	1	(0.4)	0	2	(0.8)	2	(0.8)	0	0	(0)	0	(0)	0
Pain	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0
Cardiovascular system															
Cerebral ischemia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Heart failure	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Hot flushes	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Palpitation	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Pulmonary embolus	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	4	(1.6)	4	(1.6)	0
Tachycardia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Thrombophlebitis	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0
Digestive system															
Anorexia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Cholestatic jaundice	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Diarrhea	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Gamma glutamyl transpeptidase increased	0	(0)	1	(0.4)	1	0	(0)	0	(0)	0	0	(0)	0	(0)	0

* A patient may have more than one serious adverse event

\+ One event, reported as serious in the ISS, has been amended by the investigator to non-serious

(continued)

TABLE 19 Serious drug-related adverse events during or within 2 weeks after treatment with anastrozole (ZD1033) or megestrol acetate in women with breast cancer in the controlled clinical trials (continued)

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (150 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Digestive system (continued)															
Gum hemorrhage	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Nausea	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0
Stomatitis	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Vomiting	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Hemic and lymphatic system															
Anemia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Pancytopenia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Metabolic and nutritional disorders															
Hypercalcemia	1	(0.4)	1	(0.4)	0	2	(0.8)	2	(0.8)	0	1	(0.4)	1	(0.4)	0
Hyperglycemia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Peripheral edema	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Musculoskeletal system															
Bone pain	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Nervous system															
Dementia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Depression	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Dizziness	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Insomnia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Neuropathy	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Somnolence	3	(1.1)	3	(1.1)	0	1	(0.4)	0	(0)	-1+	0	(0)	0	(0)	0

* A patient may have more than one serious adverse event

\+ One event, reported as serious in the ISS, has been amended by the investigator to non-serious

(continued)

TABLE 19 Serious drug-related adverse events during or within 2 weeks after treatment with anastrozole (ZD1033) or megestrol acetate in women with breast cancer in the controlled clinical trials (continued)

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Respiratory System															
Cough increased	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Dyspnea	2	(0.8)	2	(0.8)	0	1	(0.4)	1	(0.4)	0	8	(3.2)	8	(3.2)	0
Larynx edema	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Lung edema	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Skin and appendages															
Pruritus	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Rash	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0
Skin benign neoplasm	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Vesiculobullous rash	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Special senses															
Conjunctivitis	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Ear pain	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Urogenital system															
Vaginal hemorrhage	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0

* A patient may have more than one serious adverse event
\+ One event, reported as serious in the ISS, has been amended by the investigator to non-serious

TABLE 22 Adverse events leading to withdrawal from treatment with anastrozole (ZD1033) in the entire clinical program

Body system/ adverse event*	At cut-off for ISS (n=737)		At cut-off for 4MSU (n=749)		Difference
	n	(%)	n	(%)	
Total number of subjects withdrawn because of an adverse event	19	(2.6)	20	(2.7)	1
Body as a whole					
Aggravation reaction	1	(0.1)	1	(0.1)	0
Asthenia	1	(0.1)	0	(0)	-1#
Face edema	1	(0.1)	1	(0.1)	0
Fever	1	(0.1)	1	(0.1)	0
Headache	2	(0.3)	2	(0.3)	0
Cardiovascular system					
Arterial anomaly	1	(0.1)	1	(0.1)	0
Hypertension	1	(0.1)	1	(0.1)	0
Myocardial ischemia	1	(0.1)	1	(0.1)	0
Pulmonary embolus	1	(0.1)	1	(0.1)	0
Digestive system					
Anorexia	1	(0.1)	1	(0.1)	0
Cholestatic jaundice	1	(0.1)	1	(0.1)	0
Gamma glutamyl transpeptidase increased	0	(0)	1	(0.1)	1
Vomiting	2	(0.3)	2	(0.3)	0
Hemic and lymphatic system					
Pancytopenia	1	(0.1)	1	(0.1)	0
Thrombocytopenia	1	(0.1)	1	(0.1)	0
Metabolic and nutritional disorders					
Hypercalcemia	2	(0.3)	2	(0.3)	0
Peripheral edema	1	(0.1)	1	(0.1)	0
Nervous system					
Dizziness	1	(0.1)	1	(0.1)	0
Insomnia	1	(0.1)	1	(0.1)	0
Neuropathy	1	(0.1)	1	(0.1)	0
Paresthesia	1	(0.1)	1	(0.1)	0
Somnolence	1	(0.1)	0	(0)	-1#
Respiratory system					
Apnea	1	(0.1)	1	(0.1)	0
Dyspnea	2	(0.3)	2	(0.3)	0
Larynx edema	1	(0.1)	1	(0.1)	0

* A subject may be withdrawn because of more than one adverse event

\# Events reported as leading to withdrawal in the ISS, which have since been amended by the investigator (refer to text in Section 7.1)

(continued)

TABLE 25 Adverse events leading to withdrawal from treatment with anastrozole (ZD1033) or megestrol acetate in women with breast cancer in the controlled clinical trials

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Body as a whole															
Aggravation reaction	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Asthenia	0	(0)	0	(0)	0	1	(0.4)	0	(0)	-1#	1	(0.4)	1	(0.4)	0
Face edema	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Fever	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Headache	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0	0	(0)	0	(0)	0
Pain	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Cardiovascular system															
Arterial anomaly	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Cerebral infarct	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Cerebral ischemia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Cerebrovascular accident	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Heart failure	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Hot flushes	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Palpitation	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Pulmonary embolus	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	2	(0.8)	2	(0.8)	0
Digestive system															
Anorexia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Cholestatic jaundice	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Diarrhea	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Gamma glutamyl transpeptidase increased	0	(0)	1	(0.4)	1	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Gum hemorrhage	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Nausea	0	(0)	0	(0)	0	0	(0)	0	(0)	0	3	(1.2)	3	(1.2)	0

* A patient may be withdrawn due to more than one adverse event

\# Events reported as leading to withdrawal in the ISS, which have since been amended by the investigator (refer to text in Section 7.1)

(continued)

TABLE 25 Adverse events leading to withdrawal from treatment with anastrozole (ZD1033) or megestrol acetate in women with breast cancer in the controlled clinical trials (continued)

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Digestive system (continued)															
Stomatitis	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Vomiting	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Hemic and lymphatic system															
Pancytopenia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Metabolic and nutritional disorders															
Hypercalcemia	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0	0	(0)	0	(0)	0
Hyperglycemia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Peripheral edema	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Nervous system															
Depression	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Dizziness	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Insomnia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Neuropathy	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Somnolence	0	(0)	0	(0)	0	1	(0.4)	0	(0)	-1#	0	(0)	0	(0)	0
Respiratory system															
Apnea	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Cough increased	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Dyspnea	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	3	(1.2)	3	(1.2)	0
Larynx edema	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Lung edema	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1

* A patient may be withdrawn due to more than one adverse event

\# Events reported as leading to withdrawal in the ISS, which have since been amended by the investigator (refer to text in Section 7.1)

(continued)

TABLE 25 Adverse events leading to withdrawal from treatment with anastrozole (ZD1033) or megestrol acetate in women with breast cancer in the controlled clinical trials (continued)

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Skin and appendages															
Pruritus	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Rash	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0
Skin benign neoplasm	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Vesiculobullous rash	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Special senses															
Conjunctivitis	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Ear pain	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0

* A patient may be withdrawn due to more than one adverse event

Events reported as leading to withdrawal in the ISS, which have since been amended by the investigator (refer to text in Section 7.1)

TABLE 27 Drug-related adverse events leading to withdrawal from treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Body as a whole															
Asthenia	0	(0)	0	(0)	0	1	(0.4)	0	(0)	-1#	1	(0.4)	1	(0.4)	0
Face edema	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Fever	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Headache	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0	0	(0)	0	(0)	0
Pain	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Cardiovascular system															
Cerebral ischemia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Heart failure	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Hot flushes	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Palpitation	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Pulmonary embolus	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	2	(0.8)	2	(0.8)	0
Digestive system															
Anorexia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Cholestatic jaundice	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Diarrhea	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Gamma-glutamyl transpeptidase increased	0	(0)	1	(0.4)	1	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Gum hemorrhage	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Nausea	0	(0)	0	(0)	0	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0
Stomatitis	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Vomiting	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0

* A patient may be withdrawn due to more than one adverse event

\# One event, reported as drug-related in the ISS, has been amended by the investigator to not drug-related.

(continued)

TABLE 27 Drug-related adverse events leading to withdrawal from treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer (continued)

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Hemic and lymphatic system															
Pancytopenia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Metabolic and nutritional disorder															
Hypercalcemia	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0	0	(0)	0	(0)	0
Hyperglycemia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Peripheral edema	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Nervous system															
Depression	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Dizziness	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Insomnia	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0
Neuropathy	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Somnolence	0	(0)	0	(0)	0	1	(0.4)	0	(0)	-1#	0	(0)	0	(0)	0
Respiratory system															
Cough increased	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Dyspnea	0	(0)	0	(0)	0	0	(0)	0	(0)	0	2	(0.8)	2	(0.8)	0
Larynx edema	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Lung edema	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Skin and appendages															
Pruritus	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Rash	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0
Skin benign neoplasm	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Vesiculobullous rash	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0

* A patient may be withdrawn due to more than one adverse event
\# One event, reported as drug-related in the ISS, has been amended by the investigator to not drug-related

(continued)

TABLE 27 Drug-related adverse events leading to withdrawal from treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer (continued)

Body system/ adverse event*	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Special senses															
Conjunctivitis	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Ear pain	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0

* A patient may be withdrawn due to more than one adverse event

One event, reported as drug-related in the ISS, has been amended by the investigator to not drug-related.

TABLE 31 Causes of death other than breast cancer alone during or within 2 weeks after treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer

Body system/ adverse event	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Body as a whole															
Unknown	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Cardiovascular system															
Cardiovascular disease	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1	0	(0)	0	(0)	0
Cerebrovascular accident	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Heart arrest	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	2	(0.8)	2	(0.8)	0
Internal carotid artery aneurysm	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Pulmonary embolus	0	(0)	0	(0)	0	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0
Digestive system															
Intestinal perforation	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Small bowel infarction	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Nervous system															
Cerebrovascular disease	0	(0)	0	(0)	0	0	(0)	0	(0)	0	0	(0)	1	(0.4)	1
Respiratory system															
Pneumonia	0	(0)	0	(0)	0	0	(0)	0	(0)	0	4	(1.6)	4	(1.6)	0
Respiratory disorder	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0	0	(0)	0	(0)	0
Urogenital system															
Kidney failure	0	(0)	0	(0)	0	1	(0.4)	1	(0.4)	0	0	(0)	0	(0)	0

TABLE 36 Mean hepatic biochemistry results before and during treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer

Variable	Pre-treatment		12 weeks			24 weeks			48 weeks			Withdrawal		
	n	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean
ZD1033 1 mg daily														
Total bilirubin (µmol/l)	256	7.6	199	7.5	8.5	122	7.4	9.1	62	7.4	10.2	176	7.7	11.1
Alkaline phosphatase (U/l)	254	155.7	197	144.3	182.8	120	128.8	161.1	62	127.4	209.6	174	167.1	251.4
Albumin (g/l)	256	41.2	199	41.2	41.5	122	41.2	42.3	62	41.3	42.0	176	41.2	40.8
Gamma GT (U/l)	130	64.6	98	57.2	62.8	56	57.2	59.1	28	43.9	78.9	90	65.7	144.0
AST (SGOT) (U/l)	256	28.7	198	27.1	30.5	122	26.0	25.8	62	26.3	25.2	176	29.1	38.9
ALT (SGPT) (U/l)	256	22.5	199	22.0	25.5	122	21.3	22.2	62	22.7	19.1	176	22.0	28.8
ZD1033 10 mg daily														
Total bilirubin (µmol/l)	237	7.6	181	7.4	8.0	123	7.4	8.5	64	7.0	8.9	144	7.7	8.6
Alkaline phosphatase (U/l)	237	149.2	181	147.2	199.7	123	129.8	168.0	64	130.6	158.6	144	162.8	255.1
Albumin (g/l)	237	41.1	181	41.3	42.1	123	41.3	42.1	64	41.0	42.5	144	41.2	41.2
Gamma GT (U/l)	114	64.7	87	57.7	92.8	55	43.1	59.3	24	54.1	43.4	66	75.7	174.8
AST (SGOT) (U/l)	237	27.1	179	25.5	27.7	123	25.0	25.0	64	25.7	21.5	144	28.8	39.1
ALT (SGPT) (U/l)	237	22.8	181	22.6	24.0	123	21.5	21.5	64	22.0	17.8	144	23.6	28.8

(continued)

TABLE 36 Mean hepatic biochemistry results before and during treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer

Variable	Pre-treatment		12 weeks			24 weeks			48 weeks			Withdrawal		
	n	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean
Megestrol acetate														
Total bilirubin (µmol/l)	241	7.6	178	7.6	9.5	102	7.5	10.4	52	7.9	11.1	180	7.5	9.6
Alkaline phosphatase (U/l)	241	165.6	178	143.5	148.5	102	149.8	142.0	52	153.6	129.9	180	164.8	204.3
Albumin (g/l)	241	41.1	178	41.6	42.4	102	41.7	42.6	52	41.6	42.9	180	41.1	41.0
Gamma GT (U/l)	119	62.8	83	50.4	57.9	47	51.7	58.0	21	40.7	48.0	88	61.7	105.4
AST (SGOT) (U/l)	241	29.8	177	28.0	26.4	102	26.5	25.7	52	25.6	22.8	180	29.8	35.3
ALT (SGPT) (U/l)	240	22.2	178	21.4	21.5	102	21.7	22.5	52	19.7	21.0	180	22.3	25.3

TABLE 41 Mean biochemistry results before and during treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer

Variable	Pre-treatment		12 weeks			24 weeks			48 weeks			Withdrawal		
	n	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean
ZD1033 1 mg daily														
Sodium (mmol/l)	256	141.1	198	140.9	141.1	122	140.6	141.0	62	140.7	139.8	176	141.4	140.8
Potassium (mmol/l)	253	4.3	195	4.3	4.3	119	4.3	4.3	61	4.2	4.3	175	4.3	4.3
Glucose (mmol/l)	254	6.1	197	6.1	6.2	121	6.2	6.5	62	6.0	6.1	175	6.0	6.2
Total cholesterol (mmol/l)	256	5.3	198	5.4	5.9	122	5.5	6.2	62	5.5	5.9	176	5.3	5.6
LDH (U/l)	256	300.4	199	275.1	299.3	122	255.2	255.4	62	242.3	321.9	176	305.7	401.5
ZD1033 10 mg daily														
Sodium (mmol/l)	237	141.1	181	141.4	141.7	122	141.0	141.0	65	140.7	140.8	144	141.3	140.4
Potassium (mmol/l)	237	4.4	180	4.3	4.3	122	4.3	4.2	65	4.3	4.2	144	4.4	4.3
Glucose (mmol/l)	236	6.1	180	6.1	6.4	123	6.1	5.9	64	6.4	6.4	144	6.0	6.3
Total cholesterol (mmol/l)	237	5.5	181	5.5	5.9	123	5.4	6.0	65	5.5	6.1	144	5.5	5.7
LDH (U/l)	237	291.8	180	273.4	283.6	123	257.9	274.2	64	230.6	236.3	144	307.0	375.8

(continued)

TABLE 41 Mean biochemistry results before and during treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials in women with breast cancer (continued)

Variable	Pre-treatment		12 weeks			24 weeks			48 weeks			Withdrawal		
	n	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean	n	pre-treatment mean	mean
Megestrol acetate														
Sodium (mmol/l)	240	140.8	177	140.8	140.8	100	140.8	140.5	52	140.9	140.2	179	140.9	140.2
Potassium (mmol/l)	240	4.3	176	4.3	4.2	100	4.3	4.2	52	4.3	4.2	178	4.3	4.2
Glucose (mmol/l)	241	6.4	178	6.3	6.1	101	6.5	6.6	52	6.5	6.8	179	6.2	6.4
Total cholesterol (mmol/l)	240	5.5	177	5.5	5.4	102	5.4	5.5	52	5.4	5.4	179	5.4	5.3
LDH (U/l)	241	330.6	178	270.0	331.5	101	273.9	332.0	52	244.3	281.2	180	323.8	491.1

TABLE 42 Number of women with breast cancer who had Zeneca-defined abnormalities of biochemistry results before or during treatment with anastrozole (ZD1033) or megestrol acetate in the controlled clinical trials

Variable	ZD1033 (1 mg)					ZD1033 (10 mg)					Megestrol acetate (160 mg)				
	At cut-off for ISS (n=262)		At cut-off for 4MSU (n=262)		Difference	At cut-off for ISS (n=246)		At cut-off for 4MSU (n=246)		Difference	At cut-off for ISS (n=253)		At cut-off for 4MSU (n=253)		Difference
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Sodium	2	(0.8)	2	(0.8)	0	1	(0.4)	1	(0.4)	0	1	(0.4)	1	(0.4)	0
Total cholesterol	18	(6.9)	25	(9.5)	7	19	(7.7)	23	(9.3)	4	11	(4.3)	13	(5.1)	2
LDH	5	(1.9)	6	(2.3)	1	4	(1.6)	5	(2.0)	1	12	(4.7)	12	(4.7)	0

EXCLUSIVITY SUMMARY for NDA # 20-541 **SUPPL #** _____

Trade Name Arimidex **Generic Name** anastrozole

Applicant Name Zeneca Pharmaceuticals **HFD-** 150

Approval Date 27 December 1995

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5yrs (letter attached)

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 10331L/0004

Investigation #2, Study # 10331L/0005

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 10331L/0004 YES /___/ NO /✓/

Investigation #2 10331L/0005 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 10331L/0004 YES /___/ NO /✓/

Investigation #2 10331L/0005 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 1033 IL 10004

Investigation #2, Study # 1033 IL 10005

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # YES /✓/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # YES /✓/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

Lucie A Vaccaro
Signature

12-18-95
Date

Title: Project Manager

Robert J Temple
Signature of Division Director

12-21-95
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA RAPIFAX AND
AIRBORNE EXPRESS

DEC 15 1995

Dr. Robert L. Justice
Acting Division Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 150
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Justice:

Re: ARIMIDEX® (ZD1033)
NDA 20-541
Item 13 Amendment to Exclusivity Claim

Pursuant to 21 CFR 314.50(j) and 314.108(b)(2), Zeneca would like to amend the exclusivity claim contained in Item 13 Section 8 to be as follows::

"Applicant claims an exclusivity period of 5 years from the date of approval of this application pursuant to 21 CFR 314.108(b)(2). To the best of Applicant's knowledge or belief, a drug has not previously been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act containing anastrozole, the active moiety of the drug for which Applicant is seeking approval."

Please do not hesitate to contact me if you have any questions or require additional information.

Sincerely,

E. Jane Valas, Ph.D.
Regulatory Consultant, Drug Registration
Drug Regulatory Affairs Department
(302) 886-2122
(302) 886-2822 (fax)

EJV/car/3836/31

Desk Copy: Ms. Leslie A. Vaccari, HFD No. 150, Room No. 2092

ITEM 13: PATENT INFORMATION

For further information regarding this section, please contact:

Frances M. Kelleher, Ph.D.
Manager, Drug Registration
(302) 886-8457
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
Wilmington, DE 19850-4237

ARIMIDEX® (anastrozole)

ITEM 13: PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, the attached information is made of record.

The owner of the listed patent is Zeneca Limited, Macclesfield, Cheshire, England.

The US representative designated to receive notice pursuant to this section is:

The holder of the application for the drug which is claimed by the patent is:

Zeneca Limited
Macclesfield, Cheshire, England

US Agent:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
Wilmington, DE 19850-4237

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
Wilmington, DE 19850-4237

ARIMIDEX® (anastrozole)

ITEM 13: PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

1. Active Ingredient(s):

   2,2'[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropionitrile)

2. Strength(s):

   1 mg

3. Trade Name:

   ARIMIDEX® (anastrozole)

4. Dosage Form, Route of Administration:

   Tablet, Oral

5. Applicant Firm Name/Holder of the Approved Application:

   Zeneca Limited
   Macclesfield, Cheshire, England

   US Agent:
   Zeneca Pharmaceuticals
   A Business Unit of Zeneca Inc.
   1800 Concord Pike
   Wilmington, DE 19850-4237

6. NDA Number:

   20-541

7. Approval Date:

   N/A

8. Exclusivity (Time Period Requested):

5 years

9. The required information pursuant to 314.53(c) for the patent identified above is:

(i) 4,935,437 has, because of the recent enactment of the Uruguay Round Agreements Act, Pub. L. 103-465, Section 532, signed into law on December 8, 1994, an expiration date of June 10, 2008.

(ii) 4,935,437 contains drug, drug product and method of use claims.

(iii) The patent owner of 4,935,437 is Zeneca Limited, Macclesfield, Cheshire England.

(iv) The authorized agent of the patent owner in the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(b) of the Act and sections 314.52 and 314.95 is:

The undersigned declares that Patent No. 4,935,437 covers the formulation, composition, and/or method of use of ARIMIDEX® (anastrozole). This product is the subject of this application for which approval is being sought.

William J. Kennedy, PhD
Vice President
Drug Regulatory Affairs

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-541 Trade (generic) names Arimidex (anastrozole) Oral Tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

Indication: Tx of advanced breast cancer in postmenopausal women who have failed tamoxifen therapy.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Leslie Vaccari
Signature of Preparer

12-1-95
Date

CC: Orig NDA 50-541
HFD-93. /Div File
DA Action Package

Pharm/Tox

DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

NDA: 20-541

Date of Submission: 3/28/95

Information to be conveyed to the sponsor: Yes (X) No ( )

Reviewer: Margaret E. Brower, Ph.D.

Sponsor: Zeneca Pharmaceuticals
Wilmington, DE

Drug Name: Arimidex

Response to comments of 12/6/95 re labelling for Pharmacology/Toxicology

Labelling change acceptable with following changes:
page 16, paragraph 1
1. Delete "either" (There was no evidence of teratogenicity either in rats. . .)
There was no evidence of teratogenicity in rats administered. . . found in healthy post-menopausal humans at the recommended dose).

2. Change as indicated:
In rabbits, ARIMIDEX caused pregnancy failure at doses equal to or greater than 1.0mg/kg/day (about 16 times the recommended human dose on a mg/m^2 basis); there was no evidence of teratogenicity in rabbits administered 0.2mg/kg/day (about 3 times the recommended human dose on a mg/m^2 basis).

Margaret Brower 12/11/95

Margaret E.Brower, Ph.D.
Pharmacology

cc
NDA orig and Div File
HFD-150
/DeGeorge
/Beitz
/Vaccari
/Brower

14/11/95

L Vaccaro

OCT 26 1995

Division of Oncology and Pulmonary Drug Products

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original NDA Review

NDA: 20-541

Date of Submission: NDA Dated: 3/28/95
Received by CDER: 3/29/95

Information to be conveyed to the sponsor: Yes (X) No ( )

Reviewers: Paul A. Andrews, Ph.D. and Margaret E. Brower, Ph.D.

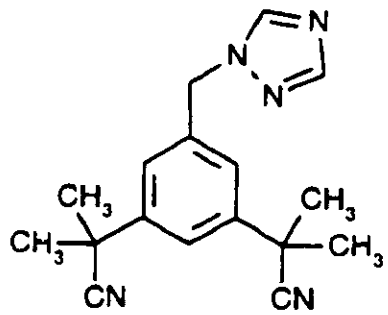
Date Review Completed: 10/26/95

Sponsor: Zeneca Pharmaceuticals
Wilmington, DE 19897

Drug Name: Primary: Arimidex
Secondary: anastrozole, ZD1033

Chemical Name: 2,2'-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropiononitrile)

Structure:



Molecular weight and formula: 293.4, $C_{17}H_{19}N_5$

Related INDs, NDAs: IND

Pharmacologic Class: Aromatase inhibitor

Indication: advanced breast cancer in post-menopausal women who have progressed following tamoxifen therapy

Clinical Formulation:

Format	Ingredient	Amount
tablet	Arimidex	1.0 mg
	lactose	
	povidone	
	sodium starch glycolate	
	magnesium stearate	
	hydroxypropylmethylcellulose	
	polyethylene glycol 300	
	titanium dioxide	

Route of administration and dosage form: oral tablet

Proposed Dosage: one 1 mg tablet daily (~0.74 mg/m^2/day using 50 kg and 37 kg/m^2 for conversion)

OVERALL SUMMARY AND EVALUATION

Arimidex is a potent (IC_{50}=15 nM) and specific inhibitor of aromatase with few other pharmacological effects at therapeutic concentrations. The majority of its inhibitory activity can be attributed to the parent drug and not to its metabolites. The ability to inhibit estrogen synthesis and deplete estrogens in plasma should thus confer antitumor activity in estrogen-dependent malignancies. No evidence of antitumor activity in animal models was provided due to a lack of relevant models to test the effect of estrogen synthesis inhibition.

Arimidex is rapidly and completely absorbed after oral administration to animals. The kinetics of tissue concentrations generally parallel plasma concentrations of Arimidex. The majority of the administered dose in rats, dogs, and rabbits is excreted in the urine. The remainder is excreted in the feces via the bile. Arimidex is apparently subjected to entero-hepatic circulation and this causes secondary peaks in the plasma concentration versus time curve after single doses. Gender dependent pharmacokinetics are observed in both rats and dogs, but the differences are dose and time dependent. After multiple doses, alterations are observed in the pharmacokinetics due to induction of metabolism at ≥30 mg/m²/day in rats and ≥60 mg/m²/day in dogs, and to saturation of elimination. Systemic exposure is thus not a simple linear function of dose. Arimidex inhibits P450 2B and 3A isozymes. The induction of metabolism is a likely explanation for the increased liver mass seen in the toxicology studies. In dogs, this was associated with hepatocyte degeneration/ necrosis, neutrophil infiltration, and increases in serum ALT, AP, and cholesterol. In rats, the enlarged livers were associated with hepatocyte hypertrophy and vacuolation, increased cholesterol, but decreased serum AP, ALT, and AST.

Toxicologic effects of Arimidex do not occur until doses that are well above the proposed dose in humans which is ~0.74 mg/m²/day. Mice readily tolerated single doses of Arimidex given at 750 mg/m² orally or 150 mg/m² i.p. Single oral or i.p. doses of 300 mg/m² Arimidex were minimally toxic to rats, but doses of 1500 mg/m² were lethal by both these routes in rats. In rats given multiple daily doses, the majority of the toxicologic effects were seen only in the 300 mg/m²/day group. This dose gave an AUC of 140-170 µg•hr/ml and a C_{max} of ~15 µg/ml. In dogs, gender-based differences in the pharmacokinetics caused parallel differences in the severity of the toxicity. The AUC exposures at 160 mg/m²/day in dogs were 276 µg•hr/ml and 150 µg•hr/ml in ♂s and ♀s respectively; the C_{max}s were 15 µg/ml and 10 µg/ml respectively. Toxicities were thus seen at a similar C_{max} and AUC in both species. The higher Arimidex exposure of ♂ dogs was seen as more severe hematologic changes, R-wave amplitude changes, kidney weight increases, and spleen weights increases compared to the ♀s. Most of the toxicities observed could be attributed to disturbances in steroid hormone biochemistry from aromatase inhibition and to the induction of detoxification enzymes. Arimidex decreased body weight in ♂ rats and dogs, but increased body weight in ♀ rats only. This was consistent with the increased food consumption that was only seen in ♀ rats. Due to the expected effect on estrogen synthesis, estrous was blocked in rats at 300 mg/m²/day and in dogs at 60 mg/m²/day which suggests that dogs are more sensitive to the pharmacodynamic effects of Arimidex. Arimidex caused minor decreases in RBC, Ht, and Hb; and increases in platelets in both species most likely due to the significant presence of aromatase in bone marrow cells and a role for estrogen in normal hematopoiesis. The end-organ toxicities were directed mainly to the liver and reproductive organs and were reversible when Arimidex was withdrawn. Ovaries were enlarged and had increased corpora lutea, cysts, and stroma. Rats had endometrial fibrosis and less cornified vaginal epithelium; dogs had uteri with hyperplasia and mucus cysts. Dogs also had reversible mammary gland hyperplasia. These uterine and mammary gland effects can be attributed to the chronic high progesterone levels induced by Arimidex. The dogs had increased testes weights, reversible Leydig cell hyperplasia, and testosterone levels which were elevated 10-fold at ≥20 mg/m²/day. It can be speculated that these effects can be explained by a lack of estradiol synthesis due to aromatase inhibition, a resulting unabated secretion of luteinizing hormone due to loss of feedback inhibition from estradiol, stimulation of Leydig cell testosterone production by LH and a concomitant hyperplasia. A non-reversible finding was adrenal cortical vacuolation in 300 mg/m²/day ♀ rats that was

similar to control ♂s; this can thus be considered a result of masculinization. Other microscopic findings were reversible hypertrophic thyroid epithelium in ♀ rats (masculinization), persistent chronic progressive glomerulo-nephropathy in rats, persistent pituitary gonadotroph hyperplasia in dogs, and reversible thymic involution in dogs. The persistent chronic progressive glomerulo-nephropathy is a common disease in rats exacerbated by high protein in the diet and thus may have resulted indirectly from the Arimidex-induced increase in food consumption. Further study would be needed, however, to rule out a direct effect of Arimidex in promoting this disease. There were thus no serious irreversible toxicities associated with long-term daily Arimidex administration. Comparisons of the $C_{ss,max}$, $C_{ss,min}$, and $AUC_{0-24\ hr}$ show that the values in post-menopausal females at the proposed dosage of 1 mg/day are 250, 80-130, and 202 times lower, respectively, than those associated with toxicities in female dogs (following table). In comparison to the values in female rats at doses causing toxicity, the $C_{ss,min}$ and $AUC_{0-24\ hr}$ values in post-menopausal females at the proposed dosage of 1 mg/day are 437 times and 237 times lower, respectively (following table).

Comparative Exposures to Arimidex

	Study	Dose		C_{ss} (ng/ml)[a]		AUC_{0-24} (µg•hr/ml)	
		mg/kg/day	mg/m²/day	max	min		$t_{1/2}$ (hr)
rat ♂	TPR/1992	50	300	14700	23, 45, LOQ	142_{0-16}	2.5
rat ♀		50	300	16600	11, 288, LOQ	176	2.5
dog ♂	TPD/652	8	160	15700	8050[b]	276	22.3
dog ♀		8	160	10400	3300[c]	150	13.7
human-single	019	0.014	0.74	18.6	-	0.548	45-53
	all	0.143	7.4	150-225	-	-	
human-multiple	002, 3, 9[d]	0.014	0.74	(38[e])	25.1[f]-(40[g])	(0.74[h])	-
	004[i]	0.014	0.74	-	40	-	-
	004[i]	0.143	7.4	-	379	-	-

[a] at week 26 in animals and at 7-14 days in humans
[b] mean of day 78, 106, 134, 162, and 182 C_{min} values
[c] mean of 106, 134, 162, and 182 day C_{min} values
[d] healthy post-menopausal volunteers
[e] ⅓ of 114 ng/ml at day 7 in post-menopausal volunteers receiving 3 mg/day (Study# 0002)
[f] in post-menopausal volunteers receiving 1 mg/day (Study# 0009)
[g] mean of 1/5 and 1/10 of 196 and 414 ng/ml at day 14 in post-menopausal volunteers receiving 5 and 10 mg/day (Study# 0003)
[h] ⅓ of 2.22 µg•hr/ml at day 7 in post-menopausal volunteers receiving 3 mg/day (Study# 0002)
[i] advanced breast cancer patients

In vitro studies with keratinocytes, contact sensitization studies in Guinea pigs, and dermal and ocular tolerance studies in rabbits indicated that Arimidex has low irritancy potential. Likewise, passive cutaneous anaphylaxis studies and active systemic anaphylaxis studies indicated that Arimidex has a very low potential for inducing anaphylactic responses.

Arimidex and/or its metabolites crossed the placenta and was detected in fetal rats and rabbits. Although variable results were seen between rat studies, Arimidex at doses of ≥0.6 mg/m²/day decreased the number of implantations and live fetuses, increased numbers of resorptions and post-implantation loss, and increased placental weights. Increased pre-implantation loss was observed at doses of ≥3

mg/m²/day and delayed fetal development was observed at 6 mg/m²/day in rats. Rabbits were generally less sensitive to the effects of Arimidex compared to rats when the dose was normalized to surface area. Arimidex consistently caused depressed pregnancy rates (≥ 1 mg/m²/day), increased pre-implantation loss (0.2 mg/m²/day), and depressed numbers of implantations and live fetuses (≥2 mg/m²/day) in rabbits. Arimidex did not cause fetal abnormalities in either species. The reproductive effects observed with Arimidex treatment are thus consistent with its pharmacological mechanism of action. It is noted that concerns about reproductive toxicity are not applicable to the indicated post-menopausal patient population.

Arimidex was not mutagenic in bacterial strains or Chinese hamster ovary cells, and was not clastogenic in human lymphocytes or in the rat micronucleus test.

In summary, Arimidex is a specific inhibitor of aromatase. At the planned doses, it is expected to have a low potential for systemic, local, and genetic toxicities. Arimidex is embryo-toxic and feto-toxic at maternally toxic doses.

RECOMMENDATIONS Approval

Discussed for Medical Officer: nothing

LABELLING ISSUES:

Labelling does not completely conform to the format specified under CFR21.Part201.Subpart B dated April 1, 1994. The proposed labelling generally reflects the preclinical data with the exception of the following:

1. Add the following text to the **Pharmacokinetics and Metabolism** section on page 2.

   Marked gender differences in the pharmacokinetics of ARIMIDEX were seen in rats and dogs. The differences were dependent upon the species, dose level, and duration of drug administration. Induction of P450 metabolism was apparent at 5 mg/kg/day in rats and 3 mg/kg/day in dogs (40 and 80 times, respectively, the recommended human dose on a mg/m² basis). It is unknown whether gender differences will also be noted in humans after chronic administration.

2. Paragraph 2 (preclinical data) on page 4 which begins. .Anastrozole was well tolerated in all animal species tested.... should be *deleted*. The following revised statement should be *added to* the **OVERDOSAGE** section on page 12; this should *replace* the final sentence in paragraph 3 of page 12.
   In rats, lethality was observed after single oral doses that were greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m² basis) and was associated with severe irritation to the stomach (necrosis, gastritis, ulceration, and hemorrhage).

3. *Delete* paragraph 3 on page 4.

4. *Delete* statement page 5, paragraph 2. *Revise* as follows:

   ARIMIDEX does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

5. **CONTRAINDICATIONS** . . *Delete* current paragraph page 7.

6. **WARNINGS** (Currently missing from labelling)

ARIMIDEX can cause fetal harm when administered to a pregnant woman. ARIMIDEX has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about ¾ and 1.5 times the recommended human dose, respectively, on a mg/m^2 basis). Studies in both rats and rabbits at doses equal to or greater than 0.1 and 0.02 mg/kg/day, respectively (about ¾ and ⅓, respectively, the recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have confirmed that ARIMIDEX will increase pregnancy loss and is embryotoxic (characterized by increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses); effects were dose related in rats. Placental weights were significantly increased in rats at doses equal to or greater than 0.1 mg/kg/day.

Evidence of fetotoxicity including delayed fetal development (i.e. incomplete ossification and depressed fetal body weights) was observed in rats administered doses of 1 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). There was no evidence of teratogenicity either in rats administered doses up to 1.0 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose), or in rabbits administered 5.0 mg/kg/day (about 30 times the recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using ARIMIDEX. If ARIMIDEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

7. **PRECAUTIONS.**

General. *Delete* current paragraph page 7. *Replace with*:

Before starting treatment with ARIMIDEX, pregnancy must be excluded. (See CONTRAINDICATIONS and WARNINGS)

8. *Delete* the following labelling categories and *replace* as follows:

Carcinogenesis: No studies have been conducted to assess the carcinogenic potential of ARIMIDEX.

Mutagenesis: ARIMIDEX has not been shown to be mutagenic in *in vitro* tests (Ames and E. Coli bacterial tests, CHO-K1 gene mutation assay), or clastogenic either *in vitro* (chromosome aberrations in human lymphocytes) or *in vivo* (micronucleus test in rats).

Impairment of Fertility: Studies to investigate the effect of ARIMIDEX on fertility have not been conducted; however, chronic studies indicated hypertrophy of the ovaries and the presence of follicular cysts in rats administered doses equal to or greater than 1 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). In addition, hyperplastic uteri were observed in chronic studies of female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 22 times and 16 times higher than the respective values found in

post-menopausal humans at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in humans.

Pregnancy: Pregnancy Category D: (See **WARNINGS**).

Nursing Mothers: It is not known if ARIMIDEX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARIMIDEX is administered to a nursing woman. (See **WARNINGS** and **PRECAUTIONS**)

Pediatric Use: The safety and efficacy of ARIMIDEX in children have not been established.

9. **Teratogenic Effects:** *Delete* paragraph on page 9 and *incorporate* effects in **WARNINGS** as indicated. *Delete* title.

10. **Nonteratogenic Effects:** *Delete* paragraph on page 9 and *incorporate* effects in **WARNINGS** as indicated. *Delete* title.

To be marketed product issues: none

Draft Letter, Requests for Sponsor

Please make the following changes to the labelling for ARIMIDEX.

1. Add the following text to the **Pharmacokinetics and Metabolism** section on page 2.

   Marked gender differences in the pharmacokinetics of ARIMIDEX were seen in rats and dogs. The differences were dependent upon the species, dose level, and duration of drug administration. Induction of P450 metabolism was apparent at 5 mg/kg/day in rats and 3 mg/kg/day in dogs (40 and 80 times, respectively, the recommended human dose on a mg/m^2 basis). It is unknown whether gender differences will also be noted in humans after chronic administration.

2. Paragraph 2 (preclinical data) on page 4 which begins...Anastrozole was well tolerated in all animal species tested.... should be *deleted.* The following revised statement should be *added to* the **OVERDOSAGE** section on page 12: this should *replace* the final sentence in paragraph 3 of page 12.
   In rats, lethality was observed after single oral doses that were greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m^2 basis) and was associated with severe irritation to the stomach (necrosis, gastritis, ulceration, and hemorrhage).

3. *Delete* paragraph 3 on page 4.

4. *Delete* statement page 5, paragraph 2. *Revise* as follows:

   ARIMIDEX does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

5. **CONTRAINDICATIONS** . . *Delete* current paragraph page 7.

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ARIMIDEX can cause fetal harm when administered to a pregnant woman. ARIMIDEX has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about ¼ and 1.5 times the recommended human dose, respectively, on a mg/m^2 basis). Studies in both rats and rabbits at doses equal to or greater than 0.1 and 0.02 mg/kg/day, respectively (about ¼ and ⅓, respectively, the recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have confirmed that ARIMIDEX will increase pregnancy loss and is embryotoxic (characterized by increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses); effects were dose related in rats. Placental weights were significantly increased in rats at doses equal to or greater than 0.1 mg/kg/day.

Evidence of fetotoxicity including delayed fetal development (i.e. incomplete ossification and depressed fetal body weights) was observed in rats administered doses of 1 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). There was no evidence of teratogenicity either in rats administered doses up to 1.0 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose), or in rabbits administered 5.0 mg/kg/day (about 10 times the recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using ARIMIDEX. If ARIMIDEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

7. **PRECAUTIONS.**

General. *Delete current paragraph page 7. Replace with:*

Before starting treatment with ARIMIDEX, pregnancy must be excluded (See CONTRAINDICATIONS and WARNINGS)

8. *Delete* the following labelling categories and *replace* as follows:

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Mutagenesis: ARIMIDEX has not been shown to be mutagenic in *in vitro* tests (Ames and E. Coli bacterial tests, CHO-K1 gene mutation assay), or clastogenic either *in vitro* (chromosome aberrations in human lymphocytes) or *in vivo* (micronucleus test in rats).

Impairment of Fertility: Studies to investigate the effect of ARIMIDEX on fertility have not been conducted; however, chronic studies indicated hypertrophy of the ovaries and the presence of follicular cysts in rats administered doses equal to or greater than 1 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in healthy post-menopausal humans at the recommended dose). In addition, hyperplastic uteri were observed in chronic studies of female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma ARIMIDEX Css_{max} and $AUC_{0\text{-}24\ hr}$ that were 22 times and 16 times higher than the respective values found in

post-menopausal humans at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in humans.

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Pediatric Use: The safety and efficacy of ARIMIDEX in children have not been established.

9. **Teratogenic Effects:** *Delete* paragraph on page 9 and *incorporate* effects in **WARNINGS** as indicated. *Delete* title.

10. **Nonteratogenic Effects:** *Delete* paragraph on page 9 and *incorporate* effects in **WARNINGS** as indicated. *Delete* title.

post-menopausal humans at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in humans.

Pregnancy: Pregnancy Category D: (See **WARNINGS**).

Nursing Mothers: It is not known if ARIMIDEX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARIMIDEX is administered to a nursing woman. (See **WARNINGS** and **PRECAUTIONS**)

Pediatric Use: The safety and efficacy of ARIMIDEX in children have not been established.

9. **Teratogenic Effects:** *Delete* paragraph on page 9 and *incorporate* effects in **WARNINGS** as indicated. *Delete* title.

10. **Nonteratogenic Effects:** *Delete* paragraph on page 9 and *incorporate* effects in **WARNINGS** as indicated. *Delete* title.

Paul A. Andrews 10/26/95

Paul A. Andrews, Ph.D.
Pharmacologist/Toxicologist

Date

Margaret A Brower 10/26/95

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Pharmacologist/Toxicologist

Date

10/26/95

————Review Notes————

Previous Review(s), Date(s), and Reviewer(s): IND 7/8/92 M.A. Goheer

Studies Reviewed in this NDA:

I. Animal Pharmacology (Vol 1.11, p. 99-209)

1) Pharmacology relevant to the use of ICI D1033 in breast cancer:

Aromatase inhibition in vitro	p. 119-122
Aromatase inhibition in rats	
Inhibition of ovulation	p. 122-125
Attenuation of the uterotrophic action of androstenedione	p. 125-126
Aromatase inhibition in monkeys	p. 127-130
Selectivity with respect to other cytochrome P-450 enzymes	
Cholesterol side-chain cleavage	p. 131-135
11β-Hydroxylase	p. 135-145
18-Hydroxylation	p. 145-147
Concurrent inhibition of 11- and 18-hydroxylation: effects on sodium and potassium excretion in rats	p. 147-150
17-Hydroxylase/17,20-Desmolase	p. 151-155
Cholesterol Biosynthesis	p. 155-160

2) General Pharmacology

Autonomic pharmacology	p. 161-168
Neuromuscular function	p. 168-170
Central nervous system pharmacology	p. 170-173
Cardiovascular function	p. 174-183
Hemostasis	p. 184-1185
Gastro-intestinal function	p. 185-188
Renal function	p. 189-190
Immune function	p. 191-192
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Respiratory function	p. 194-197
Oestrogenic/antioestrogenic activity	p. 197-198
Androgenic/antiandrogenic activity	p. 199-200
Progestational activity	p. 200-201
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Antinociceptive activity	p. 202-203

3) Pharmacology of metabolites

Major metabolite - 1,2,4-triazole	p. 204-205
Minor metabolites	p. 206

II. Pharmacokinetics

Rats

DMR/003 Excretion Study of ^{14}C-ICI D1033 After a Single Oral or Intravenous Dose to Rats. (Vol 1.21, p. 1-33)

DMR/004 Pharmacokinetics of ^{14}C-ICI D1033 in Male and Female Rats After Single 1 mg/kg Oral or Intravenous Doses (Vol 1.21, p. 34-82)

DMR/013 Biliary Excretion Study in Male and Female Rats After Single Oral or Intravenous

Administration of ^{14}C D1033, at 1 mg/kg. (Vol 1.21, p. 83-109)

DMR/018 Exploratory Absorption, Metabolism and Elimination Following Single 1 mg/kg Oral or IV Administration of an Alternate Radiolabeled Formulation of ^{14}C ICI D1033 to Male and Female Rats. (Vol 1.21, p. 110-136)

DMR/019 Exploratory Pharmacokinetic Study in Rats Following Single 1 mg/kg Oral or IV Administration of an Alternate Radiolabeled Formulation of ^{14}C ICI D1033 to Male and Female Rats. (Vol 1.21, p. 137-165)

DMR/025 Exploratory Study in Rats to Determine Metabolism to CO_2 of MPN Labeled ZD1033 After a Single 1 mg/kg Oral Dose. (Vol 1.21, p. 166-178)

DMR/027 Exploratory Study to Determine Whether $^{14}CO_2$ is Formed Following Administration of a Single 1 mg/kg Oral Dose of ^{14}CN Labeled ZD1033 to Rats. (Vol 1.21, p 179-195)

DMR/029 Pharmacokinetics of ZD1033 and Total Radioactivity Following Single Intravenous or Oral Administration of [^{14}CN]-ZD1033 to Rats. (Vol 1.22, p. 87-257)

DMR/033 Pharmacokinetics of ZD 1033 and Total Radioactivity and Routes of Excretion Study Following Single and Multiple Oral Dose of [^{14}CN]-ZD1033 to Rats. (Vol 1.23, p. 1-231)

DMR/011 Exploratory Quantitative Tissue Distribution Following Single 1 mg/kg Oral Administration of ^{14}C ICI D1033 to Male and Female Rats. (Vol 1.23, p. 232-278)

KMR/005 The Distribution of Radioactivity in Male and Female Albino and Male Hooded Rats as Determined by Whole Body Autoradiography Following Oral Administration of [^{14}C]-ICI D1033 at 1 mg/kg. (Vol 1.23, p. 279-309)

DMR/023 Quantitative Tissue Distribution in Female Rats After Single Oral Administration of ^{14}C D1033 at 1 mg/kg. (Vol 1.23, p. 310-361)

DMR/031 Quantitative Tissue Distribution in Male and Female Rats After Single and Multiple Oral Administrations of [^{14}CN]-ZD1033 at 1 mg/kg. (Vol 1.24, p. 1-129)

Dogs

DMD/012 Pharmacokinetics and Excretion of ^{14}C ICI D1033 in Male Dogs After Single Oral or Intravenous Administration of 0.02 mg/kg. (Vol 1.21, 221-259)

DMD/020 Pharmacokinetics and Excretion of ^{14}C ICI D1033 in a Male Bile Duct Cannulated Dog After Single 1 mg/kg Administration of ^{14}C Triazole or ^{14}C Methyl-Propiononitrile Labeled ICI D1033. (Vol 1.21, p. 260-299)

DMD/007 Pharmacokinetics and Excretion of ^{14}C-ICI D1033 in Male Dogs After Single 1 mg/kg Oral or Intravenous Doses. (Vol 1.21, p. 300-354)

DMD/017 Exploratory Absorption, Metabolism, Elimination and Pharmacokinetics Following Single 1 mg/kg Oral or IV Administration of an Alternate Radiolabeled Formulation of ^{14}C ICI D1033 to Male Dogs. (Vol 1.22, p. 1-34)

DMD/030 A Pharmacokinetic and Mass Balance Study of ZD1033 and Total Radioactivity in Dogs Following Single Oral and Intravenous 1 mg/kg Doses of [^{14}CN]-ZD1033. (Vol 1.22, p. 35-86)

DMD/024 Pharmacokinetic Study Following Single 1 mg/kg I.V. Administration of [^{14}C]-Triazole to Male and Female Dogs. (Vol 1.26, p. 47-78)

DMD/015 Evaluation of Hepatic Cytochrome P450 Induction and D1033 Pharmacokinetic Parameters in Female Dogs Administered ARIMIDEX for 14 Days. (Vol 1.26, p. 1-46)

Rabbits

KMB/010 The Disposition of [^{14}CN]-ZD1033 in the Female Rabbit. (Vol 1.21, p. 196-207)

KMB/011 The Disposition of [^{14}CN]-ZD1033 in the Female Rabbit. (Vol 1.21, p. 208-220)

Miscellaneous

DMN/022 The Profiling and Identification of [^{14}C]-ZD1033 Metabolites in Urine, Bile, and Plasma of Rat and Dog. (Vol 1.26, p. 79-138)

DMM/021 Protein Binding in Selected Species Using Equilibrium Dialysis. (Vol 1.24, p. 130-146)
DMX/040 Inhibitory Effects of D1033 on Cytochrome P450 Activities In Vitro in Human Hepatic Microsomes. (Vol 1.24, p. 147-193)
DMR/009, DMR//010 Mixed Function Oxidase Evaluation Study in Rats After Oral Administration (Vol 1.24, p. 194-220)
DMD/014 A Study of Pharmacokinetics, MFO Activity and Antipyrine Kinetics in the Dog After an 8 mg/kg Dose for 14 Days. (Vol 1.25, p. 1-423)

II. Toxicology

A. Single Dose Toxicity

TLM/691 Acute Toxicity (Limit) Study in Mice: Oral Administration. (Vol 1.11, p. 215-250)
TLR/1944 Acute Toxicity (Limit) Study in Rats: Oral Administration. (Vol 1.11, p. 284-342)
TLM/692 Acute Toxicity (Limit) Study in Mice: Intraperitoneal Administration. (Vol 1.11 251-283)
TLR/1945 Acute Toxicity (Limit) Study in Rats: Intraperitoneal Administration. (Vol 1.11, p. 343-273)

B. Multiple Dose Toxicity

TPR/1992 6-Month Oral Toxicity Study in Rats. (Vol 1.13-Vol 1.14, p. 348)
TAR/1946 One-Month Oral Toxicity Study in Rats. (Vol 1.12)
TPD/652 Six-Month Oral Toxicity Study in Dogs. (Vol 1.17-1.18)
TKD/631 Pilot Toxicity Study in Dogs. (Vol 1.14, p. 349-357)
TAD/636 One-Month Oral Toxicity Study in Dogs. (Vol 1.15)
TKD/634 Investigatory Study in Dogs: Oral Administration for Six Months. (Vol 1.16)

C. Special Toxicity

TKY/143 Topical Tolerance Assessment: Physiochemical Characterization. (Vol 1.19, p. 1-9)
TVN/140 Topical Tolerance Assessment: In Vitro Assessment of Cytotoxicity and Irritant Potential. (Vol 1.19, p. 10-51)
TDM/801 Passive Cutaneous Anaphylaxis Study in the Mouse/Rat. (Vol 1.19, p. 52-87)
TDG/141 Contact Sensitization Study in the Guinea Pig. (Vol 1.19, p. 88-126)
TDG/181 Passive Cutaneous Anaphylaxis Study in the Guinea Pig. (Vol 1.19, p. 127-166)
TDG/182 Active Systemic Anaphylaxis Study in the Guinea Pig. (Vol 1.19, p. 167-201)
TIB/512 Topical Tolerance Assessment: Dermal Tolerance Study in Rabbits. (Vol 1.19, p. 202-238)
TIB/513 Topical Tolerance Assessment: Ocular Tolerance Study in Rabbits. (Vol 1.19, p. 239-273)

IV. Reproductive Toxicity

TRR/2234 Sighting Teratology Study in Rats - Oral Administration. (Vol 1.2), p. 77-90)
TTR/2235 Teratology Study in Rats: Oral Administration. (Vol 1.20, p. 1-76)
TRB/609 Sighting Teratology Study in Rabbits - Oral Administration. (Vol 1.20, p. 184-199)
TTB/610 Teratology Study in Rabbits: Oral Administration. (Vol 1.20, p. 90-183)

V. Genetic Toxicity

TMV/444 Ames Test: Bacterial Mutagenicity Study Using Selected Strains of Salmonella Typhimurium: Standard Method. (Vol 1.20, p. 200-240)
TMV/542 Bacterial Mutagenicity Study Using Selected Strains of Escherichia Coli: Standard Method. (Vol 1.20, p. 241-275)

TMV/455	In Vitro Mammalian Cell Gene Mutation Assay in Chinese Hamster Ovary Cells. (Vol 1.20, p. 276-326)
TYX/43	In Vitro Cytogenetic Study Using Cultured Human Lymphocytes. (Vol 1.20, p. 327-365)
TQR/1993	Micronucleus Test in the Rat - Oral Administration. (Vol 1.20, p. 366-404)

Studies Not Reviewed in this NDA:

TKY/142	Analysis and Stability of ICI D1033 in Liquid Dosing Media. (Vol 1.26, p. 139-170)
DBQ/001	Determination in Dog and Rat Plasma by Capillary Gas Chromatography with Electron Capture Detection: Validation of Method 32P-01. (Vol 1.26, p. 171-214)
DBQ/0001	Determination in Dog and Rat Plasma by Capillary Gas Chromatography with Electron Capture Detection: Validation of Method 3201RI. (Vol 1.26, p. 215-370)
KML/004	The Synthesis of 2,2'-[5-(1*H*-[3,5-^{14}C2]-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropiononitrile). (Vol 1.26, p. 371-389)
KML/006	The Synthesis of 2,2'-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-[^{14}C]-*methyl*[3-^{14}C]*propiononitrile*). (Vol 1.26, p. 390-409)
KML/007	The Synthesis of 2,2'-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]-bis(2-methyl [1-^{14}C] propiononitrile). (Vol 1.26, p. 410-436)

Studies Previously Reviewed: all studies previously reviewed in the original IND submission have been summarized or re-reviewed herein and are thus listed above

Note that portions of this review were excerpted directly from the sponsor's submission.

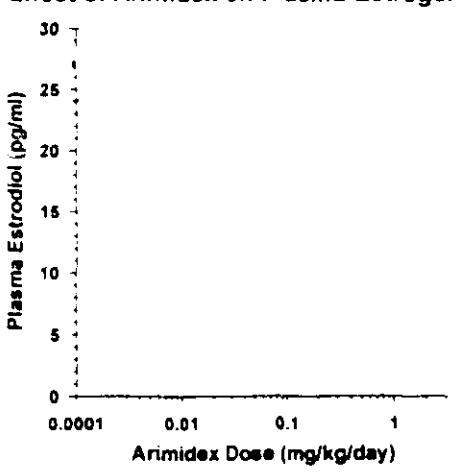
I. Pharmacology

Pharmacology relevant to the use of ICI D1033 in breast cancer:

Aromatase inhibition in vitro. Accurately reviewed by M.A. Goheer. Arimidex is a potent inhibitor of *placental mircosomal aromatase with an* IC_{50} *of 4.3 ng/ml.*

Aromatase inhibition in rats. Accurately reviewed by M.A. Goheer. Arimidex was 200 times more potent than aminoglutethimide and comparable to CGS 16949A at inhibiting ovulation presumably to due to inhibition of aromatase which prevents the surge in estradiol which triggers LH secretion. Arimidex at 0.1 mg/kg completely blocked the increase in uterine weight caused by androstenedione administration (converted to estrogen by aromatase).

Aromatase inhibition in monkeys. As for male and post-menopausal female humans, male monkeys peripherally aromatize androgens (primarily in adipose tissue). Six ♂ monkeys were treated sequentially with increasing doses of Arimidex for 7 days and the effect on plasma estradiol levels determined. The results (adjacent figure) show that the maximal *inhibition of peripheral aromatase occurred at ~0.1 mg/kg.* The effect was superimposable with the effect of CGS 16949A.



Selectivity with respect to other cytochrome P-450 enzymes. Reviewed by M.A. Goheer. Additional background is added here to assist interpretation.

Cholesterol side-chain cleavage (CSCC) is the rate limiting step in the biosynthesis of adrenal and gonadal steroid hormones. Inhibition leads to a fall in glucocorticoid concentrations which causes a rise in ACTH concentrations which leads to up regulation of CSCC which leads to adrenal hypertrophy, vacuolation of cortical cells, and cholesterol storage. The ability of Arimidex to inhibit CSCC in addition to aromatase was tested in male rats which do not have the complicating factor of the effect of Arimidex on estradiol levels which causes adrenal atrophy. Aminoglutethimide caused a 22-57% ↑ in adrenal weights, but 10 mg/kg Arimidex daily x 7 caused an 18% ↓. Up to 5 mg/kg daily x 14 caused a non-significant decline in adrenal weight in both ♂ and ♀ rats. In conclusion, this in vivo model showed that unlike aminoglutethimide (with a 5-10 fold difference in potency between aromatase and CSCC), Arimidex had no apparent CSCC inhibitory activity up to 10 mg/kg/day x 7.

11β-Hydroxylase generates cortisol and cortisone from respective precursors. The ability of Arimidex, CGS 16949A, and metapyrone to inhibit the conversion of 11-deoxycortisol to cortisol by adrenal mitochondrial preparations was assessed. The ratios of the IC_{50} to the IC_{50} for human placental aromatase were:

	Guinea pig	cow	dog
Arimidex	280	800	8800
CGS 16949A	28	17	11

Arimidex was thus a much more selective inhibitor than CGS 16949A.

In addition, escalating doses up to 3 mg/kg bid x 7 of Arimidex did not cause accumulation of 11-deoxycorticosterone in monkeys, unlike CGS 16949A.

18-Hydroxylation is the final step in the generation of aldosterone from corticosterone. While single doses of CGS 16949A caused 40-75% reductions in ♂ rat plasma aldosterone levels, up to 20 mg/kg Arimidex was without effect.

Concurrent inhibition of 11- and 18-hydroxylation in rats (but not humans or dogs) causes increased secretion of 11-deoxycorticosterone which causes reduced urinary sodium excretion. Arimidex (10 mg/kg) had no effect on urinary Na^+ or K^+ whereas CGS 16949A did.

17-Hydroxylase/17,20-Desmolase generates androsterone and testosterone from appropriate precursors. Arimidex (1 mg/kg/day x 7) had no effect on plasma testosterone or sex organ weights in ♂ rats. However, 10 mg/kg/day Arimidex x 21 in dogs caused 3.7 and 8.8 fold ↑ in plasma testosterone on days 7 and 21 respectively. Likewise, Arimidex caused a dose-dependent ↑ in plasma testosterone in monkeys (2.3-fold at 1 mg/kg bid x 7). These results were interpreted by the Sponsor to indicate that Arimidex does not inhibit adrenal or ovarian androgen synthesis at doses that maximally inhibit aromatase.

The final step in Cholesterol Biosynthesis is catalyzed by a P450 that is similar the those involved in the synthesis of steroid hormones. An earlier aromatase inhibitor developed by ICI significantly inhibited this step. Arimidex, however, did not alter the lanosterol/cholesterol ratio in rat or dog liver preparations. In addition, rats given a single dose of 10 mg/kg and dogs given 10 mg/kg/day x 21 of Arimidex had no alterations in plasma cholesterol. Note that in the 1 month study in dogs, cholesterol was lowered on day 12 with partial recovery by day 28.

General Pharmacology Reviewed by M.A. Goheer and summarized here.

Autonomic pharmacology: Arimidex had no effect on muscarinic receptors; H_1 or H_2 receptors; β_1, α_1-, or α_2-adrenoreceptors; or $5HT_1$ or $5HT_2$ receptors in *in vitro* tissue preparations. Arimidex had no effect on muscarinic receptors, sympathetic ganglion, neuro-effector transmission, or α-adrenoreceptors in cats.

Neuromuscular function: No treatment related effects in either *in vitro* or *in vivo* (cats) test systems.
Central nervous system pharmacology: Arimidex had no effects on neuromuscular coordination (rats), gross behavior (mice), depressant activity (mice), or convulsant activity (mice).
Cardiovascular function: Minor reductions in blood pressure and QT interval were seen at 10 mg/kg in dogs but not rats.
Hemostasis: No treatment related changes in rat plasma.
Gastro-intestinal function: Minor correction- Arimidex had no effect on GI motility in *mice* and no effect on acid output in rats.
Renal function: No treatment related changes in rats.
Immune function: Arimidex at 10 mg/kg depressed the immune system as indicated by its inhibition of oxazalone-induced delayed type hypersensitivity in mice.
Inflammation: Arimidex had no pro- or anti-inflammatory activity in rats.
Respiratory function: Arimidex had no effect on pulmonary resistance, dynamic lung compliance, heart rate, or blood pressure in dogs.
Oestrogenic/antiestrogenic activity: Arimidex had no effect on uterine weight in immature rats.
Androgenic/antiandrogenic activity: Arimidex had no effect on seminal vesicle weight in pubertal rats
Progestational activity Arimidex could not sustain pregnancies in ovariectomized rats.
Local anaesthesia: Arimidex infiltrated into the area of the sciatic nerve had no effect on hindlimb function.
Antinociceptive activity: Oral Arimidex did not effect the perception of heat in the feet of mice.

Pharmacology of metabolites- Previously un-reviewed
Major metabolite (1,2,4-triazole): This metabolite (100 µM) did not affect the production of estradiol or progesterone by rat granulosa cells *in vitro*. Up to 100 mg/kg triazole given orally to rats at 12 hr on day 3 of the estrous cycle had no effect on ovulation. Up to 100 mg/kg/day triazole given for 7 days had no effect on adrenal, liver, or body weight in ♂ rats. Thus, neither the aromatase inhibitory activity nor the liver hypertrophy can be attributed to this metabolite.

Minor metabolites (desmethyl and hydroxymethyl Arimidex): These metabolites were given orally to rats at 12 hr on day 3 of their estrous cycle. The results in the following table indicate that both these minor metabolites had aromatase inhibitory activity, but are 10-50 times less potent than Arimidex. Since they comprise ≤5% of the circulating Arimidex equivalents in rats and dogs, they probably do not contribute significantly to the activity of Arimidex .

Treatment	mg/kg	#treated	#ovulating
control	-	15	14
Arimidex	0.1	5	0
desmethyl-Arimidex	0.1	5	5
	0.5	5	5
	1.0	5	0
hydroxymethyl-Arimidex	1.0	5	3
	2.0	5	2
	10	5	0

II. Pharmacokinetics

- Rat studies

DMR/003 Excretion Study of ^{14}C-ICI D1033 After a Single Oral or Intravenous Dose to Rats. Previously reviewed by M.A. Goheer. Additional comments:
TLC analysis of the 0-24 hr urine collection in ♂s and ♀s indicated that only 4% and 22% of the radioactivity was intact Arimidex respectively. This accounted for 2 and 8% of the administered dose in ♂s and ♀s respectively. Females excreted ~50% more in the feces than ♂s. Less than 0.06% of the dose appeared as CO_2. The bioavailability was 88% and 100% in ♂s and ♀s based on urinary excretion.

DMR/004 Pharmacokinetics of ^{14}C-ICI D1033 in Male and Female Rats After Single 1 mg/kg Oral or Intravenous Doses. Previously accurately reviewed by M.A. Goheer.

DMR/013 Biliary Excretion Study in Male and Female Rats After Single Oral or Intravenous Administration of ^{14}C D1033, at 1 mg/kg. Conducted by The bile duct was cannulated 20 hr prior to dosing with Arimidex labelled in the triazole ring. Bile, feces, and urine were collected for 72 hr and analyzed for radioactivity. When given orally, 10% more radioactivity was excreted in the urine than by the i.v. route. The majority of the radioactivity was excreted in the first 24 hr in all cases except for the bile of ♀s where the majority was excreted in the 12-48 hr period. The major metabolite in bile was M2B which appeared to be a glucuronide that released M1 upon hydrolysis. The predominant form in urine was 1,2,4-triazole. The low fecal excretion after the oral dose indicated that the absorption was close to 100%.

species: Alpk:APfSD rats (3-5/sex)
drug: [^{14}C-triazole]Arimidex lot# 1R1 (40.9 µCi/mg)
dosage: 1 mg/kg
age; weight: not stated; 230-290 g for ♂ and 170-230 g for ♀
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as a ethanolic saline

Percent of ^{14}C Dose Excreted

	Oral		Intravenous	
	♂	♀	♂	♀
bile	29.8	26.7	31.5	27.3
urine	57.5	58	46.3	48.2
feces	3.36	6.6	1.47	3.2
cage wash	1.03	0.72	0.63	0.79
total	91.7	92.1	79.8	79.5

Biliary Metabolite TLC Profile (0-24 hr): Percent of Matrix ^{14}C

	Oral		Intravenous	
	♂	♀	♂	♀
Arimidex	16.9	19.1	18.1	17.3
M1	2.13	4.05	4.38	3.84
triazole	3.46	2.01	11.7	3.02
M2A	8.56	33.7	7.96	35.0
M2B	68.9	41.1	57.9	40.9

DMR/018 Exploratory Absorption, Metabolism and Elimination Following Single 1 mg/kg Oral or IV Administration of an Alternate Radiolabeled Formulation of ^{14}C ICI D1033 to Male and Female Rats. Conducted by Animals were dosed with Arimidex labelled in the propyl groups on the phenylene ring. Feces, urine, and expired CO_2 were collected for 120 hr and analyzed for radioactivity. The primary route of excretion was the feces, which differed from the results when Arimidex was labelled in the triazole ring. The fecal excretion may be higher in the ♂, and urinary excretion was higher in the ♀. The urinary recovery data indicate complete absorption after oral dosing. HPLC analysis of urine showed 8 peaks. The M4 metabolite was not observed when the label was in the triazole ring, indicating that this compound has probably lost the triazole ring.

species: Alpk:APfSD rats (1/sex)
drug: [^{14}C-methylpropiononitrile]Arimidex lot# 2R1 (63.8 µCi/mg)
dosage: 1 mg/kg
age; weight: *not stated; 245-285 g for ♂ and 200-210 g for ♀*
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as an ethanolic saline solution

Percent of ^{14}C Dose Excreted				
	Oral		Intravenous	
	♂[a]	♀	♂	♀[a]
urine	19.3	45.3	20.4	39.0
feces	58.5	49.9	66.7	43.5
CO_2	4.91	1.06	5.28	0.90
cage wash	4.38	0.37	3.58	1.67
total	87	96.6	95.9	85.1

[a] rat died between 30-48 hr due to CO_2 collection pump failure

Urinary Metabolite TLC Profile (0-24 hr): Percent of Matrix ^{14}C				
	Oral		Intravenous	
	♂	♀	♂	♀
M4	24.2	40.2	35.7	22.6
Arimidex	15.8	27.5	30.6	30.0
M1	33.4	14.2	-	15.9
origin	9.9	11.1	10.4	9.1

DMR/019 Exploratory Pharmacokinetic Study in Rats Following Single 1 mg/kg Oral or IV Administration of an Alternate Radiolabeled Formulation of ^{14}C ICI D1033 to Male and Female Rats. Conducted by Zeneca. Rats were dosed with [^{14}C]Arimidex either orally or i.v.; sacrificed at 14 time points to 48 hr; and exsanguinated. Analyses were conducted for radioactivity in blood and plasma, and Arimidex in plasma.

species: Alpk:APfSD rats (1/sex/time point/group)
drug: [^{14}C-methylpropionitrile]Arimidex lot# 2R1 (63.8 µCi/mg)
dosage: 1 mg/kg

age; *weight*: *not stated*; 270-330 g for ♂ and 200-250 g for ♀
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as an ethanolic saline solution

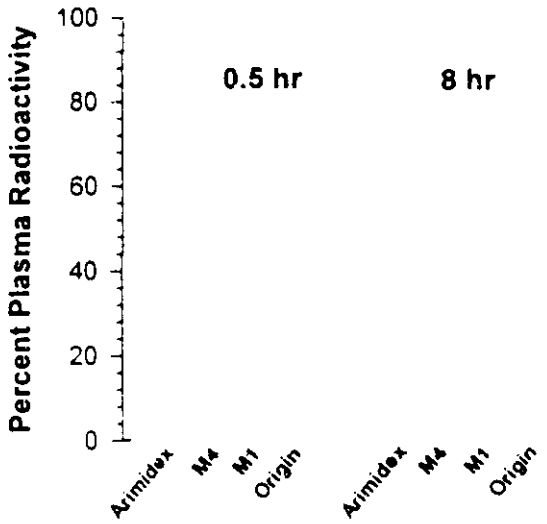
As was seen with triazole labelled Arimidex (DMR/003, DMR/004), secondary peaks and plateaus were seen by both routes in both genders for blood radioactivity, plasma radioactivity, and Arimidex concentrations. The AUC for Arimidex was 3-fold higher in ♀s by both routes and the clearance was correspondingly 3-fold higher in ♂s. Statistical analysis was precluded since only 1 rat/time point was used. The Arimidex $t_{½}$ was 2-fold longer in ♀s by both routes and the t_{peak} was later in ♀s. The bioavailability was estimated from the AUCs to be 81% and 92% in ♂s and ♀s respectively.

Oral Pharmacokinetic Data for Arimidex in Rats

		♂			♀		
	route	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex
C_{max} (µg/ml)[a]	oral						
t_{peak} (hr)	oral						
$AUC_{0-\infty}$ (µg•hr/ml)[a]	oral						
$AUC_{0-\infty}$ (µg•hr/ml)[a]	i.v.						
$t_{½}$ (hr)	oral						
	i.v.						
C_L/F (ml/hr/kg)	oral						
	i.v.						

[a] units for ^{14}C C_{max}s and AUCs are actually µg-eq/g and µg-eq•hr/g respectively

The metabolite distribution in plasma after oral dosing, as revealed by TLC analysis, is shown in the adjacent figure. A new metabolite M4, not seen when the triazole moiety was labelled, was present. The distribution after i.v. dosing was similar. Metabolism was more pronounced in ♂s at the two time points.



DMR/025 Exploratory Study in Rats to Determine Metabolism to CO_2 of MPN Labeled ZD1033 After a Single 1 mg/kg Oral Dose. Conducted by Zeneca. Urine, feces, and CO_2 were collected at 0-24 hr and 24-48 hr from dosed rats along with a final cage wash. Only the CO_2 collections were analyzed for radioactivity. The 0-48 hr mean recovery of radioactivity in CO_2 was 4.7% and 0.9% in ♂s and ♀s respectively.

species:	Alpk:APfSD rats (3/sex)
drug:	[^{14}C-methylp:opiononitrile]Arimidex lot# 2R1 (63.8 μCi/mg)
dosage:	1 mg/kg
age; weight:	not stated
route:	orally as a suspension in 0.5% HPMC/0.1% Tween 80

DMR/027 Exploratory Study to Determine Whether $^{14}CO_2$ is Formed Following Administration of a Single 1 mg/kg Oral Dose of ^{14}CN Labeled ZD1033 to Rats. Conducted by Zeneca. Urine, feces, CO_2 were collected at 0-24 hr and 24-48 hr from dosed rats along with a final cage wash.

species:	Alpk:APfSD rats (3/sex)
drug:	[^{14}C-cyano]Arimidex lot# 3R1
dosage:	1 mg/kg
age; weight:	not stated
route:	orally as a suspension in 0.5% HPMC/0.1% Tween 80

The 0-48 hr cumulative percent recoveries were:

	CO_2	urine	feces	cage	total
♂	0.09	18.5	55.0	6.8	80.4
♀	0.05	36.0	47.0	3.1	86.1

DMR/029 Pharmacokinetics of ZD1033 and Total Radioactivity Following Single Intravenous or Oral Administration of [^{14}CN]-ZD1033 to Rats. In-life phase and radioactivity measurements conducted by Arimidex measurements and pharmacokinetic calculations conducted by Zeneca.

species:	Wistar rats (3/sex/time point/group)
drug:	[^{14}C-cyano]Arimidex lot# 3R1 (221 μCi/mg)
dosage:	1 and 10 mg/kg oral and 1 mg/kg i.v.
age; weight:	not stated; 237-299 g for ♂ and 220-250 g for ♀
route:	oral gavage and i.v. via tail vein (vehicles not stated)

In whole blood and plasma, the terminal $t_{1/2}$ for total radioactivity was greater in ♂s than ♀s in all groups, but this was reflected in only slightly greater AUCs for ♂s (due to the small contribution of the terminal phase to the total AUC) (next page). At 1 mg/kg, the oral AUC for total radioactivity was virtually identical to the i.v. AUC indicating near 100% bioavailability. The blood and plasma total radioactivity C_{max} and AUC for 10 mg/kg were higher than predicted from the 1 mg/kg dose indicating saturable excretion.

The terminal $t_{1/2}$ for Arimidex was shorter in ♂s than ♀s in the 1 mg/kg groups, and this was reflected in 4-fold differences in AUCs and higher clearances. At 1 mg/kg, the oral AUC was virtually identical to the i.v. AUC indicating near 100% bioavailability for Arimidex. As seen for blood and plasma total radioactivity, C_{max} and AUC for 10 mg/kg were higher than predicted from the 1 mg/kg dose.

Pharmacokinetic Data for Arimidex in Rats

		oral						intravenous		
		1 mg/kg			10 mg/kg			1 mg/kg		
		blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex
C_{max} (µg/ml)[a]	♂									
	♀									
t_{peak} (hr)	♂									
	♀									
$AUC_{0-\infty}$ (µg•hr/ml)[a]	♂									
	♀									
$t_{½,\beta}$ (hr)	♂									
	♀									
C_L (ml/min/kg)	♂									
	♀									

[a] units for ^{14}C C_{max}s and AUCs are actually µg-eq/g and µg-eq•hr/g respectively

DMR/033 Pharmacokinetics of ZD 1033 and Total Radioactivity and Routes of Excretion Study Following Single and Multiple Oral Dose of [^{14}CN]-ZD1033 to Rats. Conducted by Pharmacokinetic and excretion studies were conducted in separate groups of rats.

species:	Wistar rats (3/sex/time point/group)
drug:	[^{14}C-cyano]Arimidex lot# 3R1
dosage:	1 mg/kg/day x 1 or 10
age; weight:	not stated; 231-289 g for ♂ and 216-244 g for ♀
route:	orally as a suspension in 0.5% HPMC/0.1% Tween 80, 10 ml/kg

The total radioactivity AUC was 1.5-fold greater in ♂s than ♀s, but the Arimidex AUC was 3-fold lower (see table, next page). The terminal $t_{½}$s for both total radioactivity and Arimidex were shorter in ♂s. Urinary and fecal recoveries are shown in the following figures (next page). Following both a single dose and multiple doses, the excretion was predominantly urinary in the ♀ and fecal in the ♂. The extent of excretion did not change with multiple dosing. The data is consistent with more rapid conversion of Arimidex in ♂s than ♀s to metabolites that are more slowly cleared than Arimidex; predominant clearance of the metabolites through the bile would explain the higher fecal excretion in the ♂s. Gender differences were thus noted in AUC, $t_{½}$, C_L, and excretion.

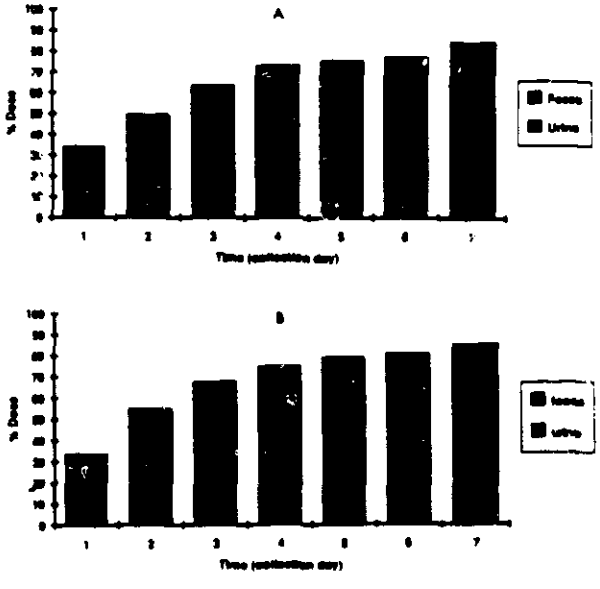
Pharmacokinetic Data for Arimidex in Rats after 10 Days of Dosing						
	♂			♀		
	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex
$C_{ss,max}$ (µg/ml)[a]						
$C_{ss,min}$ (µg/ml)						
t_{peak} (hr)						
$AUC_{0-\tau}$ (µg•hr/ml)[a,b]						
$t_{½,\beta}$ (hr)						
C_L/F (ml/hr/kg)						
blood/plasma AUC						

[a] units for ^{14}C C_{max}s and AUCs are actually µg-eq/g and µg-eq•hr/g respectively

[b] τ= 24 hr except for Arimidex in ♂s where τ=12 hr (since Arimidex was not detectable after 12 hr)

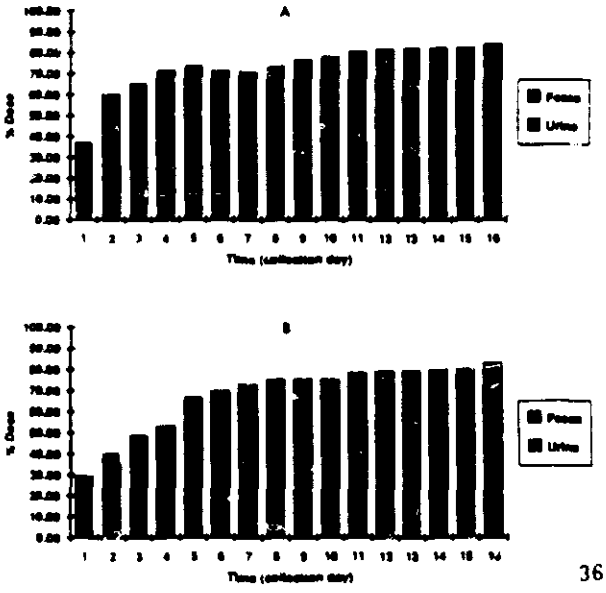
Single Dose

Figure 4: Mean Cumulative Urinary and Fecal Recoveries of Total Radioactivity as a Percentage of Dose in Male Rat (A) and in Female Rat (B) Following the Single Dose of [^{14}CH]-ZD1033



Multiple Doses

Figure 5: Mean Cumulative Urinary and Fecal Recoveries of Total Radioactivity as a Percentage of Cumulative Dosage in Male Rat (A) and in Female Rat (B) Following the Multiple Doses of [^{14}CH]-ZD1033



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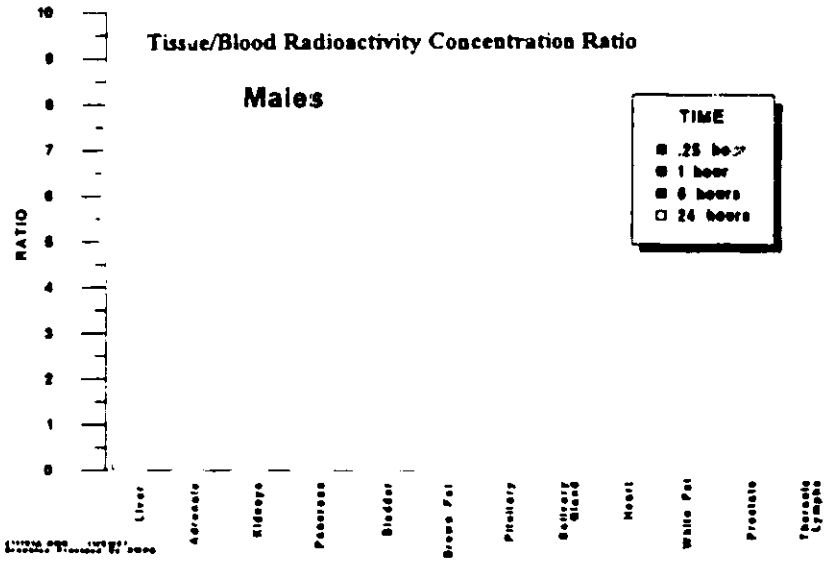
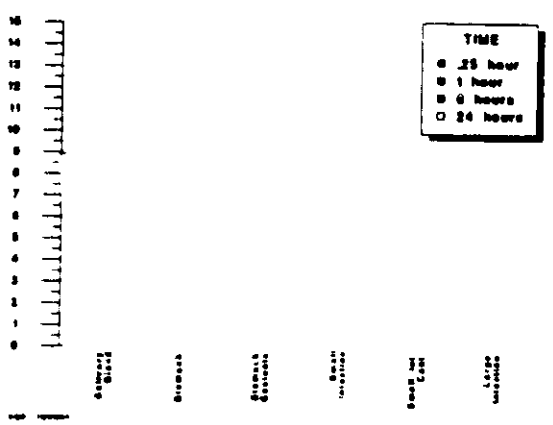
DMR/011 Exploratory Quantitative Tissue Distribution Following Single 1 mg/kg Oral Administration of ^{14}C ICI D1033 to Male and Female Rats. Conducted by Previously reviewed by M.A. Goheer, but only a fraction of the data was captured. Rats were sacrificed at 0.25, 1, 6, and 24 hr after dosing and the radioactivity in the tissues determined. Samples of liver, fat, muscle, stomach contents, and small intestine contents were analyzed by TLC for metabolite profile.

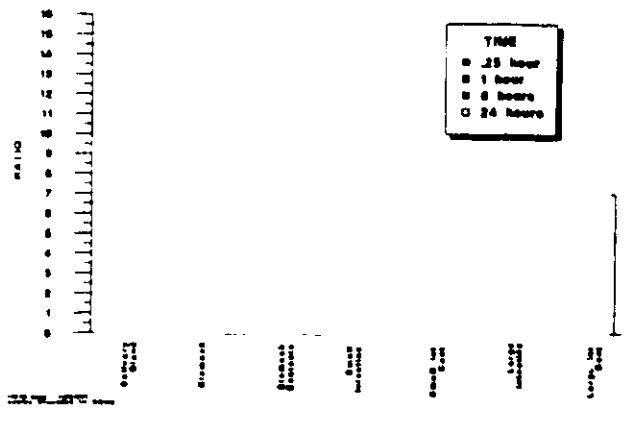
species:	Alpk:APfSD rats (1/timepoint/sex)
drug:	[^{14}C-triazole]Arimidex lot# 1R1
dosage.	1 mg/kg
age; weight:	not stated; 250-310 g for ♂ and 180-190 g for ♀
route:	orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as an ethanolic saline solution

Other than the GI tract, concentrations of radioactivity in orally dosed ♂s were highest in liver followed by the adrenal glands at 1 hr postdose (2.62 and 2.24 µg-eq/g respectively). In ♀s, the highest concentrations were in the mammary gland, adrenal glands, and liver (4.48, 3.02, and 2.25 µg-e/g respectively). The radioactivity in the liver accounted for 13% and 9% of the dose over the first 1 hr in ♂s and ♀s respectively. The ratio of tissue/blood radioactivity concentrations for ♂s are shown in the following figures for non-GI and GI tract tissues (data for ♀ not plotted by Sponsor). Results were similar after i.v. dosing except that: a) high concentrations were not found in the mammary gland of ♀s, b) 5% more radioactivity was accounted for by the liver at 1 hr, and c) the kinetics of radioactivity in the GI tract were, of course, different.





Radioactivity in GI Tract after Oral Dose



Radioactivity in GI Tract after I.V. Dose

Metabolite profiles showed the presence of 1,2,4-triazole in liver and muscle at 6-24 hr (following table). In addition, analysis of small intestine contents after an i.v. dose indicated the presence of a glucuronide of metabolite M1 which accounted for 30% and 70% of the radioactivity at 1 and 6 hr respectively.

Tissue Metabolite Profiles (Percent of tissue radioactivity)						
		1 hr		24 hr (except muscle and ♀ fat = 6 hr)		
	sex	Arimidex	triazole	Arimidex	triazole	M1
liver	♂	94	-	57	44	-
	♀	100	-	85	13	18
white fat	♂	100	-	-	-	-
	♀	-	-	95	-	5
muscle	♂	-	-	28	54	17
	♀	-	-	88	11	-
stomach contents	♂	77	23	-	-	-

KMR/005 The Distribution of Radioactivity in Male and Female Albino and Male Hooded Rats as Determined by Whole Body Autoradiography Following Oral Administration of [^{14}C]-ICI D1033 at 1 mg/kg. Conducted by Rats were dosed with 1 mg/kg [^{14}C]Arimidex; sacrificed at 1, 6, 24, and 96 hr; sectioned; and exposed to film.

species: Crl:(WI)BR albino rats (1/sex/time point)
LIS/Alpk$_h$ hooded ♂ rats (1/time point, 24 and 96 hr only)
drug: [^{14}C-triazole]Arimidex lot# 1R1 (40.9 µCi/mg)
dosage: 1 mg/kg
age; weight: 8-11 weeks; 200-256 g
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80

One hr after dosing, high levels of radioactivity were detected in the stomach with lower levels in the GI tract as far as the cecum (indicating incomplete absorption). Radioactivity was present in the urine. Radioactivity was detected in all tissues as follows:

highest- preputial gland, adrenal, liver
greater than blood- kidney, pituitary gland, cardiac muscle, lung
similar to blood- spleen, skin, skeletal muscle, pancreas, bone marrow, salivary glands
lower than blood- testes, white fat
lowest- brain, spinal cord

Six hr after dosing, the distribution of radioactivity was similar to 1 hr with slightly higher levels. Radioactivity was detected from the stomach to the rectum..

Twenty-four hr after dosing, radioactivity levels were lower than at 6 hr and were distributed as follows:

- highest- kidney
similar to blood- stomach wall, liver, lung, adrenal glands

The urine was labelled and radioactivity was present throughout the GI tract.

Ninety-six hr after dosing, radioactivity was detected in skin only.

DMR/023 Quantitative Tissue Distribution in Female Rats After Single Oral Administration of ^{14}C D1033 at 1 mg/kg. Conducted by Zeneca. Rats were dosed with 1 mg/kg [^{14}C]Arimidex; sacrificed at 1, 4, 12, 24, 72, and 168 hr; and their tissues dissected and analyzed for radioactivity.

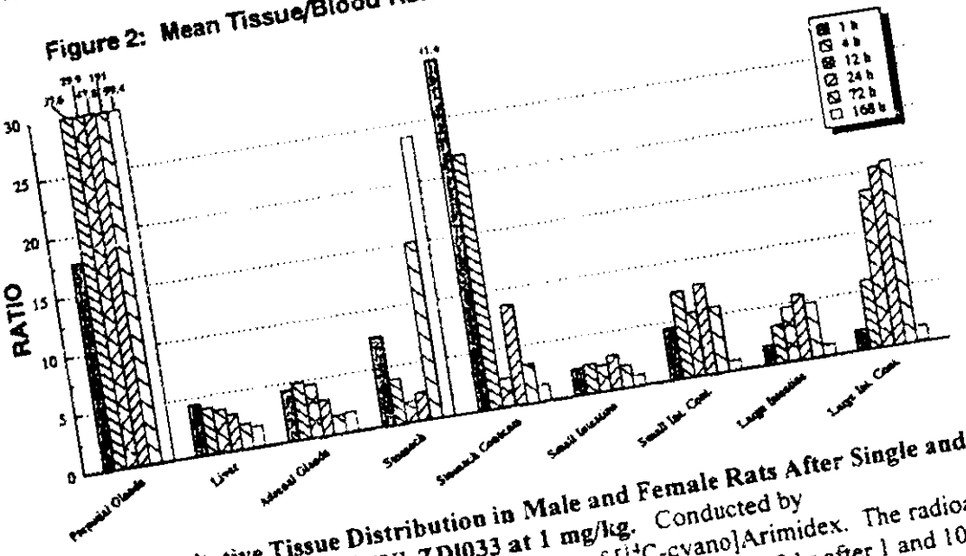
species: Long Evans hooded ♀ rats, Alpk:APfSD albino rats (1 albino ♂, 3 albino ♀, and 3 pigmented ♀ per time point)
drug: [^{14}C-triazole]Arimidex lot# 1R1 (40.9 µCi/mg)

NDA# 20-541

dosage: 1 mg/kg
age; weight: not stated; 270-350 g for ♂ and 200-250 g for ♀
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80

Distribution of radioactivity was widespread. The data in the ♂s was similar to the ♀s. There was no obvious difference between albino and pigmented rats in the radioactivity concentrations in eyes, hair, skin, liver, or kidney (implying there is no depot in any pigmented tissue). Concentrations of radioactivity in blood and plasma peaked at 1 and 4 hr in ♂s and ♀s respectively. C_{max} values in tissues were observed at these same times. The highest concentration was in preputial gland, adrenal glands, liver and the GI tract as shown in following figure. By 24 hr, concentrations declined to less than 30% of the C_{max} in over ½ the tissues. After 168 hr, urinary and fecal recoveries in ♀s were 57% and 40% respectively.

Figure 2: Mean Tissue/Blood Ratios—Albino Females (N=3/Timepoint)



DMR/031 Quantitative Tissue Distribution in Male and Female Rats After Single and Multiple Oral Administrations of [^{14}CN]-ZD1033 at 1 mg/kg. Conducted by

Animals received single or multiple doses of [^{14}C-cyano]Arimidex. The radioactivity in blood, plasma, and various tissues was determined at 1, 4, 12, 24, 72, and 168 hr after 1 and 10 doses, and at 24 hr after 5 doses.

species: Wistar rats (3/sex/time point/group)
drug: [^{14}C-cyano]Arimidex lot# 31A (1.49 MBq/mg)
dosage: 1 mg/kg/day x 1, 5 or 10
age; weight: 8 wk; 203-229 g for ♂ and 136-148 g for ♀
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80, 8 ml/kg

Single oral dose

Concentrations reached a maximum at 1 hr post-dose. Disappearance was rapid with less than 17% of the radioactivity remaining in each tissue after 3 days and less than 6% after 7 days in ♂s. In ♀s the disappearance was more rapid than ♂s with less than 9% of the radioactivity remaining after 3 days (except stomach) and more than ½ of the tissues below the LOD at 7 days. The concentrations in tissues from ♀s were higher than in ♂s.

highest concentrations of radioactivity: ♂- stomach, liver, adrenal gland, and preputial gland
♀- preputial gland, adrenal gland, and liver

concentrations comparable to plasma: ♂- all other tissues

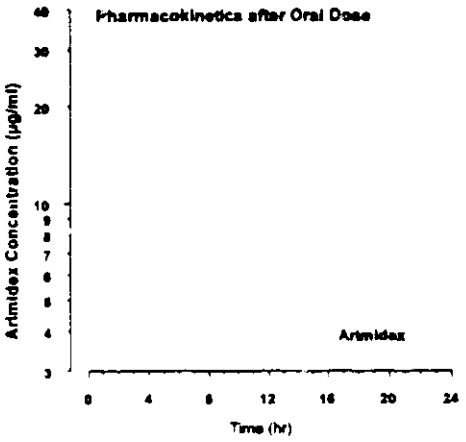
lowest concentration of radioactivity: ♂- testis, eyeball, cerebrum, and cerebellum

Multiple oral dose

Steady state concentrations were not attained after 5 doses. With multiple dosing, radioactivity concentrations in ♂s increased the most in the blood and testes which were 7.6 and 6.0 times greater than after a single dose. The increases in ♀s were less dramatic. The highest concentrations were in the preputial gland, liver, kidney, stomach, and adrenals. Disappearance after the last dose was slower than after a single dose; after 7 days tissue concentrations were 6 times higher in ♂s than after a single dose. Disappearance was more rapid in ♀s.

•Dogs

DMD/012 Pharmacokinetics and Excretion of ^{14}C ICI D1033 in Male Dogs After Single Oral or Intravenous Administration of 0.02 mg/kg. Conducted by Zeneca Pharmaceuticals. Previously reviewed by M.A. Goheer. Animals were dosed with Arimidex labelled in the triazole ring. Blood, feces, and urine were collected for 120 hr and analyzed for radioactivity; native Arimidex in plasma was analyzed by GC analysis. The ^{14}C and Arimidex vs. time plots were atypical with increasing values after the i.v. dose. Secondary peaks and plateaus were observed by both routes (as shown for the oral data to the right) and the reasons for this were unclear. Arimidex was rapidly absorbed after oral dosing and the bioavailability was >90%. The $t_{½}$ was ~11 hr and the clearance was low. Bioavailability calculations using AUC or C_{max} gave values >100%; urinary excretion values gave a bioavailability of 91%. Extensive metabolism was evident. Comparison to data in DMD/007 with 0.1 and 1.0 mg/kg doses shows proportional relationships of AUC and C_{max} with dose except for the plasma Arimidex AUC which was ½ of the expected value from the 1 mg/kg dose. This suggests that metabolism/elimination may be saturated above 0.02 mg/kg. In addition, the t_{peak} was earlier at the 0.02 mg/kg dose.



species: beagle ♂ dogs (3) used 6 mo previously in DMD/007 and crossed over between routes after a 3 wk washout

drug: [^{14}C-triazole]Arimidex lot# 1R1 (40.9 µCi/mg)

dosage: 0.02 mg/kg

age; weight: not stated; 12-13 kg

route: orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as an ethanolic saline solution

Pharmacokinetic Data for Arimidex in Dogs

	oral			intravenous		
	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex
C_{max} (ng/ml)[a]						
t_{peak} (hr)						
$AUC_{0-\infty}$ (µg•hr/ml)[a]						
$t_{½,\beta}$ (hr)						
C_L (ml/hr/kg)						

[a] units for ^{14}C C_{max}s and AUCs are actually ng-eq/g and µg-eq•hr/g respectively

Urinary Excretion of Arimidex in Dogs		
	Oral	Intravenous
time (hr):		
urinary excretion (%)		
bioavailability (%)		

DMD/020 Pharmacokinetics and Excretion of ^{14}C ICI D1033 in a Male Bile Duct Cannulated Dog After Single 1 mg/kg Administration of ^{14}C Triazole or ^{14}C Methyl-Propiononitrile Labeled ICI D1033. Conducted by Zeneca Pharmaceuticals. The common bile duct of a ♂ dog was cannulated. After 48 hr the dog was dosed orally. Blood, bile, feces, and urine were collected for 120 hr and analyzed for radioactivity; native Arimidex in plasma was determined by GC analysis. 50-60% of both labels appeared in the urine (following table). Approximately double the amount of the propyl label appeared in the bile compared to the triazole label. The AUC of the triazole label was double the propyl label, whereas the converse was true for the C_{max} (next page). Since n=1, this could be due to simple intra-animal variation. Secondary increases and plateaus were not seen in the blood or plasma, unlike studies DMD/017 and DMD/007 in non-cannulated dogs. This implicates enterohepatic recirculation in this phenomenon, although alimentary secretion cannot be ruled out. The percent of plasma ^{14}C that was Arimidex was 17% for the triazole label vs. 48% for the propyl label suggesting that metabolites without the triazole ring are cleared more rapidly from the plasma (next page). Metabolite M2B, putatively a glucuronide, accounted for 50% of the bile and 20% of the urine ^{14}C.

species: beagle ♂ dog with cross-over after 2 wk washout
drug: [^{14}C-triazole]Arimidex lot# 1R1 (43.9 µCi/mg) or
[^{14}C-methylpropiononitrile]Arimidex lot# 2R1 (63.8 µCi/mg)
dosage: 1.0 mg/kg
age; weight: not stated; 9.8-10 kg
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as a ethanolic saline

Percent Recovery of Radioactivity after Oral Arimidex in Dogs						
	Bile		Urine		Feces	
label:	triazole	propyl	triazole	propyl	triazole	propyl
0-2 hr						
2-4						
4-8						
8-12						
12-24[a]						
24-48						
48-72						
72-96						
96-120						
total						

[a] urine and feces values are for 0-24 hr

Comparative Pharmacokinetic Data for Triazole and Propyl labels of Arimidex						
	blood ^{14}C		plasma ^{14}C		plasma Arimidex	
	triazole	propyl	triazole	propyl	triazole	propyl
C_{max} (µg/ml)[a]						
$AUC_{0-\infty}$ (µg•hr/ml)[a]						
t_{peak} (hr)						
$t_{½,\beta}$ (hr)						
C_L (ml/hr/kg)						

[a] units for ^{14}C C_{max}s and AUCs are actually µg-eq/g and µg-eq•hr/g respectively

Biliary and Urinary Metabolite TLC Profile: Percent Matrix ^{14}C						
	Bile (0-12 hr)		Urine (0-24)		Urine (24-48)	
	triazole	propyl	triazole	propyl	triazole	propyl
Arimidex						
M4						
triazole						
M2B (origin)						
M1						
M2C						
M2A						

DMD/007 Pharmacokinetics and Excretion of ^{14}C-ICI D1033 in Male Dogs After Single 1 mg/kg Oral or Intravenous Doses. Conducted by Zeneca Pharmaceuticals; previously reviewed by M.A. Goheer and again here due to a clerical oversight. Animals were dosed with Arimidex labelled in the triazole ring. Blood, feces, and urine were collected for 72 hr and analyzed for radioactivity; native Arimidex in plasma was determined by GC analysis. The ^{14}C and Arimidex vs. time plots were atypical with increasing values after the i.v. dose. Secondary peaks were observed by both routes and the reasons for this were unclear. Arimidex was rapidly absorbed after oral dosing (see tables, next page). The $t_{½}$ was greater after an oral dose. Bioavailability calculations using urinary recovery data indicated a bioavailability of close to 100%. Arimidex AUC was ~50% higher after an oral dose consistent with the lower clearance. ~55% of the dose was recovered in the urine in all cases and the metabolite profile was not route dependent.

species:	beagle ♂ dogs (1/group) crossed over between routes after a 4 wk washout
drug:	[^{14}C-triazole]Arimidex lot# 1R1 (40.9 µCi/mg)
dosage:	1.0 mg/kg oral, 1.0 mg/kg i.v., and 0.1 mg/kg i.v.
age; weight:	not stated; 10.2-12.0 kg
route:	orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as a ethanolic saline

Pharmacokinetic Data for Arimidex in Dogs

	1 mg/kg oral			1 mg/kg intravenous			0.1 mg/kg intravenous		
	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex
C_{max} (µg/ml)[a]									
t_{peak} (hr)									
$AUC_{0-\infty}$ (µg•hr/ml)[a]									
$t_{½,\beta}$ (hr)									
C_L (ml/hr/kg)									

[a] units for ^{14}C C_{max}s and AUCs are actually µg-eq/g and µg-eq•hr/g respectively

Excretion Data for Arimidex in Dogs

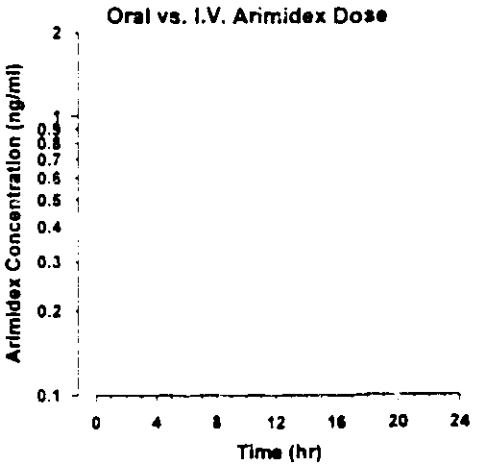
matrix:	urine	feces	total	urine	feces	total	urine	feces	tot
excretion (%)									
bioavailability (%)									

[a] based on urinary recovery of 0.1, 1.0 mg/kg doses respectively

Plasma and Urine Metabolite TLC Profile: Percent Matrix Radioactivity

	Plasma (12 hr)			Urine (0-24)	
dose:	1 p.o.	1 i.v.	0.1 i.v.	1 p.o.	1 i.v.
Arimidex					
triazole					
M2-origin					
M1					

DMD/017 Exploratory Absorption, Metabolism, Elimination and Pharmacokinetics Following Single 1 mg/kg Oral or IV Administration of an Alternate Radiolabeled Formulation of ^{14}C ICI D1033 to Male Dogs. Conducted by Zeneca Pharmaceuticals. Animals were dosed with Arimidex labelled in the propyl groups. Blood, feces, and urine were collected for 168 hr and analyzed for radioactivity; native Arimidex in plasma was analyzed by GC analysis. Excretion in the urine accounted for 55-65% of the dose regardless of route. Fecal recovery was 32% for the oral and 20% for the i.v. route. Total recovery was 90-91% in both cases. The Arimidex AUC was 45% greater and the clearance was 30% lower by the oral route. The ^{14}C and Arimidex vs. time plots were atypical with secondary peaks observed after the i.v. dose (adjacent figure)



and the reasons for this were unclear. Arimidex was rapidly absorbed after oral dosing and urinary recovery data indicated a bioavailability of 85%. Arimidex accounted for 82% and 65% of the plasma ^{14}C AUC after oral and i.v. dosing respectively. The metabolite profiles in urine and plasma were independent of route except for the distribution in M4 and M4A.

species: beagle ♂ dogs (1/group)
drug: [^{14}C-methylpropiononitrile]Arimidex lot= 2R1 (63.8 µCi/mg)
dosage: 1.0 mg/kg
age; weight: not stated; 10-11 kg
route: orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as an ethanolic saline solution

Percent Recovery of Radioactivity: Oral vs. I.V.

	Urine		Feces	
label:	oral	i.v.	oral	i.v.
0-24 hr				
24-48				
48-72				
72-96				
96-120				
120-144				
144-168				
total				

Pharmacokinetic Data for Arimidex in Dogs

	oral			intravenous		
	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex
C_{max} (µg/ml)[a]						
t_{peak} (hr)						
$AUC_{0-\infty}$ (µg•hr/ml)[a]						
$t_{1/2,\beta}$ (hr)						
C_L (ml/hr/kg)						

[a] units for ^{14}C C_{max}s and AUCs are actually µg-eq/g and µg-eq•hr/g respectively

Urinary and Plasma Metabolite TLC Profile: Percent Matrix ^{14}C

	Urine (0-24 hr)		Urine (24-48 hr)		Plasma (24 hr)	
	oral	i.v.	oral	i.v.	oral	i.v.
Arimidex						
M4						
M4A						
M1						
origin						

DMD/030 A Pharmacokinetic and Mass Balance Study of ZD1033 and Total Radioactivity in Dogs Following Single Oral and Intravenous 1 mg/kg Doses of [^{14}CN]-ZD1033. Conducted by Zeneca Pharmaceuticals. Animals were dosed with Arimidex labelled in the cyano groups. Blood, feces, and urine were collected for 168 hr and analyzed for radioactivity; native Arimidex in plasma was analyzed by GC analysis. Oral Arimidex was rapidly absorbed and based on AUC values, 80% of the dose was absorbed (following tables). Urinary recovery data indicated 83% and 100% bioavailability in ♂s and ♀s respectively. No pharmacokinetic differences were noted for parent drug that were gender dependent except a slightly higher AUC in ♂s. The ♀s, however, appear to clear metabolites more slowly than ♂s. Excretion in the urine accounted for 50-70% of the dose regardless of route. Fecal recovery was 20-30% of the dose. Total recovery was 89-99% in both cases.

species:	beagle dogs (3/sex/group)
drug:	[^{14}C-cyano]Arimidex lot# 3R1 (221 µCi/mg)
dosage:	1.0 mg/kg
age; weight:	not stated; 11.5-13.3 kg for ♂ and 10.8-13.6 kg for ♀
route:	orally as a suspension in 0.5% HPMC/0.1% Tween 80 and i.v. as an ethanolic saline solution

Pharmacokinetic Data for Arimidex in Dogs

		oral			intravenous		
	sex	blood ^{14}C	plasma ^{14}C	Arimidex	blood ^{14}C	plasma ^{14}C	Arimidex
C_{max} (µg/ml)[a]	♂						
	♀						
t_{peak} (hr)	♂						
	♀						
$AUC_{0-\infty}$	♂						
	♀						
$t_{1/2,\beta}$ (hr)	♂						
	♀						

[a] units for ^{14}C C_{max}s and AUCs are actually µg-eq/g and µg-eq•hr/g respectively

Percent Recovery of Radioactivity: Oral vs. I.V.

	Oral		I.V.	
label:	♂	♀	♂	♀
urine				
feces				
cage wash				
total				

DMD/024 Pharmacokinetic Study Following Single 1 mg/kg I.V. Administration of [^{14}C]-Triazole to Male and Female Dogs. Conducted by Zeneca. The pharmacokinetics of the major metabolite 1,2,4-triazole was studied after i.v. administration.

species: beagle dog (1/sex)
drug: [3,5-^{14}C]-1,2,4-triazole lot# CFQ6842
dosage: 1 mg/kg
age; weight: not stated
route: i.v. via cephalic vein

TLC analysis of urine and plasma indicated that triazole is not metabolized in the dog. This limited study suggests that triazole is cleared more rapidly in ♂s. Clearance was 20-fold lower than the GFR. Excretion was predominantly in the urine.

Pharmacokinetic Data for Triazole

	♂	♀
Plasma C_{max} (µg-eq/g)		
$AUC_{0-\infty}$ (µg•hr/ml)[a]		
$t_{½,\beta}$ (hr)		
C_L (ml/min/kg)		
13 day urine recovery (%)		
13 day feces recovery (%)		
cage wash recovery (%)		
total recovery(%)		

[a] all radioactivity was assumed to be triazole so the units are in µg and not µg-eq

DMD/015 Evaluation of Hepatic Cytochrome P450 Induction and D1033 Pharmacokinetic Parameters in Female Dogs Administered Arimidex for 14 Days. Conducted by Zeneca. Groups of ♀ dogs were given Arimidex for 14 days. Predose Arimidex concentrations (C_{min}) on each day and complete plasma pharmacokinetics on days 1, 7, and 14 were determined. On day 14, livers were weighed and microsomes prepared so as to assess P450 content and activities.

species: beagle ♀ dogs (3/group)
drug: Arimidex lot# 92-3200, 92-3201, 92-3202 for 0.5, 5, and 40 mg sizes
dosage: 0, 1, 3, and 8 mg/kg/day x 14
age; weight: not stated; 8-10 kg
route: oral tablets

As shown in the following table (next page), Arimidex did not induce increases in liver weight, microsomal protein content, cytochrome P450 reductase activity, or ethoxyresorufin *O*-dealkylase activity (marker for 1A subfamily). Dose-dependent increases were noted for cytochrome P450 content, ethoxycoumarin *O*-deethylase activity (marker for 2B subfamily), pentoxy resorufin *O*-dealkylase activity (marker for 2B subfamily), and erythromycin *N*-demethylase (marker for 3A subfamily). Western immunoblots showed increases in P450 2B11 and 3A proteins, but not in the P450 1A protein at all dose levels. The C_{min} values showed only drug accumulation at the HD over the first 4 days and no evidence of induction of metabolism. The C_{max} and AUC data were consistent with drug accumulation over the first 7 days followed by induction of metabolism at ≥3 mg/kg/day (next page). The accumulation and induction was particularly dramatic at the 8 mg/kg/day dose. The $t_{½}$s estimated from the dosing interval and the accumulation factor were 16, 30, and 74 hr for the 1, 3, and 8 mg/kg/day groups respectively.

Table 1: Mean Hepatic Enzyme Induction Parameters. Data represent the mean result of 3 animals ± standard error of the mean

PARAMETER	Group I (placebo)	Group II (1 mg/kg)	Group III (3 mg/kg)	Group IV (6 mg/kg)
Liver:body weight ratio	0.031 ± 0.004	0.031 ± 0.001	0.035 ± 0.001	0.0139 ± 0.001
Microsomal Protein (mg/g liver)	16.2 ± 1.1	15.5 ± 1.4	17.8 ± 1.0	21.4 ± 2.5
P450 Content (nmol/mg protein)	0.58 ± 0.02	0.79 ± 0.04 *	1.32 ± 0.27	2.76 ± 0.11 *
Reductase[#]	79 ± 7	83 ± 9	79 ± 1	1107 ± 7
ECOD[#]	1.33 ± 0.10	1.74 ± 0.14 *	4.27 ± 0.08 *	7.165 ± 0.18 *
EROD[#]	0.088 ± 0.016	0.114 ± 0.010	0.114 ± 0.015	0.124 ± 0.011
PROD[#]	0.043 ± 0.002	0.048 ± 0.004	0.141 ± 0.008 *	0.245 ± 0.012*
EMND[#]	0.91 ± 0.23	2.51 ± 0.15 *	2.47 ± 0.95	6.31 ± 0.30 *

* $p < 0.05$, treatment group mean significantly different from placebo group mean.
[#] units of activity = nmol/min/mg protein; reductase, cytochrome c reductase activity; ECOD, ethoxycoumarin O-deethylase activity; EROD, ethoxyresorufin O-deethylase activity; PROD, pentoxyresorufin O-depentylase, EMND, erythromycin N-demethylase activity.

Effect of Daily Dosing on Arimidex C_{max} and AUC Values

	dose (mg/kg/day)	day 1	day 7	day 14
C_{max} (µg/ml)				
AUC_{0-24}				

Rabbits

KMB/010 & KMB/011 **The Disposition of [^{14}CN]-ZD1033 in the Female Rabbit.** Conducted by Zeneca Pharmaceuticals. Animals were dosed with Arimidex labelled in the cyano groups. Feces and urine were collected for 120 hr and analyzed for radioactivity. In the first study, 52% of the administered drug was excreted in the urine and feces within 24 hr, 65% in 48 hr, and 67% in 120 hr. The primary route of excretion was the urine which accounted for half the administered drug. The variation was high in the 3 animals with CVs of 30-40%. When repeated in KMB/011, 73% of the administered drug was excreted in the urine and feces within 24 hr, 87% in 48 hr, and 93% in 120 hr. The urine again accounted for half the administered drug. The variation between animals was much lower than the first study.

species: New Zealand White ♀ rabbits (3)
drug: [^{14}C-cyano]Arimidex lot# 3R2 (37.9 µCi/mg)
dosage: 1.1 mg/kg
age; weight: 13-14 weeks; 2.1-2.3 kg
route: orally in water

Percent of ^{14}C Dose Excreted - KMB/010

time (hr):																								
urine																								
cage wash																								
feces																								
total																								

Percent of ^{14}C Dose Excreted - KMB/011

time:																								
urine																								
cage wash																								
feces																								
total																								

Miscellaneous

DMN/022 **The Profiling and Identification of [^{14}C]-ZD1033 Metabolites in Urine, Bile, and Plasma of Rat and Dog.** Conducted by Zeneca Pharmaceuticals. Animals were dosed with Arimidex labelled in the triazole ring or the cyano groups. Bile, plasma, and urine were pooled from numerous other studies. Metabolites were profiled by HPLC and identified by GC/MS and NMR. A metabolic pathway is proposed in the diagram below (next page). Arimidex is extensively metabolized with <15% of the dose being excreted as Arimidex. All metabolites which accounted for >5% of the administered dose have been identified and together account for ≥70% of the total dose (table, next page). Metabolism of Arimidex is similar in rats and dogs. Greater than 50% of the dose is metabolized by *N*-dealkylation resulting in loss of the triazole ring and generating the BMPN-benzoic acid. Differences were noted between ♂s and ♀s in the handling of the BMPN-benzoic acid. Hydroxylation and demethylation of the methyl groups are minor routes. Several of the metabolites are conjugated to glucuronic acid.

Excretion of Arimidex Metabolites (percent[a] of dose for urine and bile, percent of matrix for plasma)							
		rat			dog		
metabolite	name	plasma[b]	urine	bile	plasma[d]	urine	bile
	Arimidex						
M2	1, 2, 4-triazole						
M3	unknown						
M4	methylhydroxy-glucuronide						
M5	BMPN benzoic acid glucuronide						
M6	desmethyl BMPN-glucuronic acid						
M7	unknown						
M8	unknown						
M9	methylhydroxy Arimidex						
M10	BMPN-benzoic acid						
M11	desmethyl Arimidex						

[a] approximated from data for both cyano and triazole labels in both ♂s and ♀s; columns therefore do not add to 100%

[b] plasma data is for ♀s at 12 hr

[c] ♂, ♀

[d] plasma data is for ♀s at 24 hr

Proposed Metabolic Pathway for Arimidex

DMM/021 Protein Binding in Selected Species Using Equilibrium Dialysis. Conducted by Zeneca. Binding was invariant across the concentration range of 0.02-100 µg/ml. The mean percent binding was:
dog, 42%; rat, 42%; mouse, 25%; rabbit, 22%; monkey, 17%; normal human, 33%; post menopausal human, 39%; 4% human albumin, 23%; 0.08% α-1-acid glycoprotein, 8% (at 0.1 µg/ml Arimidex). In conclusion, protein binding was low to moderate and changes in disease states which affect albumin or α-1-acid glycoprotein should not alter the amount of free drug.

DMX/040 Inhibitory Effects of D1033 on Cytochrome P450 Activities In Vitro in Human Hepatic Microsomes. Conducted by Zeneca. Prolongation of phenobarbital sleep time in rats and alteration of antipyrine pharmacokinetics in dogs suggested that Arimidex inhibited P450 activity. The ability of Arimidex to inhibit specific P450 isozymes in human liver microsomes was thus studied and the results are shown in the following table. Arimidex inhibited P450 1A2, 2C8/9, and 3A4 but not 2A6 or 2D6. Arimidex is 1300 times less potent than ketoconazole as an inhibitor of 3A4 in vitro.

Table 1 IC_{50} values for the inhibition of human cytochrome P450 activities

Human Cytochrome P450	Test compound	Specific Marker Substrate	IC_{50} (uM)	Ki (uM)
1A2	ZD1033	Phenacetin		
2A6	ZD1033	Coumarin		
2C	ZD1033	Tolbutamide		
2D6	ZD1033	Dextromethorphan		
3A	ZD1033	Nifedipine		
3A	Ketoconazole	"		
3A	Cimetidine	"		
3A	Erythromycin	"		

* NI = not inhibited at concentrations less than 500 uM

DMR/009, DMR/010 Mixed Function Oxidase Evaluation Study in Rats After Oral Administration. Conducted by Previously reviewed by M.A. Goheer, but very little of the data was captured. Rats were dosed for 14 days with Arimidex or 3 days with phenobarbital and the livers removed and assayed. In a second experiment, rats were dosed with 0 or 25 mg/kg/day oral Arimidex and then 4 hr later with i.p. pentobarbital to determine sleeping time.

species: Wistar rats (4/sex/group)
drug: Arimidex lot# ADM44005/90
dosage: 0, 0.2, 1, 5, and 25 mg/kg/day x 14
age; weight: not stated; 220-350 g for ♂ and 190-250 g for ♀
route: oral Arimidex and i.p. phenobarbital

Arimidex caused a dose-dependent ↑ in liver weights, microsomal protein (♂s only), cytochrome P450 activity, and cytochrome P450 reductase activity (tables, next page). Specific increases were induced in PROD (2B isozyme) and ECOD (2B isozyme) activities. Statistically significance occurred at 5 mg/kg and 25 mg/kg/day. The pattern of induction was similar to that produced by phenobarbital. Arimidex increased sleep time by ~140% in both ♂ and ♀ rats. Arimidex is thus an inducer and inhibitor of P450 enzymes.

Assays of Hepatic Status and Function in Rats						
♂ Rats	Arimidex					PB
mg/kg:	0	0.2	1	5	25	80
liver/body weight						
microsomal protein (mg/ml)						
cytochrome P450 (nmol/mg protein)						
ethoxyresorufin-*O*-deethylase (pmol/mg protein/min)						
pentoxyresorufin-*O*-depentylase (pmol/mg						
ethoxycoumarin-*O*-dethylase (nmol/mg protein/min)						
NADPH cytochrome c reductase (nmol/mg						
♀Rats						
liver/body weight						
microsomal protein (mg/ml)						
cytochrome P450 (nmol/mg protein)						
ethoxyresorufin-*O*-deethylase (pmol/mg protein/min)						
pentoxyresorufin-*O*-depentylase (pmol/mg						
ethoxycoumarin-*O*-dethylase (nmol/mg protein/min)						
NADPH cytochrome c reductase (nmol/mg						

DMD/014 A Study of Pharmacokinetics, MFO Activity and Antipyrine Kinetics in the Dog After an 8 mg/kg Dose for 14 Days. In-life phase conducted by Arimidex and enzyme assays conducted by Zeneca, antipyrine measurements conducted by Pharmaco Analytical Laboratories (Richmond, VA). Groups of ♂ dogs were given placebo, Arimidex, or phenobarbital for 14 days.

species: beagle ♂ dogs (3/group)
drug: Arimidex lot# 91-3004 and phenobarbital
dosage: 0 and 8 mg/kg/day Arimidex x 14, and 20 mg/kg/day phenobarbital x 14
age; weight: 8 mo; 8-10 kg
route: oral tablets

Observations

- antipyrine pharmacokinetics days -7, 1, and 14
- Arimidex pharmacokinetics days 1 and 14
- liver microsome prep day 15

From day 1 to 14, Arimidex C_{max} ↑ from 15.6 to 32.5 µg/ml and AUC ↑ from 127 to 287 µg•hr/ml. C_{min} ↑ up to day 4 at which steady state appeared to have been reached. This pharmacokinetic data did not suggest induction of metabolism. Antipyrine $t_{1/2}$ was significantly ↑ in Arimidex treated dogs after 1 and 14 days of dosing. Antipyrine AUC was ↑ 50% between days 1 and 14; antipyrine clearance was ↓ 30% between days 1 and 14. This data suggests that Arimidex inhibits antipyrine metabolism. The effect of phenobarbital on antipyrine pharmacokinetics was minimal at day 1 and was not calculated on day 14 due to too few data points, but the day 14 C_{max} was ↓ 70%. Mixed function oxidase evaluation (following table) clearly shows induction (predominantly P450 2B).

Assays of Hepatic Status and Function in Dogs			
	placebo	Arin .. x	phenobarbital
liver/body weight			
microsomal protein (mg/ml)			
cytochrome P450 (nmol/mg protein)			
ethoxyresorufin-*O*-deethylase (pmol/mg protein/min)			
pentoxyresorufin-*O*-depentylase (pmol/mg			
ethoxycoumarin-*O*-dethylase (nmol/mg protein/min)			
NADPH cytochrome c reductase (nmol/mg			

SUMMARY OF PHARMACOKINETICS (does not include summary of toxicokinetics reviewed in Toxicology section; those results will be integrated under the Overall Summary)

Rats

Summary of Rat Oral Arimidex Pharmacokinetic Parameters after a 1 mg/kg Dose[a]								
study:		DMR/003	DMR/004	DMR/013	DMR/018	DMR/019	DMR/029	DMR/033[b]
label:		triazole	triazole	triazole	propyl	propyl	cyano	cyano
C_{max} (µg/ml)	♂							
	♀							
AUC (µg•hr/ml)	♂							
	♀							
$t_{½}$ (hr)	♂							
	♀							
urinary excretion (%)	♂							
	♀							
biliary excretion (%)	♂							
	♀							
fecal excretion (%)	♂							
	♀							
% triazole in plasma (12	♂							
	♀							
% triazole in urine (24 hr)	♂							
	♀							
bioavailability (%)	♂							
	♀							
C_L/F (ml/hr/kg)	♂							
	♀							

[a] C_{max}, AUC, $t_{½}$, and C_L are for Arimidex; all other pharmacokinetic values are for total radioactivity
[b] pharmacokinetic values after 10 days of dosing, [c] bile duct cannulated

Arimidex was rapidly absorbed from the GI tract of rats and the bioavailability was close to 100%. It was rapidly distributed to all tissues with the highest concentrations occurring in preputial gland, adrenal glands, mammary glands (1/4 studies), liver, and GI tract. After 10 doses, high concentrations were also seen in the kidney. Marked gender differences were apparent in the pharmacokinetic handling of Arimidex and its metabolites. The Arimidex C_{max} was higher in ♀s and the AUC was 3-4 fold greater with an associated 3-4 fold lower clearance. This appeared to be due at least in part to more rapid metabolism of Arimidex in ♂s (less Arimidex in plasma, more triazole in plasma and urine, higher recovery as CO_2). The resultant metabolites, however, may be more slowly cleared in ♂s (higher total radioactivity AUC). The $t_{1/2}$ for Arimidex was 3-fold greater in ♀s. Secondary peaks and plateaus occurred in the plasma concentrations of Arimidex and total radioactivity. When the triazole ring was labelled, 50-70% of the dose was excreted in the urine and 25-40% in the feces in both sexes. The majority of the fecal excretion appeared to result from biliary excretion of metabolites. When the propyl or cyano groups were labelled, however, only 10-20% of the radioactivity was recovered in the urine of ♂s with roughly double the amount being excreted in the urine of ♀s. The fecal excretion was 40-65% when the propyl or cyano groups were labelled. This gender difference was consistent with the greater excretion of the radiolabel as CO_2 and in the feces in ♂s in these studies. The metabolism of Arimidex was extensive with <10% being excreted as Arimidex and a number of metabolites appearing. The disposition of Arimidex was very similar after oral or i.v. dosing.

Dogs

As for rats, Arimidex was rapidly and efficiently absorbed from the GI tract of dogs (summary table next page). Secondary peaks and plateaus were also seen in the plasma concentrations of total radioactivity and Arimidex. These were abolished after cannulation of the bile duct providing strong evidence that they result from enterohepatic circulation. Approximately 50% of the administered dose appeared in the urine and 15-30% in the feces. Metabolism was extensive with <40% of the radioactivity in bile or urine appearing as unchanged Arimidex, but appeared to be less rapid than in rats. Marked gender differences were not apparent in dogs but only one study included ♀s. However, when the major metabolite, 1,2,4-triazole, was administered directly, it appeared to be cleared more rapidly in ♂s. Induction of metabolism was noted at ≥3 mg/kg/day after 7 days.

Rabbits

The excretion in rabbits was similar to rats and dogs with 50-70% of the dose appearing in the urine.

Miscellaneous

Chronic dosing with Arimidex induced P450 metabolism and specifically 2B and 3A activity and protein levels in dog livers at ≥3 mg/kg/day x 14. Arimidex also decreased antipyrine clearance, consistent with an inhibitor of antipyrine metabolism. Arimidex inhibited P450 1A2, 2C8/9, and 3A4 metabolism in human liver microsomes. In rats, Arimidex dose-dependently increased liver weights, microsomal proteins, P450 activity, cytochrome *c* P450 reductase activity, P450 2B activity, and P450 3A activity at ≥5 /day x 14. Arimidex (25 mg/kg/day x 14) also prolonged phenobarbital-induced sleep time. Arimidex is also an inhibitor of P450 metabolism as evidenced by changes in antipyrine pharmacokinetics and by specific assays with liver microsomes. Only moderate binding of Arimidex occurs to plasma proteins. All metabolites which account for >5% of the administered dose have been identified in rats and dogs; a metabolic scheme has been proposed.

Summary of Dog Oral Arimidex Pharmacokinetic Parameters after a 1 mg/kg Dose[a]

study:		DMD/012[b]	DMD/020		DMD/007	DMD/017	DMD/030
label:		triazole	triazole	propyl	triazole	propyl	cyano
C_{max} (µg/ml)	♂						
	♀						
AUC (µg•hr/ml)	♂						
	♀						
$t_{½}$ (hr)	♂						
	♀						
urinary excretion (%)	♂						
	♀						
biliary excretion (%)	♂						
	♀						
fecal excretion (%)	♂						
	♀						
% triazole in plasma (12	♂						
	♀						
% triazole in urine (24 hr)	♂						
	♀						
bioavailability (%)	♂						
	♀						
C_L/F (ml/hr/kg)	♂						
	♀						

[a] C_{max}, AUC, $t_{½}$, and C_L are for Arimidex; all other pharmacokinetic values are for total radioactivity
[b] 0.02 mg/kg Arimidex
[c] bile duct cannulated

III. Toxicology

A. Single Dose Toxicity

The following 4 studies were conducted by according to UK and OECD GLP. They were previously accurately reviewed by M.A. Goheer.

TLM/691 Acute Toxicity (Limit) Study in Mice: Oral Administration. A single oral dose of 750 mg/m² (250 mg/kg) Arimidex was administered and it was minimally toxic to the mice.

TLR/1944 Acute Toxicity (Limit) Study in Rats: Oral Administration. An oral dose of 600 mg/m² (100 mg/kg) Arimidex was minimally toxic to rats. A dose of 1500 mg/m² (250 mg/kg) killed 6/10 rats within 24 hr and caused severe signs of local irritation to the stomach.

TLM/692 Acute Toxicity (Limit) Study in Mice: Intraperitoneal. Administration. A single i.p. dose of 150 mg/m² (50 mg/kg) Arimidex was administered and it was minimally toxic to the mice.

TLR/1945 Acute Toxicity (Limit) Study in Rats: Intraperitoneal Administration. An i.p. dose of 300 mg/m² (50 mg/kg) Arimidex was minimally toxic to rats, but 1500 mg/m² was immediately lethal.

B. Multiple Dose Toxicity

TPR/1992 6-Month Oral Toxicity Study in Rats. Conducted by according to UK, OECD, and US GLP. Numerical data were analyzed for significance using the Jonckheere-Terpstra non-parametric trend test.

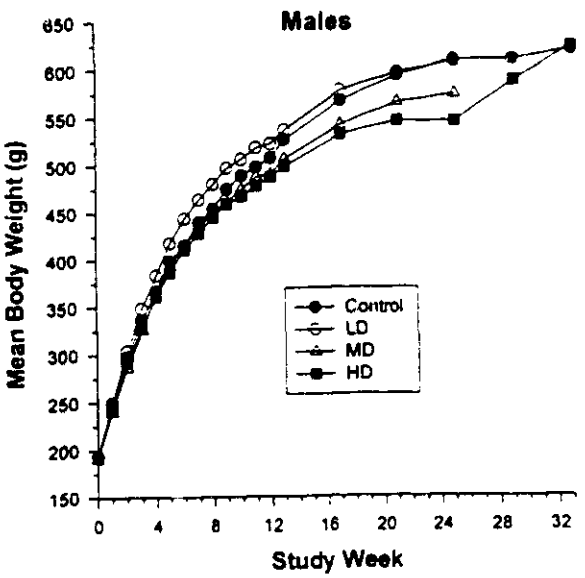
species:	Alpk:APfSD rats (20/sex/group)
drug:	Arimidex lot# 44065/91
dosage:	0, 1, 5, and 50 mg/kg/day for 182 days
age; weight:	45 days, 169-243 g for ♂ and 131-186 g for ♀
route:	oral gavage at 5 ml/kg in 0.5% methocel, 0.1% polysorbate 80
recovery:	twenty control and HD animals (10/sex) for 53 days

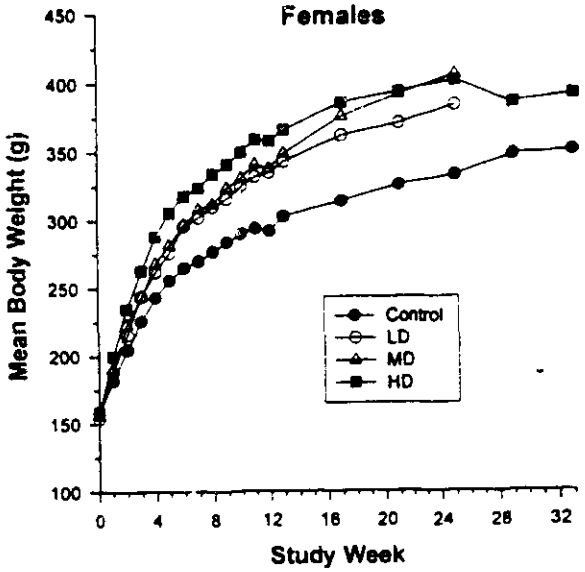
Observations

Clinical signs	twice daily for gross findings and weekly physical exams
Body weights	daily until dosing, weekly until wk 13, then monthly
Food consumption	daily until dosing, weekly until wk 13, then monthly
Ophthalmoscopy	pre-study, week 14 and 26 for control and HD only
Vaginal smears	weeks 4, 5, 13, 14, 25, 26 and weeks 30-34 for HD recovery group
Hematology	weeks 13, 25, 33
Clinical chemistry	weeks 13, 25, 33
Urinalysis	weeks 12, 24, 32
Gross pathology	at sacrifice (organs p. 23)
Histopathology	at sacrifice (organs p. 23)
Toxicokinetics	pre-dose, 2, 4, 8, 16, and 24 hr after first and final doses pre-dose and 2 hr post-dose during week 5 and 13

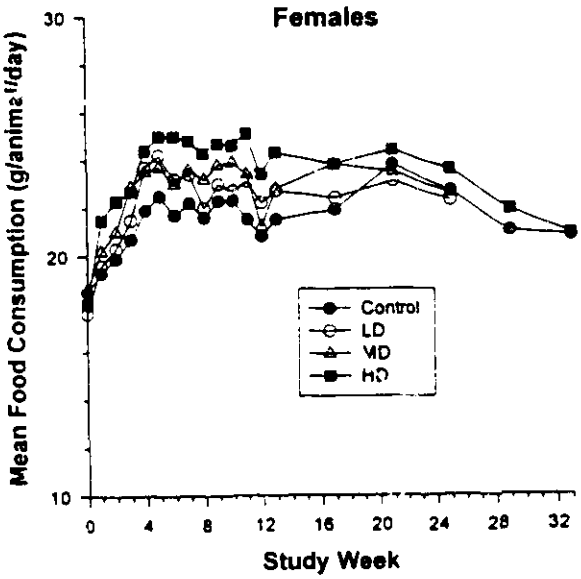
a. Clinical signs: deaths- 1 control ♀ (wk 20), 1 LD ♂ (wk 25), 1 HD ♂ (wk 3) but none attributed to Arimidex. Excessive salivation 20-30 min following dosing in HD animals.

b. Body weights: As shown in the following figures (next page), MD and HD Arimidex decreased ♂ mean body weight by 6 and 10% respectively at 25 wk. The decrease was significant at ≥17 wk for the MD group and ≥7 wk for the HD group. After 8 weeks of recovery, the body weights of the HD ♂ animals were similar to controls. In contrast, Arimidex increased body weight in all ♀ groups. Mean ♀ body weight was 15, 22, and 21% higher than controls in the LD, MD, and HD groups respectively at 25 wk. The increase was significant after 2 wk in the LD animals and after 1 wk in the MD and HD animals. After 8 weeks of recovery, the body weights of the HD ♀ animals decreased slightly but were still 12% higher than the control animals.





c. Food consumption: For ♂ animals, the only significant difference with controls was a 3% ↓ at wk 2 in the HD group. For ♀ animals, Arimidex increased food consumption in the HD group ~10% from wk 1-17 as shown in the adjacent figure. For the MD group, significant increases were noted at wks 1, 2, 3, 9, 10, and 11. The LD group had a significant increases only during wk 11.



d. Ophthalmology: no treatment related changes

e. Vaginal smears: 0/10 Animals cycled in HD group during weeks 4, 13, and 25 compared to ≥8/10 animals cycling in all other groups. LD and MD cycle lengths were prolonged 0.5 day compared to controls. After 4 wk recovery 9/10 HD animals were cycling normally.

f. Hematology: Small changes in red cell indices were seen in HD ♂ rats likely due to aromatase inhibition in the bone marrow. A 20-50% ↑ in WBC, a 35-70% ↑ in lymphocytes, and a 20-30% ↑ in platelets were seen in both HD groups. This is likely due to a fall in estrogen as a result of aromatase inhibition; e.g. increases in lymphocytes occur in ovariectomized rats. ↑Lymphocytes were also found in the MD and LD ♀ groups. All the changes appeared reversible except for the ↓Hg and ↑platelets.

Percent Change in Hematology Parameters (>5% only)

		MD		HD	
	Week	♂	♀	♂	♀
Hemoglobin	13			↓7	
	25			↓11	
	33			↓7	
MCV	25			↓5.4	↓6.3
MCH	25			↓7	↓8
WBC	13			↑17	↑29
	25			↑53	↑42
Platelets	13			↑23	↑30
	25			↑27	↑23
	33				↑22
Lymphocytes[a]	13		↑29	↑36	↑60
	25		↑59	↑69	↑70

[a] Not shown are 32 and 38% increases in lymphocytes in LD ♀ at wks 13 and 25 respectively.

g. Clinical chemistry: Numerous small changes were found particularly in the HD groups (table, next page). Most changes were only found at one time point and most showed evidence of reversal during the 8 wk recovery period. Opposite effects were noted on cholesterol, FH, and FSH levels in ♂ and ♀. Sporadic changes in chloride, phosphate and calcium levels were also seen and are not listed. The noted effects can be attributed to metabolic changes resulting from aromatase inhibition and P-450 induction. The toxicological significance of all these changes is probably minor.

Percent Change in Blood Parameters (>10% only)					
		MD		HD	
	Week	♂	♀	♂	♀
Glucose	25	↑13		↑13	↑9
Total protein	13			↑11	↑15
Alb/glob	13			↑8	↑12
	25				↑20
K^+	25		↑15	↑14	↑15
AP[a]	13	↑8		↑25	
	25		↑19	↑28	↑35
	33			↑17	
ALT	25				↑41
AST	13				↑22
	25				↑31
Cholesterol	13		↑18	↑43	↑54
	25				↑50
	33				↑12
Triglycerides	13	↑34		↑43	
	25				↑31
LH[b]	13	↑27		↑14	↑33
	25		↑42		↑49
FSH[c]	25		↑52	↑26	↑51

[a] LD ♂ had ↑8% at wk 13; LD ♀ ↑37% at wk 25

[b] LD ♂ had ↑17% at wk 13 and LD ♀ had ↑36% at week 25

[c] LD ♀ had ↑36% at week 25

h. Urinalysis: no treatment related changes

i. Gross pathology: The following macroscopic findings were noted at necropsy-

enlarged livers: 39/40 HD animals; returned to normal during recovery

enlarged ovaries: 18-19/20 animals in all 3 treated groups; after recovery only 3/10 HD animals had enlargement

distended uteri (indication of estrous): 5/20 in controls decreased dose-dependently to 0/20 in HD; no difference after recovery

Differences were found in most organ weights as shown in the following table (next page). The changes in the heart, lungs, thymus, spleen, and kidneys did not show a clear dose dependence, were not correlated with histologic changes, and could in some cases be attributed to body weight changes. All of the other changes resolved during recovery except in ovary, prostate, kidney, and thymus.

Percent Organ Weight Changes							
		Males			Females		
		LD	MD	HD	LD	MD	HD
liver	Abs			↑50	↑13	↑20	↑98
	Rel		↑5	↑62			↑61
ovary	Abs				↑91	↑100	↑87
	Rel				↑61	↑67	↑55
uterus	Abs						↑22
	Rel				↓35	↓29	↓35
adrenal	Abs				↓11	↓16	↓21
	Rel			↑9	↓27	↓30	↓37
kidney	Abs						↑16
	Rel						
prostate	Abs			↓17			
	Rel						
pituitary	Abs		↓25	↓17		↓19	↓25
	Rel				↓37	↓38	↓40
heart	Abs		↓9	↓6			↓14
	Rel				↓14	↓14	↓8
spleen	Abs				↑7	↑11	↑11
	Rel			↑17	↓12	↓2	↓8
thymus	Abs						
	Rel				↓30	↓19	↓32
lungs	Abs		↓6	↓6			↑14
	Rel				↓15	↓14	↓13

j. Histopathology:

ovaries: 16-20/20 with ↑# of corpora lutea compared to 0/20 in controls, 12-19/20 with ↑# of follicular cysts compared to 6/20 in controls; after recovery the only finding was 2/10 with ↑#corpora lutea

uterus: 7/20 HD with ↑endometrial fibrosis that disappeared after recovery

vagina: cornified epithelium ↓ from 7/20 in controls to 1/20 in HD returning to 3/10 in each recovery group

adrenal gland: ↓ zona fasciculata vacuolation and ↑ cortical vacuolization for HD ♀ only that was similar to control males; after recovery ↑ cortical vacuolation was still noted in 3/10 HD ♀

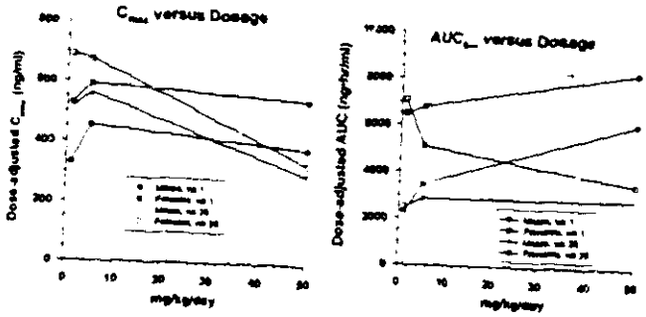
thyroid: slightly hypertrophic thyroid follicular epithelium in 6/20 LD, 6/20 MD, and 15/20 HD ♀ which diminished in recovery; ↑basophilic colloid was noted in 12/20 HD ♂ and 4/20 HD ♀ which decreased to 4/10 and 0/10 respectively after recovery

liver: incidence of lesions was as follows; none of these lesions were found after recovery

	Males				Females			
Dose:	0	LD	MD	HD	0	LD	MD	HD
hepatocyte hypertrophy	0	17	19	19	0	7	20	19
↓glycogen vacuolation	0	14	19	19	0	9	19	19
hepatocyte fat vacuolation	0	0	2	6	0	2	3	14

kidney: chronic glomerulonephropathy ↑ from 6/20 to 17/20 in HD ♂ and from 1/20 to 12/20 in HD ♀; these differences persisted after recovery

k. Toxicokinetics: Arimidex exposure was higher in ♀ than ♂ based on both C_{max} (40%) and AUC (36-180%) comparisons (next table). This was most obvious in the LD groups where the $t_{½}$ was longer in the ♀s. The $t_{½}$ was shorter and the AUCs markedly lower at week 26 in both HD groups, perhaps due to induction of metabolism. Induction of metabolism was apparent at weeks 5 and 13 as well, where the pre-dose nadir of Arimidex was ~50 ng/ml, ~20 ng/ml, and <LOQ for the LD, MD, and HD groups respectively (non-dose-adjusted). The increase in the C_{max}s and AUCs at week 26 in the LD groups suggests minor drug accumulation during the achievement of steady state. The C_{max} and $AUC_{0-\infty}$ did not increase linearly in the 1-50 mg/kg dose range as shown in the adjacent figures where the data was normalized to dose. The pharmacokinetic behavior of Arimidex was thus non-linear, gender-dependent, and altered with prolonged dosing.



Dose-normalized Pharmacokinetic Data for Arimidex[a]							
		Male			Female		
Week	Parameter	LD	MD	HD	LD	MD	HD
1	C_{max} (ng/ml)						
	$AUC_{0-\infty}$ (ng•hr/ml)						
	$t_{½}$ (hr)						
5	C_{min} (ng/ml)						
13	C_{min} (ng/ml)						
26	C_{max} (ng/ml)						
	C_{min} (ng/ml)						
	$AUC_{0-\infty}$ (ng•hr/ml)						
	$t_{½}$ (hr)						

[a] adjusted to a 1 mg/kg dose

TAR/1946 One-Month Oral Toxicity Study in Rats. The LD and MD were the same as the 6 mo study, but the HD was 25 not 50 mg/kg/day as for the 6 mo study. The findings as previously reviewed by M.A. Goheer were consistent with the 6 mo study with the following exceptions (new findings in the 6 mo study are not listed):

- ALT was ↑73% for 1 mo and ↑41% for 6 mo studies in HD ♀,
- Urinalysis showed ↑Na^+ and creatinine in ♂s and ↓Na^+ in ♀ during 1 mo but no changes during 6 mo study,
- ↓Adrenal sizes in ♂ in 1 mo but not 6 mo study,
- ↓Corpora lutea in 1 mo but ↑ in 6 mo study

TPD/[illegible]52 6-Month Oral Toxicity Study in Dogs. Conducted by according to UK, OECD, and US GLP. Numerical data was analyzed for significance using the Jonckheere-Terpstra non-parametric trend test.

species:	Beagle dogs (4/sex/group)
drug:	Arimidex lot# 44065/91
dosage:	0, 1, 3, and 8 mg/kg/day for 26 wk (182 days)
age; weight:	46-51 weeks; 12.4-19.3 kg for ♂ and 10.3-17.2 kg for ♀
route:	oral gelatin capsules containing tablets
recovery:	six control and HD animals (3/sex) for 8 wks

Observations

Clinical signs	twice daily for gross findings and weekly physical exams
Body weights	weekly
Food consumption	daily
Ophthalmoscopy	pre-study, week 5, 13, and 26
EKG	pre-study, weeks 4, 13/14, and 25 at 3 hr after dosing
Vaginal smears	weeks 4, 5, 13, 14, 25, 26 and weeks 30-34 for HD recovery group
Hematology	pre-study, weeks 13, 25, 30, and 34
Coagulation	pre-study, weeks 13 and 25
Blood chemistry	pre-study, weeks 13, 25, 30, and 34
Hormonal chemistry	♀: pre-study, weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and then weekly during recovery ♂: pre-study, weeks 13, 25, 30, and 34
Urinalysis	pre-study, weeks 13 and 25
Gross pathology	at sacrifice (organs p. 25)
Histopathology	at sacrifice (organs p. 26)
Toxicokinetics	pre-dose, 1, 2, 4, 6, 8, 12, 16, and 24 hr after doses on days 1, 14, 28, and 182; 48, 72, 96, 120, and 144 hr after final dose in HD recovery groups

a. Clinical signs: inhibition of estrous cycling in MD and HD ♀

b. Body weights: Mean body weight was ↓10-15% in HD ♂ starting at wk 2. Body weight returned to control values within 1 wk of cessation of dosing. The HD ♀ mean body weight was decreased 7% wk 3 only.

c. Food consumption: ↓ in 1/7 control ♀ and 1/4 MD ♀; ↓ in 1/7 control ♂ and 2/7 HD ♂; consumption not affected during recovery

d. Ophthalmoscopy: no treatment related changes

e. Cardiology: No changes in QT interval, SBP, DBP, MBP, or temperature; however, changes in R-wave amplitude were detected (the following values differ from those in Table 6, p. 58 because they are mean ± SD and not median values). In the absence of changes in heart histopathology or other cardiac parameters, the Sponsor did not consider the R-wave changes toxicologically important.

R-wave Amplitude in ♂ Dogs (mean ± SD, n=4)

week	control	LD	MD	HD
-2	3.16 ± 0.45	3.38 ± 0.83	2.60 ± 0.52	2.83 ± 0.80
4	3.38 ± 0.54[a]	3.35 ± 0.71	2.78 ± 0.66	2.33 ± 0.69[b]
13	3.09 ± 0.43	3.05 ± 0.65	2.35 ± 0.66	2.23 ± 0.83[b]
25	3.07 ± 0.45	3.05 ± 0.72	2.33 ± 0.21[b]	2.07 ± 0.73[b]
34	3.10 ± 0.26[a]	-	-	2.90 ± 0.36

[a] n=3; [b] statistically significant

f. Hematology: Changes were only seen in HD dogs as shown in the following table. All of the listed changes recovered after Arimidex withdrawal.

Percent Change in Median Hematology Parameters for HD Groups

	Week 13		Week 25	
	♂	♀	♂	♀
↓Hb	22	-	13	13
↓RBC	22	10	13	16
↓Hct	24	-	13	16
↑Platelets	75	37	77	33
↓WBC			22	
↓Neutrophils			25	
↓Lymphocytes			20	

g. Coagulation: no treatment related changes

h. Blood chemistry: Changes were only seen in HD dogs as shown in the following table. All of the listed changes recovered after Arimidex withdrawal. Note that the ALT values varied over a large range in the individual HD animals.

Percent Change in Median Blood Chemistry Parameters for HD Groups

	Week 13		Week 25	
	♂	♀	♂	♀
↑AP	71	160	84	162
↑Cholesterol		21		35
↓Creatinine	21	15		7
↑Alb:glob	23	12	20	13
↑ALT	183	220	255	65
ALT range Ctrl	62-87	26-101	61-75	48-139
HD	51-386	62-219	81-522	58-199

i. Hormonal chemistry:
In ♂s, testosterone levels ↓ during the treatment period, but were only 20-30% of controls during the recovery period:

Fold Difference in Testosterone Levels

week	LD	MD	HD
13	8.1	11.5	6.4
25	8.6	10.7	9.2
30	-	-	0.20
34	-	-	0.31

In ♀ dogs the following effects on r ↓productive function were found.

i) Estrous cycling of estradiol and progesterone
Control animals exhibited a normal estrous cycle (elevated plasma estradiol followed by clinical signs of estrous followed by a 6-12 week rise in plasma progesterone). In LD animals, a progesterone rise occurred in all 4 dogs, but was associated with signs of estrous in only 2/4 dogs. In MD dogs, a progesterone rise was seen in all dogs, but no signs of estrous occurred. All HD dogs showed multiple progesterone cycles with persistence of progesterone levels above 5 nM for periods of 16-34 weeks. Long intervening anestrous periods were not seen between cycles. After drug withdrawal, the progesterone levels rapidly fell and did not rise again.

ii) Peak plasma progesterone levels
As shown in the next table, progesterone levels in LD dogs were double the control values and in the HD dogs were 6-fold greater than controls. The MD animals had levels that were not statistically significantly different from controls.

Median C_{max} and AUC for Plasma Progesterone

	Control	LD	MD	HD
C_{max} (nM)	119	238	36	678
AUC (nmol•wk/l)	560	1360	290	3070

iii) Temporal relationship between estradiol and progesterone
Unlike control and LD dogs, the MD and HD animals had no clear relationship between estradiol and progesterone levels.

iv) Plasma estradiol levels
All the obtained estradiol concentrations were grouped into 3 categories (≤9 pM, 9-≤25 pM, and >25 pM). All dose groups had similar (45-60%) numbers of samples with undetectable estradiol (<9 pM). Likewise, there was no statistically significant difference between dose groups in the number of samples with estradiol between 9 and 25 pM. The percentages of samples with estradiol values >25 pM were 14.4 % in controls, 25.0% in LD, 3.6% in MD, and 16.3% in HD.

j. Urinalysis: no treatment related changes

k. Gross pathology:
enlarged liver 2 HD ♂ and 2 HD ♀
enlarged cystic/nodular ovaries all Arimidex treated ♀ and in 2 HD ♀ after the withdrawal period

The organ weight changes are listed in the following table. Not all included numbers were indicated to be significant, but were captured to show a trend. Many entries were not tested for significance by the Sponsor due to "low numbers of animals" (although all groups had 3-4 animals, apparently more are needed for the trend analysis). The most important findings were increases in liver weights in MD and HD ♂ and HD ♀; increases in testes and prostate weights; very large increases in ovarian weights; increases in kidney weights in ♂s; and decreases in pituitary weights in ♀s. Most of these changes resolved or significantly recovered after withdrawal of Arimidex except for the pituitary weights which not only resolved but then increased 50%. Arimidex had opposite effects on spleen weights in ♂ and ♀ dogs during treatment, but after Arimidex withdrawal both sexes had larger spleens.

Percent Changes in Median Organ Weights

		Week 27						Week 35	
		♂			♀			HD[a]	
		LD	MD	HD	LD	MD	HD	♂	♀
liver	Abs		↑36	↑71			↑62	↑18	
	Rel		↑34	↑107			↑65	↑13	↑16
ovary	Abs				↑122	↑278	↑700		
	Rel				↑157	↑343	↑728		↑89
testes	Abs[a]	↑56	↑44	↑40					
	Rel	↑38	↑38	↑62					
kidney	Abs	↑11	↑18	↑38					
	Rel	↑24	↑30	↑49					
pituitary	Abs				↓15	↓20	↓34	↑51	
	Rel				↓26	↓19	↓37	↑44	
spleen[a]	Abs	↑88	↑91	↑44	↓13	↓17	↓28	↑56	↑138
	Rel	↑86	↑81	↑64	↓15		↓33	↑50	↑132
prostate[a]	Abs	↑88	↑143	↑43				↓21	
	Rel	↑108	↑108	↑62				↓33	

[a] not tested for statistically significant due to "low numbers of animals (3)"

1. Histopathology:

liver: dose-related diffuse hepatocyte enlargement in MD and HD groups; minimal to mild hepatocyte degeneration/necrosis in HD dogs with ballooning, clear cell change, and neutrophil infiltration; all recovered after Arimidex withdrawal

ovary: ↑cystic follicles and ↑stroma in all Arimidex treated animals; ↑corpora lutea in 3/4 HD; after withdrawal 2/3 still had ↑corpora lutea and ↑stroma

mammary gland: multifocal hyperplasia in 2/4 LD and 3/4 HD ♀ which persisted in 1/3 HD after drug withdrawal

uterus: endometrial hyperplasia (1/4 LD, 1/4 HD), cystic endometrial hyperplasia (1/4 LD, 2/4 HD), luminal dilatation (1/4 HD), mucus cysts (1/4 HD); the hyperplasia persisted after drug withdrawal

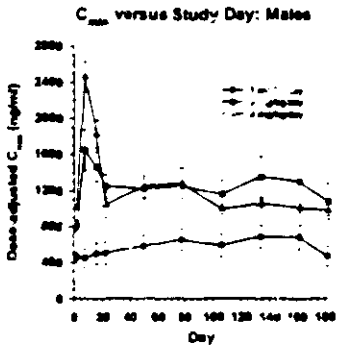
pituitary gland: gonadotroph hyperplasia in 5/8 LD, 8/8 MD, and 7/8 HD compared to 2/8 in controls; mild hyperplasia still present in 1/3 ♂ and 3/3 ♀ after drug withdrawal

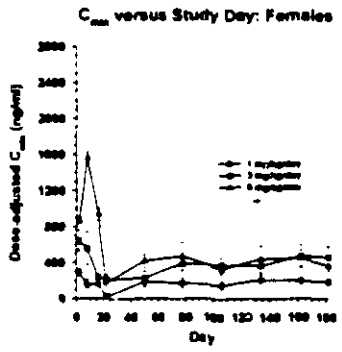
testes: mild Leydig cell hyperplasia in all treated animals which resolved after drug withdrawal

thymus: thymic involution in all Arimidex treated ♂ and 1/4 LD, 3/4 MD and 2/4 HD ♀; all which resolved after drug withdrawal

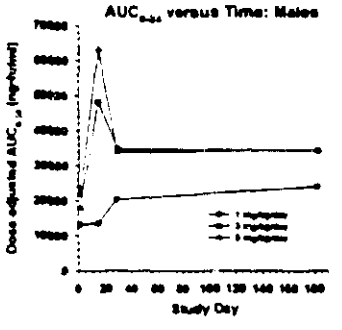
m. Toxicokinetics:

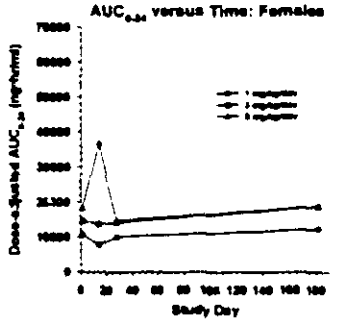
The pre-dose plasma concentrations of Arimidex normalized to dose are plotted in the adjacent figures. In LD males, the pre-dose plasma concentrations steadily accumulated throughout the 6 mo exposure period. In MD and HD males, Arimidex accumulated 2-fold over the first 8 days and then the levels dropped probably due to induction of metabolism. In females the C_{min} values were markedly lower than males. At 78 days, the C_{min} ratios of ♂:♀ were 3.8, 3.2, and 2.7 in the LD MD, and HD groups respectively. In the females, the induction of metabolism appeared to occur more rapidly (the MD levels dropped without accumulating) and at a lower dose than in the males.



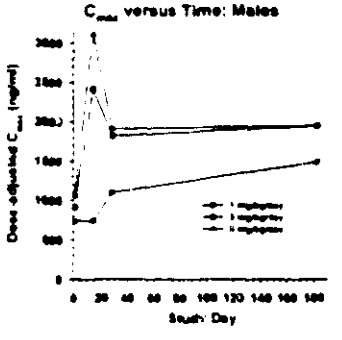


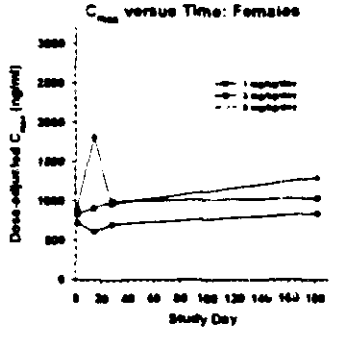
The AUC data normalized to dose is plotted in the adjacent figures. The AUCs increased non-linearly with dose. At the end of the treatment period the LD:MD:HD AUC ratios were 1:4.3:11.5 for ♂s and 1:4.5:12.2 for ♀ instead of the 1:3:8 dose ratio. The ♂:♀ AUC ratios were 2.0, 1.8, and 1.8 for the LD, MD, and HD groups respectively.





The C_{max} data normalized to dose is shown in the adjacent figures. As with the AUC, the C_{max} increased non-linearly with dose and there was evidence of drug accumulation in all groups followed by induction of metabolism at the MD and HD. The C_{max} occurred between ~4-10 hr with no clear pattern between dose groups or with study day.





No $t_{½}$ data was provided by the Sponsor, but was calculated by the reviewer using $t_{½} = 0.693/\lambda_z$. The $t_{½}$s at day 1 and 14 could not be calculated because the levels did not decline significantly over 24 hr. The $t_{½}$s in ♂s and ♀s were 26.5 and 14.4 hr respectively on day 28, and 22.3 and 13.7 hr respectively on day 182. Taken together the toxicokinetic data shows that the exposures

to Arimidex in the MD and HD groups were 50% greater than was expected from the LD exposure. In addition the AUC exposure for females was 40-50% lower than for males given the same dosages.

TKD/631 Pilot Toxicity Study in Dogs. Conducted by according to GLP except that the study was unaudited and only a summary is submitted. The doses were significantly higher than those used in the 1 mo and 6 mo studies. The findings, however, were consistent with the 6 mo study.

species: Beagle dogs (1/sex/group)
drug: Arimidex
dosage: Part A- 1 ♂ and 1 ♀ dog were treated daily with doses increasing from 15 to 30 mg/kg for 8 days
Part B- 2 fresh dogs were dosed with either 15 or 20 mg/kg/day for 21 days, and the 2 dogs from Part A were dosed with 20 mg/kg/day for ... days
route: oral gelatin capsules containing powdered formulation

TAD/636 One-Month Oral Toxicity Study in Dogs. The LD and MD were the same but the HD was 12 not 8 mg/kg/day as in the 6 mo study. The findings as previously reviewed by M.A. Goheer were consistent with the 6 mo study with the following exceptions (new findings in the 6 mo study are not listed):

- Triglycerides and cholesterol were ↓ in HD groups during 1 mo but not 6 mo study
- ↓Creatinine in 1 mo but not 6 mo study
- ↓Heart weight in 1 mo but not 6 mo study
- Lenticular degeneration in eyes of 1 HD ♀ in 1 mo study not seen in 6 mo study
- The non-linearity of the pharmacokinetics was not as obvious in the 1 mo study (assessed only at day 28)

TKD/634 Investigatory Study in Dogs: Oral Administration for Six Months. An 8 mg/kg/day regimen of Arimidex tablets was given to dogs (2/sex) for 6 mo. The findings as previously reviewed by M.A. Goheer were consistent with the full-blown 6 mo study with the following exceptions (new findings in the full-blown study are not listed):

- ↓Glucose in pilot study, but not in full-blown
- ↓Cholesterol in pilot study, but ↑ in full-blown
- Testes weight ↑only 4% in pilot study, but 50% in full-blown
- ↓Heart weight in pilot study, but no change in full-blown

C. Special toxicity

TKY/143 Topical Tolerance Assessment: Physiochemical Characterization. Conducted by according to UK and OECD GLP. The maximum solubility of Arimidex in water was 1.8 mg/ml. Arimidex dissolved in 0.9% saline changed the pH from 6.46 to 6.82. The osmolality of Arimidex in 0.9% saline was 286 mosmol/kg.

TVN/140 *Topical Tolerance Assessment:* In Vitro Assessment of Cytotoxicity and Irritant Potential. Conducted by according to UK and OECD GLP. Previously reviewed by M.A. Goheer, additional details are added here. Cultures of 3T3 Swiss mouse fibroblast and XB-2 mouse teratomal keratinocytes were exposed to 0.1, 10, 100, 250, 500, and 1000 µg/ml Arimidex. Control cultures contained DMSO.

- The highest concentration at which no effect on growth could be observed was 100 µg/ml in both cell lines. The IC_{50} for 2-day growth inhibition, however, was 744 and 286 µg/ml in 3T3 and XB-2 cells respectively. Arimidex was thus scored positive for specific toxicity to XB-2 keratinocytes.
- As for growth inhibition, the highest concentration at which no effect on keratin production in XB-2 cells could be observed was 100 µg/ml. The IC_{50} for inhibition for keratin production was 165 µg/ml and this was deemed not significantly different from the 286 µg/ml for growth inhibition. Arimidex thus scored negative for inhibiting keratinization at non-cytolethal concentrations.
- Stratification of XB-2 cells was determined by comparing colony area to cell number. The IC_{50}s for colony area and cell number were 155 and 185 µg/ml respectively. Arimidex thus scored negative for the ability to affect stratification at non-cytolethal concentrations.
- Arimidex scored negative for the ability to stimulate enzyme release (LDH and hexosaminidase) 2 hr after exposure to non-cytolethal concentrations.

Based on these evaluations, Arimidex was classified as having low topical irritant potential.

TDM/801 Passive Cutaneous Anaphylaxis Study in the Mouse/Rat. Conducted by Zeneca Pharmaceuticals according to UK and OECD GLP.

species:	Alpk:AP$_f$CD-1 ♂ mice (5/group)
	Alpk:AP$_f$SD ♂ rats (3 rats/mouse serum)
drug:	Arimidex lot#54053/93
dosage:	1.25 mg on days 1 and 15
age; weight:	mice- 33 days; 22.0-25.1 g
	rats- 56 days, 258-297 g
route:	0.25 ml x two sites s.c.

Arimidex was mixed with PEG 400:water 2:3 to give a 5 mg/ml solution that was then mixed 1:1 with aluminum hydroxide gel. An 0.5 ml aliquot was injected s.c. 2x into mice at 2 week intervals. Sera was collected 10 days after the last injection and frozen at -20°C until used for the passive cutaneous anaphylaxis (PCA) assay. Bovine gamma globulin mixed with aluminum hydroxide (final [BGG] = 0.2 mg/ml) was used as a positive control and PEG 400:water mixed with aluminum hydroxide was used as a negative control. For the PCA assay, serum was diluted 5x and injected (50 µl) intradermally into a single site of the dorsal skin of each of 3 shaved rat backs. Each rat bore 5 sites from different mouse sera and 1 saline control site. After 24 hr, an i.v. dose of 2.5 mg Arimidex or 5 mg BGG each mixed with 5 mg Evans blue was administered. After 30 min, the animals were examined for dye leakage at the injection site. A positive reaction was scored when the diameter was ≥5 mm. All BGG sites gave positive reactions (5-15 mm). The data indicate that Arimidex did not stimulate IgE antibodies in the mouse.

TDG/141 Contact Sensitization Study in the Guinea Pig. Conducted by according to UK and OECD GLP. This study was previously reviewed by M.A. Goheer. Since the treatment procedure was more complicated than depicted in his review, that data and the conclusions are captured here.

Treatment Procedure for Assessment of Contact Sensitization

	Induction Phase			Challenge Phase: Day 22-23 Topical[f]	
Group	Day 1- Intradermal[a]	Day 7- Topical	Day 8-10 Topical[e]	Test Flank	Control Flank
I	5% MTG[b]	10% SDS[d]	20% MTG	10% MTG	water
II	2.5% Arimidex[c]	10% SDS	25% Arimidex[c]	25% Arimidex[c]	diluent[c]
III	diluent[c]	10% SDS	diluent[c]	25% Arimidex[c]	10% MTG

[a] duplicate sites on each animal were injected with 0.1 ml Freund's adjuvant alone, 0.1 ml of the indicated test article alone, and 0.1 ml of the indicated test article in (indicated diluent):(Freund' adjuvant), 1:1
[b] monothioglycerol in water
[c] in 0.5% hydroxypropylmethylcellulose, 0.1% Tween 80
[d] 10% sodium dodecylsulfate in soft paraffin, massaged into skin
[e] a 2 x 4 cm Whatman #3MM filter paper saturated with the indicated solution was attached with adhesive tape on day 8 and removed on day 10
[f] a 1 x 2 cm Whatman #3MM filter paper stitched to impermeable rubber sheeting containing the indicated solution was attached to a 5 x 5 cm shaved area with adhesive tape on day 22 and removed on day 23

The challenge sites were graded 24 and 48 hr after removing the challenge bandage and compared to the Magnusson and Klingman Allergenicity rating scale. The known sensitizer MTG caused a positive response in 50% of the animals induced and challenged with MTG (Group I). Arimidex caused no positive responses in any animals that had been induced and challenged with the drug (Group II) and it was thus not considered to be a contact sensitizer. Positive reactions were noted, however, in 2/10 animals challenged with Arimidex in the irritancy controls (Group III, no induction) versus 0/10 positive reactions in animals challenged with MTG on the control flank. Arimidex may thus have irritant potential.

TDG/181 Passive Cutaneous Anaphylaxis Study in the Guinea Pig. Conducted by Zeneca Pharmaceuticals according to UK and OECD GLP.

species:	albino HSD/POC Dunkin Hartey ♂ Guinea pig (5/group)
drug:	Arimidex lot#54053/93
dosage:	0.625, 1.25, and 2.5 mg/kg on days 1 and 8
age; weight:	induction- 29-36 days; 307-401 g
	challenge- 46 days; 341-494 g
route:	1.0 ml/kg s.c. with ≤0.25 ml site

Arimidex was mixed with PEG 400:water 2:3 to give 1.25, 2.5, and 5 mg/ml solutions that were then mixed 1:1 with Freund's adjuvant. An 1 ml/kg aliquot was injected s.c. into the scapular region. One week later the animals were injected again with 1 ml/kg of 0.625, 1.25, and 2.5 mg/ml Arimidex only.

Sera was collected 14 days after the second injection and frozen at -20°C until used for the passive cutaneous anaphylaxis (PCA) assay. Bovine serum albumin mixed with Freund's adjuvant (final [BSA] = 1.0 mg/ml) was used as a positive control and PEG 400:water mixed with Freund's adjuvant was used as a negative control. For the PCA assay, serum was diluted to give 5 titers (1:1, 1:3, 1:7, 1:15, and 1:31 for control and Arimidex treated animals; 1:3, 1:7, 1:15, 1:31, and 1:63 for BSA treated animals). Aliquots to be used for the IgG assays were incubated at 56°C to inactivate IgE. Aliquots were injected (50 µl) intradermally into a single site of the dorsal skin of each of 3 shaved Guinea pig backs. Each animal bore dilutions from two different sera and 2 saline control sites. After 4 hr for IgG assessment and 24 hr for IgE assessment, an i.v. dose of 2.5 mg/kg Arimidex or 10 mg/kg BSA each mixed with 10 mg/ml (10 mg/kg) Evans blue was administered. After 30 min, the animals were examined for dye leakage at the injection site. A positive reaction was scored when the extravasated dye diameter was≥5 mm. All BSA dilutions (but not all sites) gave positive reactions (5-15 mm) in both the IgG and IgE assays. All sites with sera from Arimidex challenged animals were negative. The data indicate that Arimidex did not stimulate anaphylactic (IgE or IgG) antibodies in the Guinea pig.

TDG/182 Active Systemic Anaphylaxis Study in the Guinea Pig. Conducted by Zeneca Pharmaceuticals according to UK and OECD GLP.

species:	albino Dunkin Hartey ♂ Guinea pig (5/group)
drug:	Arimidex lot#54053/93
dosage:	0.625, 1.25, and 2.5 mg/kg on days 1 and 15
age; weight:	37 days; 312-429 g
route:	1.0 ml/kg s.c. with ≤0.25 ml site

Arimidex was mixed with PEG 400:water 2:3 to give 0, 1.25, 2.5, and 5 mg/ml solutions that were then mixed 1:1 with Freund's adjuvant. An 1 ml/kg aliquot was injected s.c. into the scapular region. Two weeks later the animals were injected again with 1 ml/kg of 0, 0.625, 1.25, and 2.5 mg/ml Arimidex only. Bovine serum albumin mixed with Freund's adjuvant (final [BSA] = 1.0 mg/ml) was used as a positive control. After another 2 weeks, an i.v. dose of PEG 400:water (2:3), 2.5 mg/kg Arimidex, or 10 mg/kg BSA was administered. The animals were examined for 3 hr for signs of anaphylaxis (labored respiration, licking/rubbing nose, retching, convulsions). Two of the first two BSA treated animals showed signs of marked anaphylaxis within 3 min and the remaining 3 animals were not injected. No reaction to challenge with Arimidex or the controls were observed. The data indicate that Arimidex did not stimulate an active anaphylactic response in the Guinea pig.

TIB/512 Topical Tolerance Assessment: Dermal Tolerance Study in Rabbits. Conducted by according to UK and OECD GLP. This study was previously reviewed by M.A. Goheer. The mean irritation score was 0.02 (out of a maximum of 8.0) and Arimidex was not considered to be an irritant to rabbit skin.

TIB/513 Topical Tolerance Assessment: Ocular Tolerance Study in Rabbits. Conducted by according to UK and OECD GLP. This study was previously reviewed by M.A. Goheer. The mean irritation scores were 0.33 and 0.0 (out of a maximum of 110) at 1-2 hr and 24 hr after dosing respectively. Arimidex was thus considered to be non-irritating to rabbit eyes.

Summary of toxicology

Single dose- Mice readily tolerated single doses of Arimidex given at 750 mg/m² orally or 150 mg/m² i.p. Single oral doses of 300 mg/m² Arimidex and i.p. doses of 300 mg/m² were minimally toxic to rats. Doses of 1500 mg/m² were lethal by both oral and i.p. routes in rats.

Multiple dose- Toxicokinetic analysis indicated that systemic exposure to Arimidex after

repetitive daily dosing in rats and dogs was not a simple linear function of dose as a result of dose-dependent drug accumulation and, at the higher doses, most likely induction of Arimidex metabolism. There were major toxicokinetic differences between rats and dogs. In rats, the exposure to ♀s was ~double the exposure to ♂s at 6 and 30 mg/m²/day; but at 300 mg/m²/day the exposure was only ~20% greater in ♀s than ♂s. In dogs, however, the opposite was true. The AUC exposure for ♂ dogs was double the exposure for ♀s at 20, 60, and 160 mg/m²/day. Since toxicity in rats occurred predominantly in the HD groups, there was thus no major gender differences in the severity of most of the toxicologic parameters for rats. In contrast, the higher Arimidex exposure of ♂ dogs was seen as more severe hematologic changes, R-wave amplitude changes, kidney weight increases, and spleen weights increases compared to the ♀s. Most of the toxicities observed could be attributed to disturbances in steroid hormone biochemistry from aromatase inhibition and to the induction of detoxification enzymes. Arimidex decreased body weight in ♂ rats and dogs, but increased body weight in ♀ rats only. This was consistent with the increased food consumption that was only seen in ♀ rats. Due to the expected effect on estrogen synthesis, estrous was blocked in rats at 300 mg/m²/day and in dogs at 60 mg/m²/day. Arimidex caused hematologic disturbances most likely due to the significant presence of aromatase in bone marrow cells and a role for local estrogen in normal hematopoiesis. These disturbances were 10-20% decreases in RBC, Ht, and Hb; and increases in platelets in both species. Lymphocytes and WBCs increased in rats, but decreased in ♂ dogs. The end-organ toxicities were directed mainly to the liver and reproductive organs and were reversible when Arimidex was withdrawn. Liver mass increased. In dogs, this was associated with hepatocyte degeneration/necrosis, neutrophil infiltration, and increases in serum ALT, AP, and cholesterol. In rats, the enlarged livers were associated with hepatocyte hypertrophy and vacuolation, increased cholesterol, but decreased serum AP, ALT, and AST. It is reasonable to attribute the liver changes to induction of metabolic enzymes. Ovaries were enlarged and had increased corpora lutea, cysts, and stroma. Rats had endometrial fibrosis and less cornified vaginal epithelium; dogs had uteri with hyperplasia and mucus cysts. Dogs also had reversible mammary gland hyperplasia. These uterine and mammary gland effects can be attributed to the chronic high progesterone levels induced by Arimidex. The dogs had increased testes weights, reversible Leydig cell hyperplasia, and testosterone levels which were elevated 10-fold at ≥20 mg/m²/day. It can be speculated that this was due to a lack of estradiol synthesis due to aromatase inhibition, an expected unabated secretion of luteinizing hormone due to loss of feedback inhibition from estradiol, stimulation of Leydig cell testosterone production by LH and a concomitant hyperplasia. Further studies would be needed to confirm this proposed cascade. A non-reversible finding was adrenal cortical vacuolation in 300 mg/m²/day ♀ rats that was similar to control ♂s; this can thus be considered a result of masculinization. Other microscopic findings were reversible hypertrophic thyroid epithelium in ♀ rats (masculinization), persistent chronic progressive glomerulonephropathy in rats (a common disease in rats exacerbated by high protein in the diet), persistent pituitary gonadotroph hyperplasia in dogs, and reversible thymic involution in dogs. There were thus no serious irreversible toxicities associated with long-term daily Arimidex administration.

Special toxicity- *In vitro* studies with keratinocytes, contact sensitization studies in Guinea pigs, and dermal and ocular tolerance studies in rabbits indicated that Arimidex would have low irritancy potential in humans. Likewise, passive cutaneous anaphylaxis studies in mouse/rat and Guinea pig/Guinea pig systems, and active systemic anaphylaxis studies in Guinea pigs indicated that Arimidex has a very low potential for inducing anaphylactic responses.

Histopathology Inventory for ND #20-541

Study	TLM/691	TLP/1944	TLM/692	TPR/1992	TAR/1946	TKD/631	TAD/636	TKD/634	TPD/652
Species	mouse	rat	mouse	rat	rat	dog	dog	dog	dog
Adrenals				X	X		X	X	X
Aorta				X	X		X	X	X
Bone Marrow smear				X	X		X	X	X
Bone				X	X		X	X	X
Brain				X	X		X	X	X
Bronchus				X	X		X	X	X
Cecum				X	X				X
Cervix				X	X		X	X	X
Colon				X	X		X	X	X
Duodenum				X	X		X	X	X
Epididymis				X	X		X	X	X
Esophagus				X	X		X	X	X
Eye				X	X		X	X	X
Fallopian tube									
Gall bladder							X	X	X
Gross lesions	L	L	L	X	X		X	X	X
Harderian gland				X	X				
Heart				X	X		X	X	X
Hyphophysis									
Ileum				X	X		X	X	X
Injection site									
Jejunum				X	X		X	X	X
Kidneys				X	X		X	X	X
Lachrymal gland									
Larynx									
Liver				X	X		X	X	X
Lungs				X	X		X	X	X
Lympn nodes. bronchial							X	X	X
Lymph nodes. cervical					X		X	X	X
Lymph nodes mandibular				X	X				
Lymph nodes. mesenteric				X	X		X	X	X
Mammary Gland				X	X		X	X	X
Nasal cavity									
Optic nerves									
Ovaries				X	X		X	X	X
Pancreas				X	X		X	X	X
Parathyroid				X	X		X	X	X
Peripheral nerve									
Pharynx									
Pituitary				X	X		X	X	X
Prostate				X	X		X	X	X
Rectum									
Salivary gland				X	X		X	X	X
Sciatic nerve				X	X		X	X	X
Seminal vesicles				X	X				
Skeletal muscle				X	X		X	X	X
Skin				X				X	X
Spinal cord				X	X		X	X	X
Spleen				X	X		X	X	X
Sternum				X	X				
Stomach				X	X		X	X	X
Testes				X	X		X	X	X
Thymus				X	X		X	X	X

Thyroid				X	X		X	X	X
Tongue				X	X		X	X	X
Trachea				X	X		X	X	X
Urinary bladder				X	X		X	X	X
Uterus				X	X		X	X	X
Vagina				X	X		X	X	X
Zymbal gland									
Not stated						X			

L- limited to thoracic and abdominal cavities

Preclinical Arimidex Formulations						
		TPR/1992	TAR/1946	TPD/652[a]	TAD/634[a]	TAD/636[a]
		rat	rat	dog	dog	dog
	NDA	6 mo	1 mo	6 mo	1 mo	1 mo
Arimidex	1.0			1.0	1.0	1.0
lactose	93.0			68.0	68.0	68.0
povidone	2.0			2.0	2.0	2.0
sodium starch glycolate	3.0			3.0		
Explotab					3.0	3.0
magnesium stearate	1.0			1.0	1.0	1.0
hydroxymethylcellulose	1.5					
				25.0	25.0	25.0
	0.3					
titanium dioxide	0.45					
			X			
		X				

[a] adjusted to 1.0 mg Arimidex from nearest size

IV. Reproductive Toxicity

TRR/2234 Sighting Teratology Study in Rats: Oral Administration. Conducted by Zeneca Pharmaceuticals, Cheshire, England in 1994. Not conducted according to GLP; complete study report not provided.

Methods

species: Alpk:APfSD rats (mated ♀)
drug: Arimidex (lot# not provided)
dosage: 0, 0.002, 0.02, 0.1, 0.5, and 1.0 mg/kg/day from day 7 to 16 of gestation (10♀/group; 6 additional ♀ allocated to control, 0.1, and 0.5 mg/kg groups in order to study maternal exposure and placental transfer assessment)
route: oral gavage (specifics not provided)

Results

Radiolabelled Arimidex administered to 0.1 and 0.5 mg/kg ♀ was found to cross the placenta; fetal concentrations of Arimidex in plasma (25 and 136 ng-equiv/g, respectively) were 40% of corresponding maternal plasma concentrations (63 and 343 ng-equiv/g, respectively). Plasma

progesterone concentrations were increased by 15 and 19%, respectively, in 0.1 and 0.5 mg/kg-dosed ♀ as compared to concurrent controls; high dose progesterone concentrations were not reported. Maternal body weights were depressed 10, 7, 11, and 21%, respectively, in 0.02, 0.1, 0.5, and 1 mg/kg ♀ as compared to control weights during the study duration; weights of empty uteri were depressed 6 and 26% in ♀ administered 0.5 and 1 mg/kg.

The number of live fetuses and total number of implants were decreased in a dose-related manner in ♀ administered 0.1 mg/kg and above; post-implantation loss and number of resorptions were also increased in these animals. Pre-implantation loss was increased at 0.5 mg/kg and above. Placental weights were significantly increased (43-65%) in ♀ administered 0.1 mg/kg and above; placentas of ♀ administered 0.5 mg/kg and above were discolored in appearance. There were no fetal abnormalities reported.

TTR/2235 Teratology Study in Rats: Oral Administration. Conducted by Zeneca Pharmaceuticals, Cheshire, England in 1994 according to UK, OECD, and US GLP.

Methods

species:	Alpk:APfSD rats (22♀/group + 4 additional ♀/control, 0.1 mg/kg groups designated for determination of placental transfer)
drug:	Arimidex, lot # 44065/91
dosage:	0, 0.02, 0.1, 1.0 mg/kg/day (based on results of study described above)
route:	oral gavage at dose volume of 0.5 ml/100g BW in distilled water
duration:	gestation day 7 to 16

Results

Radiolabelled Arimidex administered to 0.1 mg/kg ♀ was found to cross the placenta within 2 hours of dosing, fetal concentrations of Arimidex in plasma (29 ng-equiv/g) were 45% of corresponding maternal plasma concentrations (64 ng-equiv/g). All Arimidex-dosed ♀ exhibited pregnancy with the exception of one LD (no sign of implantation) and one HD (late resorptions only) animal. Body weights (13%↓) and food consumption (6%↓) of HD ♀ were reduced during the dosing period, but recovered within the following 5 days.

Macroscopically, a dose-related increased incidence of blood in the uterus and hemorrhagic placentas was observed in Arimidex-treated animals; however, there was no microscopic evidence of these observations. These changes may have been a result of increased blood flow to these organs.

Numbers of live fetuses, total implants, and implantation loss were similar in control and Arimidex-treated ♀. However, placental weights were increased 38 and 50%, respectively, in MD and HD ♀ as compared to concurrent controls; fetal bodyweights were depressed 3 and 6%, respectively, in these dose groups. Evidence of delayed fetal development (incomplete ossification) was observed at the HD. A slight increase in the incidence of umbilical artery variation (from right side to left side of bladder) in fetuses from Arimidex-dosed animals was indicated to be a spontaneous strain-related variation .

TRB/609 Sighting Teratology Study in Rabbits: Oral Administration. Conducted by Zeneca Pharmaceuticals, Cheshire, England in 1994. Not conducted according to GLP; complete study report not provided.

Methods

species:	NZW/DB Hybrid rabbits (7 mated ♀/group; 8 additional ♀ designated to 0.1 and 0.5 mg/kg groups to provide samples for study of maternal exposure and placental transfer)
drug:	Arimidex
dosage:	0,0.002, 0.02, 0.1, 0.5, 1.0 mg/kg/day from gestation days 7 to 19
route:	oral (not specified)

Results: Radiolabelled Arimidex was found to cross the placenta; fetal plasma concentrations (18 and 89 ng-equiv/g, respectively) were 40% of maternal plasma concentrations (50 and 227 ng-equiv/g, respectively) in ♀ administered 0.1 and 0.5 mg/kg. Arimidex-treated animals exhibited depressed pregnancy rates (6/7,6/7, 5/7, 3/7, and 4/7 pregnant ♀ with live fetuses, respectively, at 0.002, 0.02, 0.1, 0.5, and 1 mg/kg). Estradiol levels in Arimidex-treated ♀ were depressed in a dose-related manner; progesterone levels were depressed at doses >0.02 mg/kg . Hemorrhagic follicular cysts were observed microscopically in Arimidex-treated animals; this finding was most prevalent at 0.5 and 1 mg/kg (3/6 and 3/7 dams, respectively).

Fetal bodyweights were depressed 15% at the HD when compared to concurrent controls. There were no fetal abnormalities.

TTB/610 Teratology Study in Rabbits: Oral Administration. Conducted by Zeneca Pharmaceuticals, Cheshire, England in 1994 according to UK, OECD, and US GLP.

Methods

species:	NZW/DB Hybrid rabbits (20 pregnant ♀/group + additional 3 control and 5 MD♀ allocated for assessment of placental transfer)
drug:	Arimidex lot# 44065/91
dosage:	0, 0.02, 0.2, 1.0, 5.0 mg/kg/day
age; weight:	age not reported (sexually mature); 2.38-3.61 kg on gestation day 1
route:	gastric intubation (control and HD ♀) and drench method (LD, MD1, MD2) in distilled water

Results: Radiolabelled Armidex was found to cross the placenta; fetal plasma concentrations (36 ng-equiv/g) were 38% of corresponding maternal plasma concentrations (97 ng-equiv/g) in ♀ administered 0.2 mg/kg. Arimidex caused pregnancy failure in rabbits administered 1 and 5 mg/kg; approximately 33% of these animals exhibited signs of implantation. Body weights, food consumption, and effects on pregnancy parameters were not measured in HD♀. Estradiol and progesterone concentrations were depressed in Arimidex-treated ♀ in a dose related manner.

Pre-implantation loss was increased in ♀ administered 0.02 and 0.2 mg/kg; this was associated with decreased numbers of implantations and live fetuses at 0.2 mg/kg. Body weights (depressed 14, 27, and 36%, respectively) and food consumption were depressed in ♀ administered 0.02, 0.2, and 1 mg/kg Arimidex. There was an absence of corpora lutea, and an increased incidence of mild, moderate, or severely hemorrhagic graafian follicles in ♀ administered 1 and 5 mg/kg. The rabbit is reported to be highly dependent on estrogen for the maintenance and function of the corpora lutea in pregnancy.

There were no Arimidex-related fetal developmental changes.

Summary of Reproductive Toxicity Studies

Approximately 40% of radiolabelled Arimidex and/or metabolites were found to cross the placenta and was observed in fetal rats and rabbits when dams were administered from 0.1 to 0.5 mg/kg. Rats administered 0.1 mg/kg and above were not consistent in observed response. Females of the preliminary rat teratology study exhibited increased numbers of resorptions and post-implantation loss with a dose-related decrease in the number of implantations and live fetuses. There were no fetal abnormalities. Fetuses of the primary rat teratology study exhibited delayed fetal development. Dams of both studies exhibited increased placental weights.

F_0 ♀ rabbits were more sensitive to the effects of Arimidex when compared to rats. At less than or similar doses of 0.1 to 0.5 mg/kg, mated ♀ consistently exhibited depressed pregnancy rates, depressed numbers of implantations and live fetuses, and increased pre-implantation loss. Hemorrhagic follicular cysts were observed in ♀ administered 0.5 mg/kg. There were no fetal abnormalities in rabbits. Reproductive effects observed with Arimidex treatment are consistent with the pharmacological mechanism of action.

V. Genetic Toxicity

TMV/444 Ames Test: Bacterial Mutagenicity Study Using Selected Strains of Salmonella Typhimurium: Standard Method. Conducted by according to UK, and OECD GLP.

Arimidex did not exhibit mutagenic activity in the five tester strains (TA 1535, TA 1537, TA 1538, TA 98, and TA 100) with or without metabolic activation.

TMV/542 Bacterial Mutagenicity Study Using Selected Strains of Escherichia Coli: Standard Method. Conducted by according to UK and OECD GLP.

Escherichia coli strains WP_2 pKM101 and WP_2 uvrA pKM101 with/without metabolic activation were assayed up to 5000 µg Arimidex (batch # 44065/91)/plate dissolved in DMSO. Positive controls included N Methyl-N'-nitro-N-nitrosoguanidine and Mitomycin C.

Arimidex did not exhibit mutagenic activity; the mean revertant colony counts on plates treated with Arimidex were similar to the negative and vehicle control either in the presence or absence of the S-9 mixture.

TMV/ 455 In Vitro Mammalian Cell Gene Mutation Assay in Chinese Hamster Ovary Cells. Conducted by according to UK and OECD GLP.

CHO-K1 cells were exposed to Arimidex (batch No. 44065/91) at concentrations of 93.8 to 3000 µg/ml with and without metabolic activation (preliminary study) and 187.5 to 3000 µg/ml with and without metabolic activation (main study). Ethyl methane sulphonate and 20-methylcholanthrene were used as positive controls.

Minimal cytotoxicity was observed at doses up to 1500 µg/ml with or without metabolic activation. Arimidex was 58-94% cytotoxic at 2000 µg/ml and 100% cytotoxic at 3000 µg/ml without metabolic activation; the 3000 µg/ml concentration was also 93-95% cytotoxic in one of two assays with metabolic activation. Insoluble concentrations were not assayed; 3000 µg/ml was indicated to be the limit of solubility. Arimidex did not induce mutations in Chinese hamster ovary cells at doses up to the cytotoxic limit of 187.5 to 3000 µg/ml with or without metabolic activation and 125 to 2000 µg/ml without metabolic activation.

TYX/43 In Vitro Cytogenetic Study Using Cultured Human Lymphocytes. Conducted by according to UK and OECD GLP

Cultures of human lymphocytes were exposed to 15, 75, 150, 500, 750, or 1500 µg/ml Arimidex with metabolic activation and 10, 25, 250, 500, 750, or 1000 µg/ml Arimidex without metabolic activation and sampled at 72 and 92 hours following study initiation. Cyclophosphamide and mitomycin C were included as positive controls.

Reductions in mitotic index were observed at 1500 µg/ml with metabolic activation (14% reduction at 72 hrs; no reduction at 92 hrs) and 500 µg/ml at 72 hrs and 250 µg/ml at 92 hrs without metabolic activation (41 and 15% reduction, respectively). In the absence of metabolic activation, excessive cytotoxicity was observed at 750 and 1000 µg/ml. In a repeat study, at a dose of 500 µg/ml, reductions in mitotic index were observed at 31 and 71% for the 72 and 92 hr sampling times, respectively.

There were no biologically significant increases in the incidence of chromosomally abnormal cells; Arimidex is not clastogenic. In one culture of the repeat study, an increase in the incidence of endoreduplicated cells was observed at a dose of 1500 µg/ml without metabolic activation; this was

considered by the study author to be a cytotoxic effect of Arimidex.

The threshold of cytotoxicity using cultured human lymphocytes in these studies is 250 µg/ml.

TQR/1993 Micronucleus Test in the Rat: Oral Administration. Conducted by according to UK and OECD GLP.

Alderley Park Wistar-derived (Alpk:AP$_f$SD) rats (10 rats/group) were administered 20, 100, or 200 mg/kg Arimidex by gavage 1x; additional groups were administered vehicle control (hydroxypropyl methylcellulose in 0.1% polysorbate 80) and positive control (cyclophosphamide).

There was no biologically significant increase in the incidence of micronucleated polychromatic erythrocytes in Arimidex-treated animals when compared to vehicle controls. The mean number of micronucleated polychromatic erythrocytes in Arimidex-treated rats was 2.3, 2.0, and 2.0 at 20, 100, and 200 mg/kg, respectively, at 24 hrs post dosing, compared with 2.6 in concurrent controls. At 48 hrs post dosing, the mean number of micronucleated polychromatic erythrocytes was 2.6, 3.2, and 2.2 at the same doses, respectively, compared to 1.2 in concurrent controls. Arimidex is not clastogenic. There was no information provided regarding the basis of dose selection.

Summary of Genetic Toxicity

Arimidex was not found to be mutagenic in bacterial strains or CHO-K1 cells with or without metabolic activation. Arimidex was not clastogenic in human lymphocytes with or without metabolic activation or in the rat micronucleus test. The threshold of cytotoxicity was 250 µg/ml in human lymphocytes and 2000 µg/ml in Chinese hamster ovary cells.

History

8/23/95	1st draft
9/6/95	2nd draft
10/13/95	3rd draft
10/26/95	final draft

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cc:
IND ORIG. and Div. File
HFD-150
/JJDeGeorge
/JBeitz
/LVaccari
/PAAndrews
/MEBrower

Division of Oncology and Pulmonary Drug Products

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
45 Day Fileability Review

NDA: 20-541

Date of Submission: NDA Dated: 3/28/95
Received by CDER: 3/29/95

Information to be conveyed to the sponsor: Yes ( ) No (X)

Reviewers: Paul A. Andrews, Ph.D. and Margaret Brower, Ph.D.

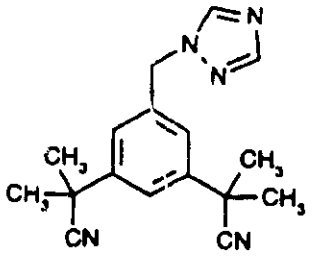
Date 45 day Review Completed: 5/1 95

Sponsor: Zeneca Pharmaceuticals
Wilmington, DE 19897

Drug Name: Primary: Arimidex
Secondary: anastrozole, ZD1033

Chemical Name: 2,2'-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropiononitrile)

Structure:



Molecular weight and formula: 293.4, $C_{17}H_{19}N_5$

Related INDs, NDAs: IND

Pharmacologic Class: Aromatase inhibitor

Indication: advanced breast cancer in post-menopausal women who have progressed following tamoxifen therapy

Clinical Formulation:

	Format Ingredient	Amount
tablet	Arimidex	1.0 mg
	lactose	[redacted]
	povidone	
	sodium starch glycolate	
	magnesium stearate	
	hydroxypropylmethylcellulose	
	polyethylene glycol 300	
	titanium dioxide	

Route of administration and dosage form: oral tablet

Proposed Dosage: one 1 mg tablet daily

RECOMMENDATIONS This NDA submission is fileable with respect to Pre-clinical Pharmacology and Toxicology issues. No significant deficiencies are noted at this time.

Paul A. Andrews, Ph.D.
Pharmacologist/Toxicologist
5/11/95
Date

Margaret Brower, Ph.D.
Pharmacologist/Toxicologist
5/11/95
Date

cc:
IND ORIG. and Div. File
HFD-150
/JJDeGeorge
/JBeitz
/LVaccari
/PAAndrews
/MBrower

----------Review Notes---------

Previous Review(s), Date(s), and Reviewer(s): IND 7/8/92 Goheer

Studies Submitted with this NDA ----------

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY
60 reports

A. **Summary of Nonclinical Pharmacology and Toxicology (2/1E/US/1013206)**. Vol 1.11, p. 1-99

B. **Animal Pharmacology Studies Report (2/1E/1012991)**. Vol 1.11, p. 99-209

1) Pharmacology relevant to the use of ICI D1033 in breast cancer:

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Note that portions of this review were excerpted directly from the sponsor's submission.

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45 DAY SUMMARY AND EVALUATION

As inventoried above, the following pivotal studies with Arimidex given by the oral route are included in this NDA submission.

	GLP Compliance			
	UK	OECD	FDA	Formulation
acute toxicity in mice and rats	x	x		suspension[a]
1 month toxicity in rats and dogs	x	x	x	suspension, tablets
6 month toxicity in rats and dogs	x	x	x	suspension, tablets
Stage C reproductive toxicity in rats (Segment II)	x	x	x	solution[b]
Stage C reproductive toxicity in rabbits (Segment II)	x	x	x	solution
bacterial mutagenicity test (Ames' test)	x	x		-
mammalian mutagenicity test (CHO cells)	x	x		-
in vitro clastogenicity test (human lymphocytes)	x	x		-
in vivo clastogenicity test (micronucleus test in rats)	x	x		suspension

[a] in 0.5% (w/vol) hydroxymethylcellulose, 0.1% aqueous polysorbate 80

[b] in water

All these studies include signed GLP statements complying with the indicated regulations. In addition, 33 ADME studies, 116 pages of pharmacology studies, and 8 studies on topical tolerance, passive cutaneous anaphylaxis, and acute systemic anaphylaxis were submitted that were not all necessarily GLP compliant. Note that a 1 year toxicity study in a non-rodent species was not submitted, but this is not necessarily required for an antineoplastic. The oral formulation varied in the pre-clinical studies, and the tablets in the dog studies were of a slightly different composition than the marketed drug product. This NDA thus has the appropriate studies required for fileability.

TIMELINE

5/12/95	Finish multiple dose toxicity review
6/2/95	Finish acute dose toxicity review
6/9/95	Finish special toxicity review
6/16/95	Finish animal pharmacology review
7/14/95	Finish ADME review
7/19/95	Finish reproductive toxicity and genetic toxicity review
7/21/95	Finish review and editing of labeling
7/28/95	Submit draft final review

Questions for Medical Officer: none

Questions for Chemist: Are the formulation changes from the preclinical stage of significant concern?

Draft Letter, Requests for Sponsor: none

Stat

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-541

Applicant: Zeneca

Name of Drug: Arimidex (Anastrozole)

Indication: Treatment of advanced breast cancer in post menopausal women who have progressed following tamoxifen therapy

Documents Reviewed: Vols. 1.1, 1.2, 1.74-1.78, 1.90-1.92

SAS DataBase

Medical Officer: Julie Beitz, M.D.

REVIEW SUMMARY

Zeneca Inc. has submitted results from two phase III, controlled clinical trials in support of an application for use of Arimidex for treatment of advanced breast cancer in post menopausal women who have progressed following tamoxifen therapy.

1. Primary efficacy endpoints, viz., objective tumor response (OTR) and the time to disease progression (TTP), were confirmed by the FDA MO. There was no statistical evidence of longer TTP or higher OTR rate using either the sponsor's original data or the FDA MO's assessment (for confidence intervals, see TTP and OTR Tables in p.9-10).

2. The study was originally planned to show 3.5 months longer TTP in either 1mg or 10mg Arimidex. The studies (IL1033/0004 and IL1033/0005) failed to show superior efficacy. This reviewer calculated that either study would have had about 22%-24% power to detect 3-week therapeutic equivalence, based on a combination of current trial experience and protocol defined parameters (*i.e.*, assuming median TTP of 4.5 months of Megestrol Acetate, accrual period of 15 months, follow-up period of one half year, 2-sided 5% type I error rate).

REVIEW INDEX

1. DESCRIPTION OF STUDIES

PIVOTAL TRIALS

TRIAL 1033IL/0004

The 1033IL/0004 Trial was a randomized multicenter phase III study to evaluate Arimidex (1mg and 10 mg) compared with megestrol acetate (MEGACE™ of Bristol-Myers, active control). A total of 386 postmenopausal women with advanced breast cancer from 49 centers in were recruited. Of those, 258 were randomized (double-blind) to receive Arimidex [1 mg (n=128) and 10 mg (n=130)] and 128 were randomized (open-label) to receive megestrol acetate. Arimidex was administered orally once daily. MEGACE (40 mg) was administered orally four times daily. During treatment, patients were seen at 4-week intervals for the first 24 weeks and at 12-week intervals thereafter, until disease progression was detected or death occurred without evidence of progression. The study recruitment began on March 3, 1993 and completed on June 24, 1994 (15.5 months). Recruitment was not uniform in the early part of the trial. The sponsor decided that "centers would be added and the number of patients would be increased to 360" and stated that "the treatments were balanced in blocks of three within each center". The study cutoff was Sept. 15, 1994.

Prior to randomization, each patient's breast cancer history was recorded and disease state evaluated. This evaluation includes the identification and measurement of lesions to be monitored during treatment and the assessment of nonmeasurable disease. In addition, "a physical examination was given, hematologic and clinical chemistry laboratory tests were performed, and quality of life assessments (Rotterdam Symptom Checklist, analgesic use, bone pain, and performance scores) were made". Sponsor's Table 1 of Vol. 1.74 summarized the schedule of assessments at each visit. Estrogen and drug levels were measured in the Arimidex arms only, at baseline and at regular intervals during the trial. The data monitoring committee (DMC), consisting of two clinicians (one from the USA and one from Europe) and one statistician, met on May 3, 1994 to review an interim analysis of efficacy and safety for both trials (1033IL/0004 and 1033IL/0005). The DMC recommended that "a second interim analysis of the trial be performed. After reviewing the second interim analysis, the DMC recommended that both trials continue unchanged". These interim analyses were planned in the protocol.

STUDY OBJECTIVES

The primary objectives were to compare each dose of Arimidex with MEGACE on (1) time to disease progression (TTP), (2) objective tumor response (OTR), and (3) safety and tolerability. The secondary objectives were to compare the two dosages of Arimidex on time to treatment failure (TTF), duration of response (DR), quality of life (QOL) in the first year of treatment, and survival (SURV). For each end point, two treatment comparisons were made, i.e., 1 mg of Arimidex against MEGACE, and 10 mg of Arimidex against MEGACE. The sponsor performed two interim analyses on TTP and OTR using an O'Brian and Fleming adjustment, i.e., using 0.005 level of significance at the first interim analysis, 0.006 at the second interim analysis, and 0.046 at the final analysis. With two primary endpoints, the sponsor used a Bonferroni adjustment in reporting the results, i.e., the TTP and OTR were each analyzed at the 0.023 level of significance.

STATISTICAL CONSIDERATIONS

The protocol was originally designed as follows. The sample size for the study was estimated based on TTP and OTR. It was assumed that if the median TTP of MEGACE was 26 weeks (6.5 months), and patients were recruited at a uniform rate over 12 months, with a minimum follow-up period of 6 months, then a total of 300 patients (100 per arm) would be sufficient to detect a treatment difference of approximately 14 weeks (2.5 months) in median TTP, with 80% power and a two-sided significance level of 0.05. It was assumed that if the OTR of MEGACE was 25%, then a treatment difference in OTR of approximately 20% would be statistically detectable with 90% power and a two-sided significance level of 0.05.

The sponsor stated that the OTR was "to be analyzed using logistic regression, with factors fitted for treatment estrogen receptor status (ER, positive, negative or unknown), progesterone receptor status (PR, positive, negative or unknown), and previous hormonal treatment history (HX, adjuvant or advanced)". A Chi-square test was planned as a secondary analysis. In addition, for each treatment comparison, the sponsor stated that "the results of the time to event analyses were to be expressed as hazard ratios, calculated using Cox's proportional hazards model, with corresponding confidence intervals (97.7% for TTP, 97.5% for TTF and SURV)" and the log-rank test was a planned secondary analysis. The prespecified factors of the Cox's model for the analysis of OTR were the same as those for the logistic model.

For the TTP, TTF or SURV, patients who had not reached progression or treatment failure or death, at the time of data cutoff were right-censored in the analysis at the time of their most recent visit. The TTP was also assessed for patients who withdrew before progression. The TTF was set to zero if a patient did not receive randomized treatment.

For QOL, the physical, psychological, and functional activity dimensions were analyzed using Rotterdam Symptom Checklist scores. The methods used for "unavailable repeated measurements" were last observation carry forward (LOCF), observed average (OA), missing excluded (ME), and nonparametric analyses, *e.g.*, Wilcoxon Rank-Sum Test (WRST). The LOCF was used for patients who didn't return their questionnaires either at Week 12 or Week 24 and data recorded at progression was used for patients who progressed in the 12 Weeks before these visits. For OA, the average of the available scores for a given dimension was used for the missing response to any question. For ME, patients with missing observation were excluded from the analyses.

The sponsor stated that "Assumptions of normality were not met for the analysis of covariance of the change in physical, psychological, and functional dimensions at Week 12, and for the functional dimension at Week 24. The nonparametric results were presented." The sponsor presented the WRST for the physical and psychological dimensions at Weeks 12 and 24, with the estimated difference between two treatments groups defined as the difference in the median change for the groups with 97.5% confidence intervals. The change in functional scores was reparameterized for a logistic regression model as the binary outcome of an increase or no change in score versus a decrease in score from entry, with an indicator term for an entry score of 24 versus <24.

TRIAL 1033IL/0005

The 1033IL/0005 trial was a randomized, multicenter, phase III study to evaluate Arimidex (1mg and 10 mg) compared with megestrol acetate (MEGACE™ of Bristol-Myers, active control). A total of 378 postmenopausal women with advanced breast cancer from 73 centers in Europe, Australia and South Africa were recruited. Of those, 353 were randomized (double-blind) to receive Arimidex [1 mg (n=135) and 10 mg (n=118) once daily] and 125 were randomized (open-label) to receive megestrol acetate (40 mg four times daily). During treatment, patients were seen every 4 week for the first 24 weeks and then at 12-week interval until disease progression was detected or death occurred without

evidence of progression. The study recruitment began on April 22, 1993 and completed on June 24, 1994, about 14 months. Treatment was assigned by the sponsor according to computer-generated randomization schemes produced for each center. The sponsor stated that "the treatments were allocated in balanced blocks of six". The study cutoff was Sept. 15, 1994.

Prior to randomization, each patient's breast cancer history was recorded and the disease state evaluated, including identification and measurement of lesions to be monitored during treatment and assessment nonmeasurable disease. In addition, physical examination, hematologic and clinical chemistry laboratory tests were performed, quality of life assessments (Rotterdam Symptom Checklist, analgesic use, bone pain, and performance scores) were made. The sponsor Table 1, Vol. 1.90 summarized the schedule of assessments at each visit.

STUDY OBJECTIVES

The primary objectives were to compare the effect of two doses of Arimidex with MEGACE on (1) time to disease progression (TTP), (2) objective tumor response (OTR), and (3) safety and tolerability. The secondary objectives were to compare the two dosages of Arimidex on time to treatment failure (TTF), duration of response (DR), quality of life (QOL) in the first year of treatment, and survival (SURV). For each end point, two treatment comparisons were made, i.e., 1 mg of Arimidex against MEGACE, and 10 mg of Arimidex against MEGACE. The sponsor performed one interim analyses on TTP and OTR using O'Brian and Fleming adjustment, i.e., using 0.005 level of significance at the first interim analysis, and 0.048 at the final analysis. A Bonferroni adjustment was performed. Thus, the TTP and OTR were each analyzed at the 0.024 level of significance.

STATISTICAL CONSIDERATIONS

The sample size planning and method of analyses on OTR and time to events were the same as Trial 1033IL/0004.

For the QOL, Rotterdam Symptom Checklist scores were analyzed separately for the physical, psychological and functional activity dimensions. The changes in dimension score from entry to Week 12 and from entry to Week 24 were analyzed using analysis of covariance, with entry score as a covariate. The methods used to impute the unavailable repeated measurement were the same as for Trial 1033IL/0004.

Overview of study results

In Trial 1033IL/0004, 386 patients who have progressed following tamoxifen therapy were randomized to receive treatment Arimidex 1mg (n=128), 10mg (n=130) and MFGACE (n=128). One patient, patient 0015/0015, was randomized but not treated. This patient was included in the intent-to-treat (ITT) efficacy but not the ITT safety analyses. Three treatment groups had similar baseline demographic characteristics. Overall, the mean age was 66 yrs (SD, 11 yrs), the mean height was 161 cm (SD, 7.2 cm), and the mean weight was 69 kg (SD, 15 kg). The majority of the patients (87%) were Caucasian.

The proportions of patients who received tamoxifen as either first hormonal treatment for early disease (~43%) or treatment for advanced disease (~57%) were similar in the three arms (see sponsor's table 4 of Vol. 1.74). The baseline disease characteristics, including breast cancer history, site and extent of disease were summarized in the sponsor Tables 5 - 8 of Vol. 1.74. Patients withdrew from the study due to disease progression (47%), death (1.3%), adverse event or concurrent illness (2.9%), failure to return for follow-up or refusal to continue (1.8%). One and a half percent of the patients were withdrawn for protocol noncompliance or other reasons. Approximately 46% of the patients continued the treatment at the cutoff date. There were 9.3% protocol violations, all were included in the ITT analyses.

In Trial 1033IL/0005, 378 patients who have progressed following tamoxifen therapy were randomized to receive treatment Arimidex 1mg (n=135), 10mg (n=118) and MEGACE (n=125). Three patients were randomized but not treated. These patients were included in the intent-to-treat (ITT) analyses. At study entry, the demographic characteristics of the three treatment groups were very similar, with the mean age of 65 yrs (SD, 9.8 yrs), the mean height of 160 cm (SD, 6.9 cm), and the mean weight of 67 kg (SD, 13.1 kg). The vast majority of the patients (98%) were Caucasian.

There was no major imbalance in previous tamoxifen treatment status (see sponsor's table 4 of vol. 1.90). The baseline disease characteristics, including breast cancer history, site and extent of disease were summarized in the sponsor Tables 5 - 8 of vol. 1.90. In general, patients withdrew from the trial due to disease progression (43.4%), death (4%), adverse event or concurrent illness (3.7%), failure to return for follow-up or refusal to continue (0.5%), 3.7% of the patients withdrawn due to protocol noncompliance, informed consent withdrawl, or other reasons, 44.7% of the patients continued the treatment after the cutoff

date. There were 3.4% protocol violations - all were included in the ITT analyses.

PRIMARY EFFICACY ENDPOINTS -

The median duration of follow-up for all randomized patients was 180 days for Trial 0004 and 192 days for Trial 0005. It is noted that the numerical difference in the median TTP were one month in MEGACE arm and 1.3 month in 1mg Arimidex arm between the two trials. Although the protocol plan were very similar, each trial should be evaluated individually.

The results of the analyses indicated that there were no differences in TTP between either arm of Arimidex versus MEGACE (p=.481 and .969 of Trial 0004; p=.770 and .302 of Trial 0005). The Kaplan-Meier probability plot of TTP was presented (see the sponsor's Figure 4 of Vol. 1.74 and Figure 4 of Vol. 1.90). The HR of Arimidex 1mg against MEGACE was .89 (95%CI .61-1.3) of Trial 0004 and 1.04 (95%CI .74-1.46) of Trial 0005. The HR of Arimidex 10mg against MEGACE was 1.0 (95%CI .69-1.45) of Trial 0004 and .84 (95%CI .58-1.22) of Trial 0005.

♦ Time to Disease Progression

TTP	1033IL/0004			1033IL/0005		
	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg
Median (days)	170	143	151	132	156	120
range	14-512+	4-533	23-490+	24-458+	10-484	20-458+
censor	46.1%	42.3%	39.1%	33.3%	39.8%	32%
n	128	130	128	135	118	125
HR(A:M)	.89	1.0		1.04	.84	
CI	.61-1.3*	.69-1.45*		.74-1.46#	.58-1.22#	
p-value Primary@	.481	.992		.816	.298	
p-value log-rank	.481	.969		.770	.302	

*97.7%CI, #97.6%CI. The critical p-value for stat. sig. is .023.
@ Primary analysis is Cox's proportional hazards model adjusted

for estrogen receptor status, progesterone receptor status, and hormonal treatment history.

When the TTP was compared between subgroups, i.e., by adjuvant or advanced hormonal treatment history; by positive, negative, or unknown estrogen receptor status; and by positive, negative, or unknown progesterone receptor status, the proportion of patients having disease progression tended to be lower in the subgroup of advanced prior hormonal therapy (41%:54%:59% of Arimidex 1mg:10mg:MEGACE, see the sponsor Table T.4.2.3), or ER positive (49%:61%:56% of Arimidex 1mg:10mg:MEGACE, see the sponsor Table T.4.2.4), or PR positive (46%:66%:59% of Arimidex 1mg:10mg:MEGACE, see the sponsor Table T.4.2.5) of the Arimidex 1 mg arm of Trial 0004. However, these lower rate were not seen in Trial 0005, *i.e.*, the progression rates were very similar across the three arms with respect to advanced prior hormonal therapy, ER positive, or PR positive status.

- Objective Tumor Response

	1033IL/0004			1033IL/0005		
	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg
# CR+PR	13	7	7	14	15	13
% of OTR	10.2	5.4	5.5	10.4	12.7	10.4
95%CI	4.9-15.5	1.5-9.3	1.5-9.5	5.2-15.6	6.6-18.8	5.0-15.8
OR(A:M)	1.95	.98		.99	1.28	
CI of OR	.65-5.91*	.28-3.43*		.4-2.5#	.51-3.2#	
p-value Primary@	.169	.976		.989	.542	
p-value chi-sq.	.162	.976		.994	.573	

^ Duration of response in patients with CR or PR
*97.7%CI, #97.6%CI. The critical p-value for stat. sig. is .023.
@ Primary analysis is logistic regresion where treatment is the only explanatory variable.

It is noted that the numerical estimate of OTR rate for MEGACE was approximately twice higher in Trial 0005 (10.4%) than in Trial 0004 (5.5%). The results of the OTR analyses showed that there was no difference between either arm of Arimidex as compared to MEGACE arm (p=.162 and .976 in Trial 0004; p=.994 and .573 in Trial 0005). The estimated OTR rate and a 95% CI were summerized: (a) for the Arimidex 1mg arm, they were 10.2% (95%CI 4.9%-15.5%) in Trial 0004 and 10.4% (95%CI 5.2%-15.6%) in Trial 0005; (b) for the Arimidex 10mg arm, they were 5.4% (95%CI 1.5%-9.3%) in Trial 0004 and 12.7% (95%CI 6.6%-18.8%) in Trial 0005; (c) for the MEGACE arm, they were 5.5% (95%CI 1.5%-9.5%) in Trial 0004 and 10.4% (95%CI 5.0%-15.8%) in Trial 0005.

SECONDARY EFFICACY ENDPOINTS - DR, SURV, TTF, and QOL

♦ Duration of Response

Duration of response was shown in the following Table. A number of the estimated median DRs cannot be calculated as a majority of the responder patients were still responding at the study cutoff.

	1033IL/0004			1033IL/0005		
	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg
Median DR (days)	357	533	NC	261	NC	257
Range of DR (days)^						
p-value chi-sq.	.880	.581		.745	.249	

NC: Median DR not computable

The TTF and SURV were summarized in the following Table. From the observed data, there was no evidence suggesting a difference in TTF between either dose of Arimidex and MEGACE (p=.913 and .080 in Trial 0004; p=.252 and .567 in Trial 0005). For the TTF, the estimated HR of Arimidex 1mg against MEGACE was .96 (97.5%CI .45-2.08) in Trial 0004 and .72 (97.5%CI .38-1.37)

in Trial 0005. The estimated HR of Arimidex 10mg against MEGACE was .50 (97.5%CI .21-1.21) in Trial 0004 and .85 (97.5%CI .44-1.62) in Trial 0005.

♦ Time to Treatment Failure

	1033IL/0004			1033IL/0005		
	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg
TTF Median (days)	168	133	125	121	128	115
Censor	42.2%	36.9%	33.6%	29.6%	33.9%	28.8%
HR(A:M)	.85	.99		1.01	.87	
97.5%CI	.59-1.23	.7-1.41		.72-1.40	.61-1.23	
p-value	.326	.968		.965	.357	
SURV % dead	13.3	7.7	14.8	15.6	18.6	22.4
HR(A:M)	.96	.50		.72	.85	
97.5%CI	.45-2.08	.21-1.21		.38-1.37	.44-1.62	
p-value	.913	.080		.252	.567	

The critical p-value for statistical significance is .025.

For survival, the results of analysis from the observed data indicated that there was no evidence suggesting a difference in survival of either dose of Arimidex and MEGACE (p=.806 and .110 in Trial 0004; p=.242 and .593 in Trial 0005). The estimated HR of Arimidex 1mg against MEGACE was .92 (97.5%CI .43-1.95) in Trial 0004 and .54 (97.5%CI .22-1.29) in Trial 0005. The estimated HR of Arimidex 10mg against MEGACE was .71 (97.5%CI .37-1.36) in Trial 0004 and .85 (97.5%CI .45-1.63) in Trial 0005.

♦ Survival

	1033IL/0004			1033IL/0005		
	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg	Arimidex 1 mg	Arimidex 10 mg	MEGACE 40 mg
SURV Range (days)						
Censor	86.7%	92.3%	85.2%	84.4%	81.4%	77.6%
HR(A:M)	.92	.54		.71	.86	
97.5%CI	.43-1.95	.22-1.29		.37-1.36	.45-1.63	
p-value	.806	.110		.242	.593	

♦ Quality Of Life

QOL results based on the Rotterdam Symptom Checklist - including physical, psychological, and functional dimensions were presented; in Table 24, Vol. 1.74 and Table T5.1.7, Vol. 1.74 for Trial 0004; and Table 23, Vol. 1.90 for Trial 0005. In Trial 0004, the sponsor stated "At Week 24, there was statistical evidence of better physical QOL for patients treated with Arimidex 1 mg than for those treated with MEGACE. There was statistical evidence of better psychological QOL for patients treated with 1 mg of Arimidex at Week 12 and with both 1 and 10 mg of Arimidex at Week 24 than for those treated with MEGACE. At Weeks 12 and 24, there was no statistical evidence of a difference in functional QOL between either dose of Arimidex and MEGACE". In Trial 0005, the sponsor stated "At Weeks 12 and 24, there was no statistical evidence of a difference between either dose of Arimidex and MEGACE in the physical or functional dimensions of QOL. At Week 12 there was statistical evidence of better psychological QOL or better functional QOL in patients in the MEGACE group than in those in the Arimidex groups. However, there was no evidence of a difference at Week 24".

For analgesic use (Table 25 of Vol. 1.74 and Table 24 of Vol. 1.90), there was no statistical evidence of a difference between either dose of Arimidex and MEGACE. For bone pain (Table 26 of Vol. 1.74 and Table 25 of Vol. 1.90), there was no difference shown in Trial 0004, however, the data was suggestive of less bone pain in patients in the 1 mg Arimidex group compared with those in the MEGACE group at both Week 12 and 24 (p=.060 and .067). For WHO performance status (Table 27 of Vol. 1.74 and Table 26 of Vol. 1.90), there was no difference shown in Trial 0004, however, the data was suggestive of better performance

status in patients in the 1 mg Arimidex group compared with those in the MEGACE group at both Week 12 and 24 (p=.007 and .046).

Safety Summary

Events occurring to at least 5% of patients in any group were summarized in Tables 26 (Trial 0004) and 28 (Trial 0005) of Vol. 1.2. In Trial 0004, the most frequently reported adverse events were asthenia, nausea, headache, pain, and dyspnea. Dyspnea and asthenia were frequently reported in the MEGACE arm, and asthenia, nausea, headache, and pain were frequently reported in the Arimidex groups. In Trial 0005, the most frequently reported adverse events were dyspnea, peripheral edema, nausea, and headache.

3. Reviewer's evaluation, assessments of primary efficacy endpoints based on the FDA MO's assessment, and comments

Based on the REVIEWER analysis, patients allocation within centers (49 centers of the US trial and 73 centers of the European trial) did not appear to be unbalanced in either trial. The balance of patient allocation still holds within "large centers" (defined by the FDA MO as those centers having patient size 5 or more).

3.1 Primary efficacy endpoints - TTP and OTR

The FDA MO confirmed the TTP for all randomized patients. In Trial 0004, dates of first observed progression were available for the 211 patients with disease progression either during treatment or after treatment withdrawal. There were 11 additional patients who died before disease progression was documented. Inclusion of 3 patients in 11 additional patients, patients questioned by the FDA MO. The REVIWER TTP analyses showed that the results based on log-rank comparison excluding either the 11 patients (p=.455 and p=.968 for 1mg:M and 10mg:M, respectively), or the 3 patients

(p=.466 and p=.968 for 1mg:M and 10mg:M, respectively) showed that there was no statistical evidence of a TTP difference between either dose of Arimidex and MEGACE. In Trial 0005, dates of first observed progression were available for the 226 patients with disease progression either during treatment or after treatment withdrawal. There were 20 additional patients who died before disease progression was documented. Inclusion of 8 patients in 20 additional patients, patients

were questioned by the FDA MO. This reviewer's log-rank analysis results of the TTP comparison excluding either the 20 patients (p=.874 and p=.290 for 1mg:M and 10mg:M, respectively), or the 8 patients (p=.728 and p=.404 for 1mg:M and 10mg:M, respectively) showed that there was no statistical evidence of a TTP difference between either dose of Arimidex and MEGACE.

The FDA MO confirmed the 7 CRs and 20 PRs in Trial 0004 and in Trial 0005, 8 CRs and 34 PRs. It was noted by the FDA MO that responses of 2 patients in Trial 0004 and of 2 patients in Trial 0005 were based on non-measurable lesions. According to the protocol, PRs could not be assigned to these patients, only disease stabilization. In addition, there was one patient in Trial 0004 and two patients in Trial 0005 whose responses observed were not confirmed 4 weeks later. This reviewer's analysis of the OTR comparison excluding three patients in Trial 0004 and four patients in Trial 0005 showed that there was no statistical evidence of an OTR difference between either dose of Arimidex (10.2% of 1mg and 3.9% of 10mg in Trial 0004; 9.0% of 1mg and 12.7% of 10mg in Trial 0005) and MEGACE (4.7% in Trial 0004 and 8.9% in Trial 0005).

3.2 Secondary efficacy endpoints

For TTF, the FDA MO confirmed the data for all randomized patients. It was noted by the FDA MO that treatment was continued for several of the patients following documentation of treatment failure.

The QOL results reported by the sponsor (see Table 24, Vol. 1.74 and Table 23, Vol. 1.90) did not show consistent pattern between the two studies. Using comparison between 1 mg Arimidex arm and MEGACE, for example, there was no statistical evidence that the physical QOL was better at Week 12 but there was statistical evidence at Week 24 (p=.02) in Trial 0004. This physical QOL was no difference at either Week 12 or Week 24 in

Trial 0005. Those statistical significant findings at Week 12 or Week 24 cannot be concluded due to heavy multiple testings without p-value adjustment and inconsistent patterns demonstrated in the unadjusted p-values between the two studies (those unadjusted p-value may give spurious significance).

A concern about death rate and progression rate differences between large centers (accruing >= 5 patients each) and small centers (accruing < 5 patients each) was raised by The FDA MO. The data on demographic characteristics and baseline hormonal therapy, ER positive, and PR positive status were examined by this reviewer. The results of the analyses showed that except for the distribution of ER positive (10.2%, 1.0%, and 7.2% for MEGACE, 1mg, 10mg of Arimidex) in the "large center" group of Trial 0004 these disease characteristics and the patient allocation appeared to be well balanced within centers or between centers.

3.3 Design Considerations

Based on the sponsor's results, the median TTP for MEGACE is 5 months (range 3.2 - 6.8 months) in Trial 0004 and 4 months in Trial 0005. The integrated efficacy summary shows that the overall median TTP for MEGACE was 139 days, approximately 4.5 months. This estimate is used below to illustrate the sample size requirements for showing the superority and the therapeutic equivalence of either dose of Arimidex compared to MEGACE.

Assuming the median time to disease progression of MEGACE is 4.5 months and the accrual time is 15 months, the following REVIEWER analysis tables describe the scenarios considered.

3.3.1 Superiority

Reviewer Table 1. Two Superiority Designs

Original Protocol Planning (100 patients per arm)	TTP for Megace: 26 weeks(6.5mons) TTP improvement: 14 weeks(3.5mons) Accrual Period: 1.25 year Minimum Follow-up: 0.5 year
Trial Estimates & Design Considerations	TTP for Megace: 4.5 mons TTP improvement: 1 to 2 mons Accrual Period: 1.25 year Minumum Follow-up: 0.5 to 1.0 year

Reviewer Table 1 summarizes two superiority designs, the original protocol plan and a reasonable TTP improvement plan based on the current trial estimates. Sample size estimation using the trial estimates and design consideration is shown in Reviewer Table 2. Based on the current trial sample sizes, i.e., approximately 130 per arm in each study, the study has an 80% power to show a two-month improvement in TTP.

Reviewer Table 2. Sample Size Estimation* Based on Trial Estimates & Design Considerations

Improvement (in months)	Follow-up (in months)	Sample size per arm
1	6; 12	480; 425
2	6; 12	150; 135
3	6; 12	80; 70

*Assuming a 2-sided 5% type I error rate, sample sizes were calculated based on achieving an 80% power.

3.3.2 Therapeutic Equivalence

The therapeutic equivalence range based on TTP (the primary endpoint) is shown in Reviewer Table 3. For example, to show a 20% therapeutic equivalence (i.e., the median TTP for Arimidex could be lower than 4.5 months but not lower than 3.6 months), the upper boundary of the 95% CI for hazard ratio of either dose of Arimidex against Megace needs to be at most 1.25. On the other hand, since this is a hormonal agent, the objective tumor response rate is also an important issue. Reviewer Table 4 shows the lower boundary of the 95% CI for hazard ratio of either dose of Arimidex against Megace based on objective tumor response rate therapeutic equivalence. For example, to show a 20% therapeutic equivalence on the objective tumor response rate (i.e., the responser rate for Arimiex could be lower than 5% but not lower than 4%), the lower boundary of the 95% CI for hazard ratio of either dose of Arimidex against Megace needs to be at least 0.79.

Reviewer Table 3. Therapeutic Equivalence Range Based on Time to Disease Progression

Equivalence (% of 4.5 Months)	Upper Bound of 95%CI for HR(A:M)	Lower Bound of 95%CI for Arimidex Median TTP
5%	1.05	4.275 months
10%	1.11	4.05 months
15%	1.18	3.825 months
20%	1.25	3.6 months

Reviewer Table 4. THERAPEUTIC EQUIVALENCE RANGE FOR OBJECTIVE TUMOR REPONSE

Equivalence (% of 5%)	Lower Bound of 95%CI for OR(A:M)*	Lower Bound of 95%CI for Arimidex OTR
5%	.95	4.75 %
10%	.90	4.50 %
15%	.84	4.25 %
20%	.79	4.00 %

4. Overall Summary and Conclusions

The studies (IL1033/0004 and IL1033/0005) were designed to show superiority (3.5 months longer TTP or equivalent to a 20% higher objective response rate) of at least one of the Arimidex arms compared to the MEGACE (assumed median TTP of 6.5 months or OTR of 25%) arm.

As demonstrated by the sponsor's efficacy results, the studies failed to provide statistical evidence for a claim of superiority of either dose of Arimidex to MEGACE with respect to the study endpoints, including both primary endpoints (OTR and TTP), and secondary endpoints (DR, TTF, and SURV).

As described in section 3.3, the studies do not have sufficicent sample size to demonstrate the therapeutic equivalence of either Arimidex dose with MEGACE. With the protocol-specified sample sizes, the studies had about 22%-24% power of declaring a 3-week (approximately within 16.7% equivalence of 4.5 months median TTP) therapeutic equivalence. From the Reviewer TTP Table, the observed CIs for the hazard ratio of Arimidex 1mg against MEGACE were .61 to 1.3 in Trial

0004 (97.5% CI) and .69 to 1.45 in Trial 0005 (97.6% CI). The observed CIs for the hazard ratio of Arimidex 10mg against MEGACE were .74 to 1.46 in Trial 0004 (97.5%) and .58 to 1.22 in Trial 0005 (97.5%). These studies were not powered to be equivalence studies.

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Gneccoc
Dr. Chi

cc:
NDA 20-509
HFD-150
HFD-150/ Dr. Justice
Dr. Beitz
Ms. Vaccari
HFD-344/ Dr. Lisook
HFD-713/ Dr. Dubey [File: DRU 1.3.2. NDA]
Dr. Chi
HFD-713/ Dr. Wang

SWANG/9-5-95/WP60-ARIMIDEX.NDA
This review consists of 18 pages of text, including 5 REVIEWER summary Tables and 4 REVIEWER analysis Table, and 35 pages of attachments, including 30 tables and 2 figures from the sponsor.

TABLE 1 Schedule of assessments

Assessment / Week	0	4	8	12	16	20	24	36	48*	Withdrawal
Demographic, history, ECG	x									
Objective disease										
Local or regional disease	x	x	x	x	x	x	x	x	x–	x
Bone scan	x						x		x#	x
Skeletal radiography (of positive sites on bone scan)	x			x	o	o	x	x	x	x
Chest radiography	x			o+			o+	o+	x	x
CT scan of liver	o			o			o	o	o	o
CT scan of head	o			o			o	o	o	o
Quality-of-life										
Rotterdam Symptom Checklist	x	x	x	x	x	x	x	x	x	x**
Analgesic, bone-pain, and performance score	x	x	x	x	x	x	x	x	x	x
Endocrine										
Estradiol and estrone sulfate concentrations	x	x	x	x	x	x	x	x	x	x
Pharmacokinetic										
Drug concentrations (for patients who received ZD1033)	x	x	x	x	x	x	x	x	x	x
Safety										
Adverse events		x	x	x	x	x	x	x	x	x
Clinical laboratory	x	x	x	x	x	x	x	x	x	x
Physical examination, weight, blood pressure, pulse	x	x	x	x	x	x	x	x	x	x

*Assessments continued every 3 months if progression was not documented during the first 48 weeks of the trial.
#Repeated every 6 months until disease progression.
+If positive before treatment, otherwise every 12 months.
**If patient received less than 12 months of trial treatment.
o Only if clinically indicated
CT Computed tomography

Screening assessments (Week 0) took place within 4 weeks before randomization. The disease assessments used to determine response were, ideally, performed within 2 weeks before randomization. However, Assessments that could not be repeated at short intervals, such as bone scans or chest radiography, were acceptable if performed up to 12 weeks before randomization. Medical history, demography, height, and ECG results (repeated, if necessary)

TABLE 4 Previous tamoxifen treatment

Previous treatment	Number of patients (%)			
	ZD1033 1 mg (n = 128)	ZD1033 10 mg (n = 130)	Megestrol acetate (n = 128)	All patients (n = 386)
Adjuvant tamoxifen	60 (46.9)	54 (41.5)	50 (39.1)	164 (42.5)
Tamoxifen for advanced disease	68 (53.1)	76 (58.5)	78 (60.9)	222 (57.5)

Patients who relapsed after they received adjuvant tamoxifen treatment were classified as adjuvant status, and patients whose disease progressed while they received tamoxifen for advanced disease were classified as advanced disease status.

The proportions of patients who received tamoxifen as either first hormonal treatment for early disease or treatment for advanced disease were similar across treatment groups.

Table 5 summarizes breast cancer history and characteristics at entry, by treatment, and for all patients.

TABLE 5 Breast cancer history for all randomized patients

Medical history	ZD1033 1 mg (n = 128)	ZD1033 10 mg (n = 130)	Megestrol acetate (n = 128)	All patients (n = 386)
Previous treatment (n;%)				
Surgery	124 (96.9)	126 (96.9)	122 (95.3)	372 (96.4)
Cytotoxic chemotherapy	58 (45.3)	59 (45.4)	57 (44.5)	174 (45.1)
Radiotherapy	72 (56.3)	74 (56.9)	76 (59.4)	222 (57.5)
Receptor status (n;%)				
ER +, PR +	80 (62.5)	76 (58.5)	70 (54.7)	226 (58.5)
ER +, PR -	25 (19.5)	20 (15.4)	17 (13.3)	62 (16.1)
ER +, PR unknown	4 (3.1)	6 (4.6)	14 (10.9)	24 (6.2)
ER -, PR +	2 (1.6)	0 (0)	3 (2.3)	5 (1.3)
ER -, PR -	1 (0.8)	8 (6.2)	8 (6.3)	17 (4.4)
Unknown	16 (12.5)	20 (15.4)	16 (12.5)	52 (13.5)
Duration of tamoxifen treatment for advanced disease*				
Number of patients#	60	69	76	205
Median duration of treatment (weeks)	100	105	86	100

TABLE 5 Breast cancer history for all randomized patients (continued)

Medical history	ZD1033 1 mg (n = 128)	ZD1033 10 mg (n = 130)	Megestrol acetate (n = 128)	All patients (n = 386)
Relapsed during adjuvant tamoxifen treatment*				
Number of patients#	57	47	50	154
Median disease-free interval (weeks)	136	158	189	158
Previous best response to tamoxifen treatment (n;%)				
Number of patients	68 (100)	76 (100)	78 (100)	222 (100)
Complete	3 (4.4)	5 (6.6)	7 (9.0)	15 (6.8)
Partial	6 (8.8)	8 (10.5)	12 (15.4)	26 (11.7)
Stable disease	31 (45.6)	34 (44.7)	27 (34.6)	92 (41.4)
Progression	3 (4.4)	5 (6.6)	5 (6.4)	13 (5.9)
Unknown	25 (36.8)	24 (31.6)	27 (34.6)	76 (34.2)
WHO performance status score+ (n;%)				
0	69 (53.9)	59 (45.4)	60 (46.9)	188 (48.7)
1	41 (32.0)	55 (42.3)	51 (39.8)	147 (38.1)
2	18 (14.1)	13 (10.0)	15 (11.7)	46 (11.9)
3	0 (0)	3 (2.3)	1 (0.8)	4 (1.0)
4	0 (0)	0 (0)	1 (0.8)	1 (0.3)

*Tamoxifen was not taken or duration on tamoxifen could not be calculated for 11 patients treated with 1 mg of ZD1033, 14 patients treated with 10 mg of ZD1033, and 2 patients treated with megestrol acetate.
#For 11 patients treated with 1 mg of ZD1033, 15 patients treated with 10 mg of ZD1033, and 2 patients treated with megestrol acetate, either tamoxifen was not taken, or duration on tamoxifen could not be calculated.
+For treatment of primary disease (after mastectomy or lumpectomy) and metastatic lesions.
**Defined in Section 2.6.5(d).
ER Estrogen receptor; PR Progesterone receptor

Overall, previous breast cancer treatment and WHO performance status scores were similar among treatment groups. The majority (96.4%) of patients enrolled in this trial had surgical resection of the primary breast tumor and either relapsed while receiving adjuvant tamoxifen treatment for early disease or had disease progression while receiving tamoxifen as hormonal treatment for advanced disease. Approximately 45% of patients had cytotoxic treatment and approximately 58% of patients had radiotherapy for treatment of primary disease or metastatic lesions before they entered the trial. The majority (58.5%) of patients had estrogen receptor-positive (ER-positive), progesterone-positive (PR-positive) breast cancer at similar proportions among treatment groups. Approximately 14% of patients had unknown estrogen-receptor status.

3.1.3 Site and extent of disease at entry

Summary tables: *Patients with measurable and no measurable disease; T1.9*
Site of disease at entry; T1.10.1
Extent of disease at entry; T1.10.2
Liver metastases at entry, T1.10.3

Individual patient data: *Site and extent of disease at entry; G1.7*

Table 6 summarizes the number of patients with measurable and no measurable disease.

TABLE 6 Number of patients with measurable disease

Extent of disease	Number of patients (%)			
	ZD1033 1 mg (n = 128)	ZD1033 10 mg (n = 130)	Megestrol acetate (n = 128)	All patients (n = 386)
Measurable disease	82 (64.1)	79 (60.8)	81 (63.3)	242 (62.7)
No measurable disease	46 (35.9)	51 (39.2)	47 (36.7)	144 (37.3)

The proportions of patients who had measurable and nonmeasurable disease were similar across treatment groups. Approximately 63% of all patients had measurable disease and approximately 37% had nonmeasurable disease.

Table 7 summarizes the sites of metastatic disease for all patients at entry, by treatment. Patients with multiple disease sites are included in more than one category.

TABLE 7 Sites of metastatic disease at entry

Disease sites	Number of patients (%)			
	ZD1033 1 mg (n = 128)	ZD1033 10 mg (n = 130)	Megestrol acetate (n = 128)	All patients (n = 386)
Soft tissue	42 (32.8)	45 (34.6)	39 (30.5)	126 (32.6)
Bone	87 (68.0)	83 (63.8)	79 (61.7)	249 (64.5)
Visceral	51 (39.8)	51 (39.2)	60 (46.9)	162 (42.0)
Liver	18 (14.1)	17 (13.1)	18 (14.1)	53 (13.7)
No evidence of liver involvement	110 (85.9)	113 (86.9)	110 (85.9)	333 (86.3)
No evaluable metastatic disease*	5 (3.9)	12 (9.2)	3 (2.3)	20 (5.2)

*Includes patients with excised or irradiated local or distant disease at entry

The sites of metastatic disease at entry were similar across treatment groups. For all patients, 92.6% had soft tissue, 64.5% had bone, and 42.0% had visceral sites of disease. The majority (86.3%) of patients had no documented evidence of liver metastases.

Table 8 summarizes the extent of metastatic disease at entry for all patients, by treatment.

TABLE 8 Extent of metastatic disease at entry

Disease sites	Number of patients (%)			
	ZD1033 1 mg (n = 128)	ZD1033 10 mg (n = 130)	Megestrol acetate (n = 128)	All patients (n = 386)
Soft tissue only	17 (13.3)	14 (10.8)	16 (12.5)	47 (12.2)
Bone only	45 (35.2)	37 (28.5)	41 (32.0)	123 (31.9)
Visceral only	14 (10.9)	15 (11.5)	22 (17.2)	51 (13.2)
Mixed	47 (36.7)	52 (40.0)	46 (35.9)	145 (37.6)
No evaluable metastatic disease*	5 (3.9)	12 (9.2)	3 (2.3)	20 (5.2)

*Includes patients with excised or irradiated local or distant disease at entry.

The proportions of patients with either single or mixed sites of metastatic disease, at entry, were similar among treatment groups. For all patients, 12.2 % had soft tissue disease only, 31.9% had bone disease only, 13.2% had visceral disease only, and 37.6% had mixed sites of disease.

3.1.4 Concurrent abnormalities at entry

Summary table: *Concurrent abnormalities at entry; T1.11*

Individual patient data: *Past medical history; G1.8*
Concurrent abnormalities at entry; G1.9

Each treatment group included a similar proportion of patients with concurrent abnormalities at entry.

Overall, relatively low proportions (0.5% through 9.6%) of patients had abnormalities that were identified on examination of the head, eye, ear, nose, throat, heart, neck, genitourinary tract, and neurologic system. Relatively higher proportions (10.4% through 37.3%) of patients had abnormalities that were identified on examination of the abdomen, extremities, lymph nodes, lungs and thorax, skin, and musculoskeletal system. The highest proportion of patients had abnormalities that were identified in the breast (71.2%).

As expected in a middle-age to elderly population, patients in each treatment group had diverse medical histories at entry. Abnormalities present at entry did not result in the exclusion of any patient from the trial.

Table 24 summarizes the comparative statistical analysis of results of the Rotterdam Symptom Checklist scores.

TABLE 24 Statistical analysis of quality of life (Rotterdam Symptom Checklist)

Dimension and time point	ZD1033 1 mg vs megestrol acetate			ZD1033 10 mg vs megestrol acetate		
	Estimated difference* or odds ratio#	97.5% CI	p-value+	Estimated difference* or odds ratio#	97.5% CI	p-value+
Physical*						
Week 12	-1.00	-2.00 to 1.00	0.5064	0.00	-1.00 to 1.00	0.8690
Week 24	-1.00	-4.00 to -1.00	0.0163	-1.00	-3.00 to 0.00	0.1624
Psychological*						
Week 12	-1.00	-2.00 to -1.00	0.0206	-1.00	-1.00 to 0.00	0.0729
Week 24	-2.00	-3.00 to -1.00	0.0018	-2.00	-3.00 to -1.00	0.0038
Functional#						
Week 12	1.05	0.51 to 2.16	0.8834	1.01	0.49 to 2.06	0.9797
Week 24	2.70	0.74 to 9.88	0.0869	0.89	0.30 to 2.62	0.8087

*The estimated differences between treatment groups of greater than zero indicate that the first treatment is associated with worse physical or psychological quality of life.
#Odds ratios greater than 1.00 indicate that the first treatment has a higher probability of a stable or increased functional dimension relative to the second treatment.
+The critical p-value for statistical significance is 0.025.
CI Confidence interval

The Wilcoxon Rank-Sum Test results are presented in Table 24 for the physical and psychological dimensions at Weeks 12 and 24. Analyses of covariance results for physical and psychological dimensions are found in Table T5.1.7. The results for functional dimension are expressed in Table 24 as odds ratios with 97.5% confidence intervals.

At Week 24, there was statistical evidence of better physical quality of life for patients treated with 1 mg of ZD1033 than for those treated with megestrol acetate. There was statistical evidence of better psychological quality of life for patients treated with 1 mg of ZD1033 at Week 12 and with both 1 and 10 mg of ZD1033 at Week 24 than for those treated with megestrol acetate. At Weeks 12 and 24, there was no statistical evidence of a difference in functional quality of life between either dose of ZD1033 and megestrol acetate.

4.2.2 Analgesic use

Table 25 summarizes the statistical analysis of analgesic use between visits at Weeks 12 and 24.

TABLE 25 Statistical analysis of analgesic use

Time point	ZD1033 1 mg vs megestrol acetate			ZD1033 10 mg vs megestrol acetate		
	Odds ratio*	97.5% CI	p-value#	Odds ratio*	97.5% CI	p-value#
Week 12	0.75	0.35 to 1.60	0.3895	0.73	0.34 to 1.57	0.3588
Week 24	1.35	0.45 to 4.08	0.5382	0.68	0.23 to 2.02	0.4287

*Odds ratios greater than 1.00 indicate that the first treatment is associated with less aggressive analgesic use than is the second treatment.
#The critical p-value for statistical significance is 0.025.
CI Confidence interval

At Weeks 12 and 24, there was no statistical evidence of a difference in analgesic use between either dose of ZD1033 and megestrol acetate.

4.2.3 Bone pain

Table 26 summarizes the statistical analysis of bone pain score between visits at Weeks 12 and 24.

TABLE 26 Statistical analysis of bone pain score

Time point	ZD1033 1 mg vs megestrol acetate			ZD1033 10 mg vs megestrol acetate		
	Odds ratio*	97.5% CI	p-value#	Odds ratio*	97.5% CI	p-value#
Week 12	1.13	0.62 to 2.07	0.6478	0.99	0.54 to 1.81	0.9741
Week 24	1.06	0.45 to 2.51	0.8793	0.84	0.36 to 1.96	0.6383

*The odds ratios greater than 1.00 indicate that the first treatment is associated with less bone pain than is the second treatment.
#The critical p-value for statistical significance is 0.025.
CI Confidence interval

At Weeks 12 and 24, there was no statistical evidence of a difference in bone pain between either dose of ZD1033 and megestrol acetate.

4.2.4 WHO performance status

Table 27 summarizes the statistical analysis of WHO performance status between visits at Weeks 12 and 24.

Statistical analysis of WHO performance status

t	ZD1033 1 mg vs megestrol acetate			ZD1033 10 mg vs megestrol acetate		
	Odds ratio*	97.5% CI	p-value#	Odds ratio*	97.5% CI	p-value#
	0.89	0.42 to 1.86	0.7189	1.00	0.47 to 2.10	0.9889
	1.23	0.47 to 3.25	0.6258	1.18	0.45 to 3.11	0.7070

ios greater than 1.00 indicate that the first treatment is
d with a better performance status than is the second treatment.
ical p-value for statistical significance is 0.025.
dence interval

2 and 24, there was no statistical evidence of a difference in performance status
ither dose of ZD1033 and megestrol acetate.

ndocrine assessments

ables: *Estrone sulfate; T6.2.1*
Estrone sulfate suppression; T6.2.2

patient data: *Endocrinology normal ranges glossary; G6.1*
Endocrinology; G6.2 Estradiol suppression; G6.3

trial, blood samples were collected from patients to determine serum estradiol and
lfate concentrations. The determinations were performed to detect any differences in
uppression between the 1- and 10-mg doses of ZD1033.

radiol concentrations could not be statistically analyzed. The nature of the analytical
d several confounding factors such as insufficient sample volume, variable column
orrections for blank samples, and variability in limits of quantitation ([LOQ] varied at
fold for estradiol and ranged from pmol/l) resulted in a
eneous data set, which could not be utilized for statistical analysis.

, a significant number of patients in each of the three treatment groups had estradiol
tions at entry that were at or below the limit of assay sensitivity. It was difficult to
additional estradiol suppression in these patients.

1 10 mg of ZD1033 consistently suppressed serum estrone sulfate concentrations by
% of concentrations at entry compared with 26% to 66% for megestrol acetate.

of the difficulties encountered during sample analyses, the estradiol suppression
be quantitated. However, for patients treated with either 1 or 10 mg of ZD1033,
lfate suppression was greater than that observed in the patients treated with
acetate. There was no apparent difference in estrone sulfate suppression between
10-mg doses of ZD1033.

TABLE T4.2.3 PROGRESSION STATUS - BY HORMONAL TREATMENT HISTORY
(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

HORMONAL TREATMENT HISTORY		ZD1033 1MG		ZD1033 10MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		128		130		128	
		N	%	N	%	N	%
ADJUVANT HORMONAL	ALIVE WITHOUT PROGRESSION	20	33.3	21	38.9	22	44.0
	PROGRESSION DURING TREATMENT	31	51.7	30	55.6	24	48.0
	PROGRESSION AFTER TREATMENT WITHDRAWAL	5	8.3	3	5.6	3	6.0
	DEATH BEFORE PROGRESSION	4	6.7	0	0	1	2.0
	TOTAL	60	100.0	54	100.0	50	100.0
ADVANCED HORMONAL	ALIVE WITHOUT PROGRESSION	39	57.4	34	44.7	28	35.9
	PROGRESSION DURING TREATMENT	26	38.2	39	51.3	43	55.1
	PROGRESSION AFTER TREATMENT WITHDRAWAL	2	2.9	2	2.6	3	3.8
	DEATH BEFORE PROGRESSION	1	1.5	1	1.3	4	5.1

(CONTINUED)

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 AND G4.3

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TABLE T4.2.3 PROGRESSION STATUS - BY HORMONAL TREATMENT HISTORY
(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

HORMONAL TREATMENT HISTORY		ZD1033 1MG		ZD1033 10MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		128		130		128	
		N	%	N	%	N	%
ADVANCED HORMONAL	TOTAL	68	100.0	76	100.0	78	100.0

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 AND G4.3

(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

OESTROGEN RECEPTOR STATUS		ZD1033 1MG		ZD1033 10MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		128		130		128	
		N	%	N	%	N	%
UNKNOWN	ALIVE WITHOUT PROGRESSION	6	37.5	14	70.0	6	37.5
	PROGRESSION DURING TREATMENT	8	50.0	5	25.0	6	37.5
	PROGRESSION AFTER TREATMENT WITHDRAWAL	0	0	1	5.0	2	12.5
	DEATH BEFORE PROGRESSION	2	12.5	0	0	2	12.5
	TOTAL	16	100.0	20	100.0	16	100.0
+	ALIVE WITHOUT PROGRESSION	53	48.6	39	38.2	42	41.6
	PROGRESSION DURING TREATMENT	46	42.2	58	56.9	53	52.5
	PROGRESSION AFTER TREATMENT WITHDRAWAL	7	6.4	4	3.9	3	3.0
	DEATH BEFORE PROGRESSION	3	2.8	1	1.0	3	3.0

(CONTINUED)

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 AND G4.3

... INCLUDED : ALL RANDOMISED PATIENTS)

OESTROGEN RECEPTOR STATUS		ZD1033 1MG		ZD1033 10MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		128		130		128	
		N	%	N	%	N	%
+	TOTAL	109	100.0	102	100.0	101	100.0
-	ALIVE WITHOUT PROGRESSION	0	0	2	25.0	2	18.2
	PROGRESSION DURING TREATMENT	3	100.0	6	75.0	8	72.7
	PROGRESSION AFTER TREATMENT WITHDRAWAL	0	0	0	0	1	9.1
	TOTAL	3	100.0	8	100.0	11	100.0

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 AND G4.3

TABLE T4.2.5 PROGRESSION STATUS - BY PROGESTERONE RECEPTOR STATUS
(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

PROGESTERONE RECEPTOR STATUS		ZD1033 1MG		ZD1033 10MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		128		130		128	
		N	%	N	%	N	%
UNKNOWN	ALIVE WITHOUT PROGRESSION	6	30.0	18	69.2	14	46.7
	PROGRESSION DURING TREATMENT	12	60.0	7	26.9	11	36.7
	PROGRESSION AFTER TREATMENT WITHDRAWAL	0	0	1	3.8	3	10.0
	DEATH BEFORE PROGRESSION	2	10.0	0	0	2	6.7
	TOTAL	20	100.0	26	100.0	30	100.0
+	ALIVE WITHOUT PROGRESSION	42	51.2	25	32.9	28	38.4
	PROGRESSION DURING TREATMENT	33	40.2	48	63.2	41	56.2
	PROGRESSION AFTER TREATMENT WITHDRAWAL	5	6.1	2	2.6	2	2.7
	DEATH BEFORE PROGRESSION	2	2.4	1	1.3	2	2.7

(CONTINUED)

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 AND G4.3

(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

PROGESTERONE RECEPTOR STATUS		ZD1033 1MG		ZD1033 10MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		128		130		128	
		N	%	N	%	N	%
+	TOTAL	82	100.0	76	100.0	73	100.0
-	ALIVE WITHOUT PROGRESSION	11	42.3	12	42.9	8	32.0
	PROGRESSION DURING TREATMENT	12	46.2	14	50.0	15	60.0
	PROGRESSION AFTER TREATMENT WITHDRAWAL	2	7.7	2	7.1	1	4.0
	DEATH BEFORE PROGRESSION	1	3.8	0	0	1	4.0
	TOTAL	26	100.0	28	100.0	25	100.0

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 AND G4.3

TABLE T5.1.7 ROTTERDAM SYMPTOM CHECKLIST QUALITY OF LIFE : ANALYSIS RESULTS
NON-PARAMETRIC ANALYSIS

WEEK 12

CHANGE IN TOTAL SCORE FROM ENTRY		N	ZD1033 MEDIAN	N	MEG. ACE. MEDIAN	TREATMENT DIFFERENCE	LOWER 97.5% CONFIDENCE LIMIT	UPPER 97.5% CONFIDENCE LIMIT	WILCOXON P-VALUE
PHYSICAL	ZD1033 1MG VS MECESTROL ACETATE	105	-1.00	103	0.00	-1.00	-2.00	1.00	0.5064
	ZD1033 10MG VS MEGESTROL ACETATE	109	0.00	103	0.00	0.00	-1.00	1.00	0.8690

WEEK 24

CHANGE IN TOTAL SCORE FROM ENTRY		N	ZD1033 MEDIAN	N	MEG. ACE. MEDIAN	TREATMENT DIFFERENCE	LOWER 97.5% CONFIDENCE LIMIT	UPPER 97.5% CONFIDENCE LIMIT	WILCOXON P-VALUE
PHYSICAL	ZD1033 1MG VS MEGESTROL ACETATE	58	-1.00	51	0.00	-1.00	-4.00	-1.00	0.0163
	ZD1033 10MG VS MEGESTROL ACETATE	58	-1.00	51	0.00	-1.00	-3.00	0.00	0.1624

FOR INDIVIDUAL PATIENT DATA SEE TABLE G5.1

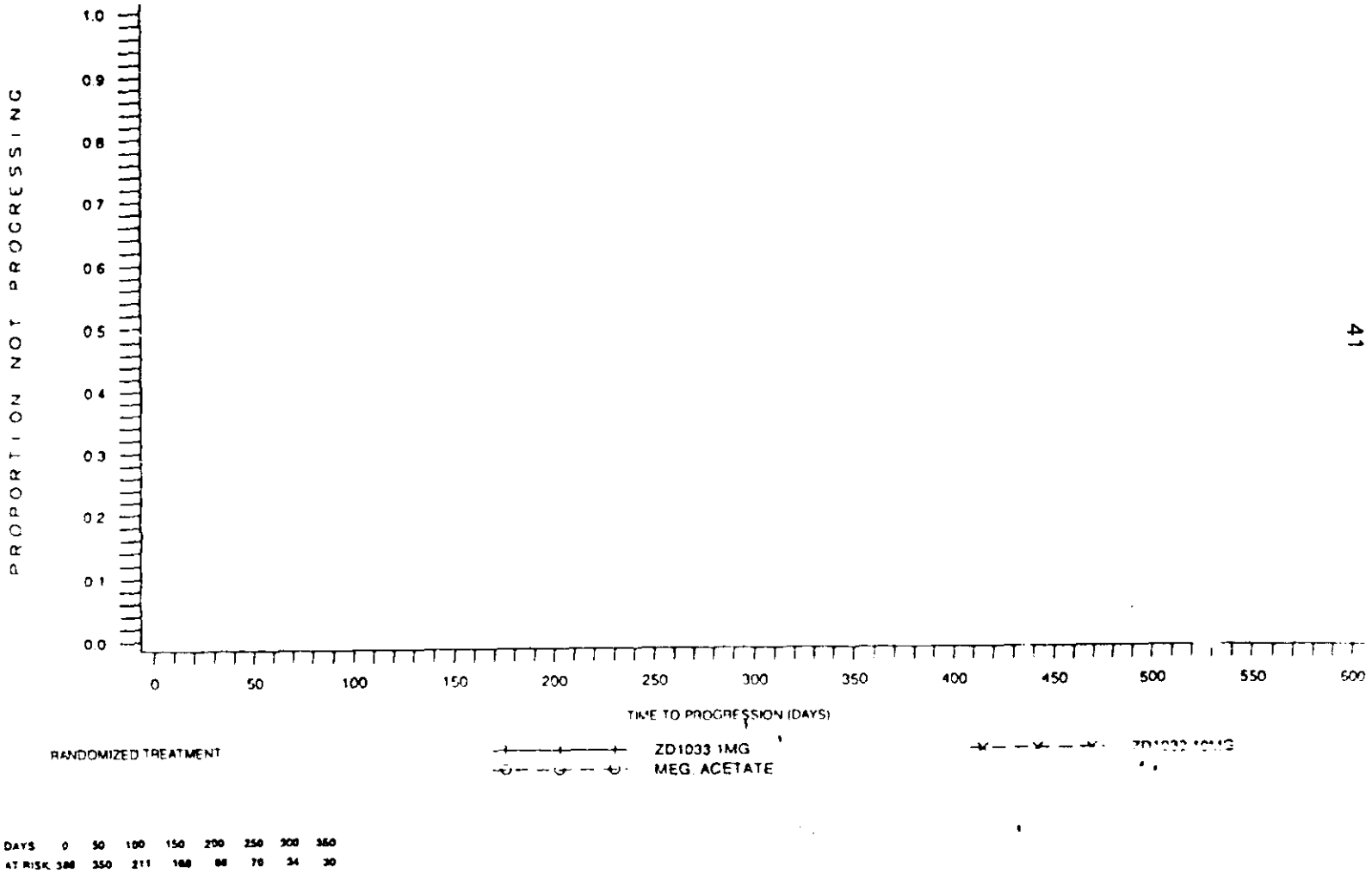
TABLE T5.1.7 ROTTERDAM SYMPTOM CHECKLIST QUALITY OF LIFE : ANALYSIS RESULTS
ANALYSIS OF COVARIANCE

WEEK 24

CHANGE IN TOTAL SCORE FROM ENTRY		N	ZD1033 MEDIAN	N	MEG. ACE. MEDIAN	TREATMENT DIFFERENCE	LOWER 97.5% CONFIDENCE LIMIT	UPPER 97.5% CONFIDENCE LIMIT	P-VALUE
PHYSICAL	ZD1033 1MG VS MEGESTROL ACETATE	58	-2.30	51	0.71	-3.01	-5.09	-0.93	0.0013
	ZD1033 10MG VS MEGESTROL ACETATE	58	-0.74	51	0.71	-1.45	-3.54	0.64	0.1180

FOR INDIVIDUAL PATIENT DATA SEE TABLE G5.1

FIGURE 4 Kaplan-Meier probability of time to progression



trial arm 5

TABLE 1 Schedule of assessments

Assessment / Week	0	4	8	12	16	20	24	36	48	Withdrawal of study treatment
Demography, history, ECG	x									
Objective disease										
Local/regional disease	x	x	x	x	x	x	x	x	x	x
Bone scan	x						x		x*	x
Skeletal x-ray (of sites positive on bone scan)	x			x	o	o	x	x	x	x
Chest x-ray	x			o#			o#	o#	x	x
CT scan of liver/head	o			o#			o#	o#	o#	- o
Quality of life										
Rotterdam Symptom Checklist	x			x			x	x	x	x+
Analgesic use, bone pain and performance status	x	x	x	x			x	x	x	x
Endocrine (oestradiol concentrations)	x	x	x	x			x	x	x	x
Safety										
Adverse events		x	x	x	x	x	x	x	x	x
Clinical laboratory	x	x	x	x			x	x	x	x
Physical examination, weight, pulse rate, blood pressure	x	x	x	x	x	x	x	x	x	x

* repeated every 6 months until disease progression
\# if positive before treatment, otherwise every 12 months
\+ if after less than 12 months of study treatment
o only if clinically indicated

Screening assessments (Week 0) took place within 4 weeks before randomisation, and the assessments of disease that would be used to determine response were ideally performed within 2 weeks before randomisation. However, investigations that cannot be repeated at short intervals, such as a bone scan, were acceptable if performed up to 12 weeks before

3.1.2 Breast cancer history

Summary tables:
Previous treatment for breast cancer; T1.4.1 to T1.4.2
Most recent receptor status; T1.5
Disease-free interval; T1.6
Duration of tamoxifen treatment; T1.7
Previous tumour responses; T1.8

Individual patient data:
Previous systemic treatment for breast cancer; G1.3
Previous surgery for breast cancer; G1.4
Previous radiotherapy for breast cancer; G1.5
Breast cancer history; G1.6

All patients eligible to enter this study had previously relapsed while on adjuvant tamoxifen treatment for early disease, and/or had disease progression during or after receiving tamoxifen as treatment for advanced disease. Some patients received a course of tamoxifen as adjuvant treatment and subsequently received further tamoxifen treatment for advanced disease. Table 4 summarises the number of patients in each of the above categories by randomised study treatment.

TABLE 4 Previous tamoxifen treatment

Previous treatment	Number of patients (%)			
	ZD1033 1 mg	ZD1033 10 mg	Megestrol acetate	All patients
	(n = 135)	(n = 118)	(n = 125)	(n = 378)
Adjuvant tamoxifen only	66 (48.9)	46 (39.0)	52 (41.6)	164 (43.4)
Tamoxifen for advanced disease only	64 (47.4)	64 (54.2)	65 (52.0)	193 (51.1)
Tamoxifen as adjuvant treatment and for advanced disease	5 (3.7)	8 (6.8)	8 (6.4)	21 (5.6)

There was no major imbalance in previous tamoxifen treatment status between the three groups; however slightly more patients in the ZD1033 1 mg group had received adjuvant tamoxifen only (49%) compared with patients in the ZD1033 10 mg group (39%) and the megestrol acetate group (42%). The analyses of objective efficacy end-points have been adjusted for this covariate, so this imbalance is unlikely to cause any bias in the comparison of the treatments.

Table 5 summarises breast cancer history and characteristics at entry by randomised treatment and for all patients.

TABLE 5 Breast cancer history and characteristics at entry for all randomised patients

	ZD1033 1 mg (n = 135)	ZD1033 10 mg (n = 118)	Megestrol acetate (n = 125)	All patients (n = 378)
Previous treatment (n; %)				
Surgery	122 (90.4)	104 (88.1)	115 (92.0)	341 (90.2)
Cytotoxic chemotherapy	40 (29.6)	33 (28.0)	32 (25.6)	105 (27.8)
Radiotherapy	81 (60.0)	72 (61.0)	80 (64.0)	233 (61.6)
Receptor status (n; %)				
ER +, PR +	54 (40.0)	39 (33.1)	49 (39.2)	142 (37.6)
ER +, PR -	20 (14.8)	14 (11.9)	17 (13.6)	51 (13.5)
ER -, PR +	2 (1.5)	4 (3.4)	2 (1.6)	8 (2.1)
ER -, PR -	3 (2.2)	4 (3.4)	3 (2.4)	10 (2.6)
ER +, PR unknown	10 (7.4)	11 (9.3)	6 (4.8)	27 (7.1)
ER unknown, PR unknown	46 (34.1)	46 (39.0)	48 (38.4)	140 (37.0)
Duration of tamoxifen treatment				
Number of patients treated with tamoxifen*	132	114	124	370
Median time on tamoxifen (weeks)	103	105	112	105
Relapse during adjuvant tamoxifen treatment				
Number of patients treated with adjuvant tamoxifen	71	53#	60	184
Median disease-free interval (months)	27.0	28.0	32.0	29.0
Previous best response to tamoxifen for advanced disease (n; %)				
Number of patients treated for advanced disease	69 (100.0)	72 (100.0)	73 (100.0)	214 (100.0)
Complete response	9 (13.0)	12 (16.7)	9 (12.3)	30 (14.0)
Partial response	16 (23.2)	25 (34.7)	18 (24.7)	59 (27.6)
Stable disease	33 (47.8)	25 (34.7)	33 (45.2)	91 (42.5)
Progression	9 (13.0)	10 (13.9)	11 (15.1)	30 (14.0)
Unknown	2 (2.9)	0 (0.0)	2 (2.7)	4 (1.9)
Performance status (n;%)				
0	69 (51.1)	50 (42.4)	56 (44.8)	175 (46.3)
1	50 (37.0)	46 (39.0)	52 (41.6)	148 (39.2)
2	16 (11.9)	21 (17.8)	17 (13.6)	54 (14.3)
3	0 (0)	1 (0.8)	0 (0)	1 (0.3)

ER = oestrogen receptor; PR = progesterone receptor

* excludes 5 patients who had not received previous tamoxifen treatment and 3 for whom dates of treatment were not available

\# a total of 54 patients received tamoxifen as adjuvant treatment, however, for one patient the disease-free interval was not known. This patient was not included in the calculation of median disease-free interval.

Overall, previous breast cancer treatment was similar for patients randomised to ZD1033 1 mg, ZD1033 10 mg, or megestrol acetate. Approximately 25% of patients had received cytotoxic treatment and approximately 60% of patients had received radiotherapy before entry into the study. ER-positive breast cancer was found in approximately 58% of all patients and the proportion of ER-positive patients was similar in each of the treatment groups. Thirty-seven percent of all patients were of unknown oestrogen receptor status.

The median disease-free interval on adjuvant tamoxifen was similar for patients randomised to ZD1033 1 mg, ZD1033 10 mg, or megestrol acetate. The median time on tamoxifen for advanced disease was also similar for patients in each of the treatment groups.

The proportions of patients with each previous best tumour response to tamoxifen were similar in the ZD1033 1 mg group compared with the megestrol acetate group; these responses were assessed by the investigator and were not substantiated by objective criteria. However, in the ZD1033 10 mg group there was a greater proportion of patients with partial response and a smaller proportion with stable disease than in the other groups.

3.1.3 Site and extent of disease at entry

Summary tables: *Patients with measurable and no measurable disease; T1.9*
Site of disease at entry; T1.10.1
Extent of disease at entry; T1.10.2
Liver involvement at entry; T1.10.3

Individual patient data: *Site and extent of disease at entry; G1.7*

Table 6 summarises the number of patients with measurable and no measurable disease.

TABLE 6 Number of randomised patients with measurable disease

	Number of patients (%)			
	ZD1033 1 mg	ZD1033 10 mg	Megestrol acetate	All patients
	(n=135)	(n=118)	(n=125)	(n = 378)
Measurable disease	109 (80.7)	89 (75.4)	99 (79.2)	297 (78.6)
No measurable disease	26 (19.3)	29 (24.6)	26 (20.8)	81 (21.4)

The proportions of patients with measurable or no measurable disease were balanced between the three treatment groups, with more than 75% of patients in each treatment group having some form of measurable disease.

Table 7 summarises the sites of metastatic disease at entry by randomised treatment. Some patients have multiple sites of disease and therefore the sum of the percentage figures for each treatment group will be more than 100%.

TABLE 7 Sites of metastatic disease at entry

Disease sites	Number of patients (%)			
	ZD1033 1 mg	ZD1033 10 mg	Megestrol acetate	All patients
	(n = 135)	(n = 118)	(n = 125)	(n = 378)
Soft tissue	57 (42.2)	50 (42.4)	53 (42.4)	160 (42.3)
Bone	79 (58.5)	66 (55.9)	77 (61.6)	222 (58.7)
Visceral	73 (54.1)	51 (43.2)	53 (42.4)	177 (46.8)
Liver	28 (20.7)	21 (17.8)	23 (18.4)	72 (19.0)
No evidence of liver involvement	107 (79.3)	97 (82.2)	102 (81.6)	306 (81.0)
No evaluable metastatic disease*	2 (1.5)	2 (1.7)	0 (0.0)	4 (1.1)

* includes three patients with local or distant metastases that were excised or eradicated before entry and one patient in the ZD1033 10 mg group who was found to have no evaluable disease

Of all patients in the study, 42.3% had soft tissue disease, 58.7% had bone disease, and 46.8% had visceral disease. The sites of metastatic disease at entry were similar in the three treatment groups, however, there was some small imbalance in the proportion of patients with visceral disease: 54.1% of patients in the ZD1033 1 mg group had visceral disease compared with only 43.2% in the ZD1033 10 mg group and 42.4% in the megestrol acetate group.

Table 8 summarises the extent of metastatic disease at entry by randomised treatment and for all randomised patients.

TABLE 8 Extent of metastatic disease at entry

Disease sites	Number of patients (%)			
	ZD1033 1 mg	ZD1033 10 mg	Megestrol acetate	All patients
	(n = 135)	(n = 118)	(n = 125)	(n = 378)
Soft tissue only	15 (11.1)	22 (18.6)	25 (20.0)	62 (16.4)
Bone only	30 (22.2)	29 (24.6)	36 (28.8)	95 (25.1)
Visceral only	28 (20.7)	19 (16.1)	16 (12.8)	63 (16.7)
Mixed	60 (44.4)	46 (39.0)	48 (38.4)	154 (40.7)
No evaluable metastatic disease*	2 (1.5)	2 (1.7)	0 (0.0)	4 (1.1)

* includes three patients with local or distant metastases that were excised or eradicated before entry and one patient in the ZD1033 10 mg group who was found to have no evaluable disease

TABLE 23 Statistical analysis of quality of life (Rotterdam Symptom Checklist)

Dimension	ZD1033 1 mg versus megestrol acetate			ZD1033 10 mg versus megestrol acetate		
	Estimated difference*	97.5% Confidence interval	p-value #	Estimated difference*	97.5% Confidence interval	p-value #
Physical						
Week 12	1.71	-0.42 to 3.84	0.0719	1.58	-0.60 to 3.76	0.1032
Week 24	1.96	-0.82 to 4.74	0.1116	0.22	-2.66 to 3.10	0.8624
Psychological						
Week 12	1.52	0.25 to 2.80	0.0077	1.82	0.51 to 3.13	0.0019
Week 24	0.52	-1.32 to 2.35	0.5235	0.83	-1.07 to 2.72	0.3254
Functional						
Week 12	0	-1 to 0	0.4037	0	0 to 0	0.8979
Week 24	0	-1 to 0	0.4572	0	-2 to 0	0.5268

* estimated differences between treatment groups of greater than zero indicate that the first treatment is associated with worse physical or psychological quality of life or better functional quality of life than the second treatment.

\# critical p-value for statistical significance = 0.025

At Weeks 12 and 24, there was no statistical evidence of a difference between either dose of ZD1033 and megestrol acetate in the physical or functional dimensions of quality of life. At Week 12 there was statistical evidence of better psychological quality of life or better functional quality of life in patients in the megestrol acetate group than in those in the ZD1033 groups. However, there was no evidence of a difference at week 24.

Results of the additional question which asked to what extent patients were bothered by weight changes (scored from 0 = not at all to 3 = very much) were not analysed statistically. At Week 12 the mean weight change score was 1 in all three treatment groups; at Week 24 the mean score was 1 in the ZD1033 1 mg and megestrol acetate groups and zero in the ZD1033 10 mg group. This indicates that at Week 24, patients in the ZD1033 10 mg group were experiencing less severe problems associated with weight change than those in the other groups.

4.2.2 Analgesic use

Table 24 summarises the statistical analysis of analgesic use for the 24 hours before assessment at Week 12 and Week 24.

TABLE 24 Statistical analysis of analgesic use

	ZD1033 1 mg versus megestrol acetate			ZD1033 10 mg versus megestrol acetate		
	Odds ratio*	97.5% Confidence interval	p-value #	Odds ratio*	97.5% Confidence interval	p-value #
Week 12	1.01	0.48 to 2.17	0.9657	1.04	0.48 to 2.30	0.9004
Week 24	0.79	0.25 to 2.46	0.6438	1.29	0.40 to 4.17	0.6218

* odds ratios greater than 1.00 indicate that the first treatment is associated with less aggressive analgesic use than the second treatment.
\# critical p-value for statistical significance = 0.025.

At Weeks 12 and 24, there was no statistical evidence of a difference in analgesic use between either dose of ZD1033 and megestrol acetate.

4.2.3 Bone pain

Table 25 summarises the statistical analysis of bone pain score for the 24 hours before assessment at Week 12 and Week 24.

TABLE 25 Statistical analysis of bone pain score

	ZD1033 1 mg versus megestrol acetate			ZD1033 10 mg versus megestrol acetate		
	Odds ratio*	97.5% Confidence interval	p-value #	Odds ratio*	97.5% Confidence interval	p-value #
Week 12	1.91	0.88 to 4.14	0.0602	2.53	1.12 to 5.68	0.0105
Week 24	2.60	0.81 to 8.36	0.0666	1.32	0.45 to 3.92	0.5669

* odds ratios greater than 1.00 indicate that the first treatment is associated with less bone pain than the second treatment.
\# critical p-value for statistical significance = 0.025

At Week 12 there was statistical evidence of less bone pain in patients in the ZD1033 10 mg group compared with those in the megestrol acetate group. At Week 24 there was no statistical evidence of any difference in bone pain score between either dose of ZD1033 and megestrol acetate. However, at both Week 12 and Week 24 the results favoured ZD1033.

4.2.4 WHO Performance status

Table 26 summarises the statistical analysis of WHO performance status for the 24 hours before assessment at Week 12 and Week 24.

TABLE 26 Statistical analysis of WHO performance status

	ZD1033 1 mg versus megestrol acetate			ZD1033 10 mg versus megestrol acetate		
	Odds ratio*	97.5% Confidence interval	p-value #	Odds ratio*	97.5% Confidence interval	p-value #
Week 12	2.47	1.17 to 5.24	0.0069	1.89	0.86 to 4.18	0.0702
Week 24	2.66	0.89 to 7.98	0.0457	1.37	0.47 to 4.02	0.5115

* odds ratios greater than 1.00 indicate that the first treatment is associated with a better performance status than the second treatment

\# critical p-value for statistical significance = 0.025

At Week 12 there was statistical evidence of better performance status in the ZD1033 1 mg group than in the megestrol acetate group. However, by Week 24 there was no statistical evidence of any difference between either dose of ZD1033 and megestrol acetate for performance status, although the results favoured ZD1033 10 mg at Week 12 and ZD1033 1 mg at Week 24.

4.3 Endocrine results

Summary tables:
Oestradiol; T6.1.1, T6.1.3
Oestradiol suppression; T6.1.2

Individual patient data:
Oestradiol normal ranges glossary; G6.1
Oestradiol; G6.2
Oestradiol suppression; G6.3

The plot of mean oestradiol concentration against time is presented in Figure 8. When oestradiol concentrations were below the limit of quantification of the assay, the limit of quantification was used. The plot indicates that over time, mean serum oestradiol concentrations were suppressed to below the concentrations at entry to a similar extent in both the ZD1033 groups, whereas mean oestradiol concentrations were raised compared with concentrations at entry in the megestrol acetate group. Measurement of oestradiol in this study was performed using a commercially available assay and was used primarily as a compliance indicator. The observed oestradiol suppression in both ZD1033 treatment groups is indicative of good compliance in these groups.

The effect of ZD1033 on serum oestradiol concentrations was further investigated for patients with a pre-dose oestradiol concentration of less than 100 pmol/l, including only results from samples measured at the central laboratory. These results are presented in Table T6.1.3.

STUDY NUMBER 1033IL/0005

TABLE T4.2.3 PROGRESSION STATUS BY HORMONAL TREATMENT HISTORY

(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

HORMONAL TREATMENT HISTORY		ZD1033 1 MG		ZD1033 10 MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		135		118		125	
		N	%	N	%	N	%
ADJUVANT	ALIVE WITHOUT PROGRESSION	18	27.3	15	32.6	12	23.1
	PROGRESSION DURING TREATMENT	41	62.1	28	60.9	35	67.3
	PROGRESSION AFTER TREATMENT WITHDRAWAL	2	3.0	0	0	2	3.8
	DEATH BEFORE PROGRESSION	5	7.6	3	6.5	3	5.8
	TOTAL	66	100.0	46	100.0	52	100.0
ADVANCED	ALIVE WITHOUT PROGRESSION	27	39.1	32	44.4	28	38.4
	PROGRESSION DURING TREATMENT	36	52.2	35	48.6	39	53.4
	PROGRESSION AFTER TREATMENT WITHDRAWAL	3	4.3	3	4.2	2	2.7
	DEATH BEFORE PROGRESSION	3	4.3	2	2.8	4	5.5
	TOTAL	69	100.0	72	100.0	73	100.0

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.3 & G4.3

STUDY NUMBER 1033IL/0005

TABLE T4.2.4 PROGRESSION STATUS BY OESTROGEN RECEPTOR STATUS

(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

OESTROGEN RECEPTOR STATUS		ZD1033 1 MG		ZD1033 10 MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		135		118		125	
		N	%	N	%	N	%
+	ALIVE WITHOUT PROGRESSION	30	35.7	27	42.2	22	30.6
	PROGRESSION DURING TREATMENT	48	57.1	33	51.6	43	59.7
	PROGRESSION AFTER TREATMENT WITHDRAWAL	4	4.8	2	3.1	4	5.6
	DEATH BEFORE PROGRESSION	2	2.4	2	3.1	3	4.2
	TOTAL	84	100.0	64	100.0	72	100.0
-	ALIVE WITHOUT PROGRESSION	1	20.0	1	12.5	2	40.0
	PROGRESSION DURING TREATMENT	4	80.0	6	75.0	3	60.0
	PROGRESSION AFTER TREATMENT WITHDRAWAL	0	0	1	12.5	0	0
	TOTAL	5	100.0	8	100.0	5	100.0
UNKNOWN	ALIVE WITHOUT PROGRESSION	14	30.4	19	41.3	16	33.3

(CONTINUED)

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 & G4.3

STUDY NUMBER 1033IL/0005

TABLE T4.2.4 PROGRESSION STATUS BY OESTROGEN RECEPTOR STATUS

(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

OESTROGEN RECEPTOR STATUS		ZD1033 1 MG		ZD1033 10 MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		135		118		125	
		N	%	N	%	N	%
UNKNOWN	PROGRESSION DURING TREATMENT	25	54.3	24	52.2	28	58.3
	PROGRESSION AFTER TREATMENT WITHDRAWAL	1	2.2	0	0	0	0
	DEATH BEFORE PROGRESSION	6	13.0	3	6.5	4	8.3
	TOTAL	46	100.0	46	100.0	48	100.0

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 & G4.3

STUDY NUMBER 1033IL/0005

TABLE T4.2.5 PROGRESSION STATUS BY PROGESTERONE RECEPTOR STATUS

(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

PROGESTERONE RECEPTOR STATUS		ZD1033 1 MG		ZD1033 10 MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		135		118		125	
		N	%	N	%	N	%
+	ALIVE WITHOUT PROGRESSION	18	32.1	16	37.2	16	31.4
	PROGRESSION DURING TREATMENT	34	60.7	23	53.5	31	60.8
	PROGRESSION AFTER TREATMENT WITHDRAWAL	2	3.6	2	4.7	2	3.9
	DEATH BEFORE PROGRESSION	2	3.6	2	4.7	2	3.9
	TOTAL	56	100.0	43	100.0	51	100.0
	ALIVE WITHOUT PROGRESSION	10	43.5	7	38.9	6	30.0
	PROGRESSION DURING TREATMENT	11	47.8	10	55.6	13	65.0
	PROGRESSION AFTER TREATMENT WITHDRAWAL	2	8.7	1	5.6	1	5.0
	TOTAL	23	100.0	18	100.0	20	100.0
UNKNOWN	ALIVE WITHOUT PROGRESSION	17	30.4	24	42.1	18	33.3

(CONTINUED)

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 & G4.3

STUDY NUMBER 1033IL/0005

TABLE T4.2.5 PROGRESSION STATUS BY PROGESTERONE RECEPTOR STATUS

(PATIENTS INCLUDED : ALL RANDOMISED PATIENTS)

PROGESTERONE RECEPTOR STATUS		ZD1033 1 MG		ZD1033 10 MG		MEGESTROL ACETATE	
		NUMBER OF PATIENTS		NUMBER OF PATIENTS		NUMBER OF PATIENTS	
		135		118		125	
		N	%	N	%	N	%
UNKNOWN	PROGRESSION DURING TREATMENT	32	57.1	30	52.6	30	55.6
	PROGRESSION AFTER TREATMENT WITHDRAWAL	1	1.8	0	0	1	1.9
	DEATH BEFORE PROGRESSION	6	10.7	3	5.3	5	9.3
	TOTAL	56	100.0	57	100.0	54	100.0

FOR INDIVIDUAL PATIENT DATA SEE TABLES G1.6 & G4.3

STUDY NUMBER 10331I/0005

TABLE I5.1.7 ROTTERDAM SYMPTOM CHECKLIST QUALITY OF LIFE : ANALYSIS RESULTS

(PATIENTS INCLUDED : ALL PATIENTS ANALYSED)

WEEK 12

CHANGE IN TOTAL SCORE FROM ENTRY		N	ZD1033 LSMEAN	N	MEG. ACE. LSMEAN	TREATMENT DIFFERENCE	LOWER 97.5% CONFIDENCE LIMIT	UPPER 97.5% CONFIDENCE LIMIT	P-VALUE
PHYSICAL	ZD1033 1 MG VS MEGESTROL ACETATE	87	0.52	76	-1.18	1.71	-0.42	3.84	0.0719
	ZD1033 10 MG VS MEGESTROL ACETATE	79	0.40	76	-1.18	1.58	-0.60	3.76	0.1032
PSYCHOLOGICAL	ZD1033 1 MG VS MEGESTROL ACETATE	87	-0.76	76	-2.28	1.52	0.25	2.80	0.0077
	ZD1033 10 MG VS MEGESTROL ACETATE	76	-0.46	76	-2.28	1.82	0.51	3.13	0.0019

WEEK 24

CHANGE IN TOTAL SCORE FROM ENTRY		N	ZD1033 LSMEAN	N	MEG. ACE. LSMEAN	TREATMENT DIFFERENCE	LOWER 97.5% CONFIDENCE LIMIT	UPPER 97.5% CONFIDENCE LIMIT	P-VALUE
PHYSICAL	ZD1033 1 MG VS MEGESTROL ACETATE	49	0.79	47	-1.18	1.96	-0.82	4.74	0.1116
	ZD1033 10 MG VS MEGESTROL ACETATE	43	-0.96	47	-1.18	0.22	-2.36	3.10	0.8624
PSYCHOLOGICAL	ZD1033 1 MG VS MEGESTROL ACETATE	49	-1.79	47	-2.31	0.52	-1.32	2.35	0.5235
	ZD1033 10 MG VS MEGESTROL ACETATE	43	-1.48	47	-2.31	0.83	-1.07	2.72	0.3254

FOR INDIVIDUAL PATIENT DATA SEE TABLE G5.1

STUDY NUMBER 1033IL/0005

TABLE T5.1.7 ROTTERDAM SYMPTOM CHECKLIST QUALITY OF LIFE : ANALYSIS RESULTS

(PATIENTS INCLUDED : ALL PATIENTS ANALYSED)

WEEK 12

CHANGE IN TOTAL SCORE FROM ENTRY		N	ZD1033 MEDIAN	N	MEG. ACE. MEDIAN	TREATMENT DIFFERENCE	LOWER 97.5% CONFIDENCE LIMIT	UPPER 97.5% CONFIDENCE LIMIT	P-VALUE
FUNCTIONAL	ZD1033 1 MG VS MEGESTROL ACETATE	87	0	76	0	0	-1	0	0.4037
	ZD1033 10 MG VS MEGESTROL ACETATE	78	0	76	0	0	0	0	0.8979

WEEK 24

CHANGE IN TOTAL SCORE FROM ENTRY		N	ZD1033 MEDIAN	N	MEG. ACE. MEDIAN	TREATMENT DIFFERENCE	LOWER 97.5% CONFIDENCE LIMIT	UPPER 97.5% CONFIDENCE LIMIT	P-VALUE
FUNCTIONAL	ZD1033 1 MG VS MEGESTROL ACETATE	50	0	47	0	0	-1	0	0.4572
	ZD1033 10 MG VS MEGESTROL ACETATE	42	0	47	0	0	-2	0	0.5268

FOR INDIVIDUAL PATIENT DATA SEE TABLE G5.1

FIGURE 4 ***Kaplan Meier probability of time to progression***

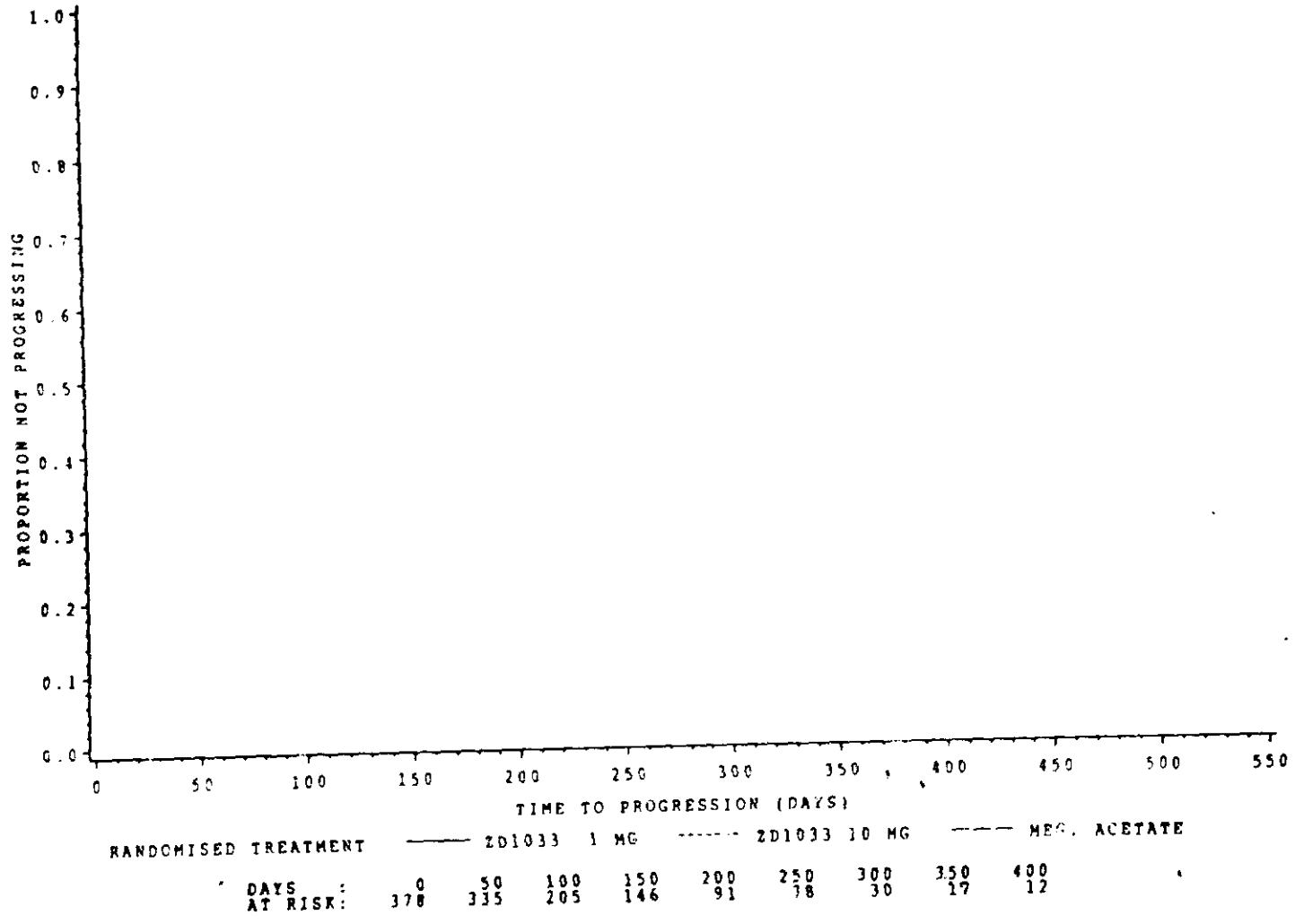


TABLE 26 Adverse events occurring in more than 5% of patients in any treatment group (Trial 0004)

Body system	COSTART-preferred term	Number of patients (%)		
		Anastrozole 1 mg (n = 128)	Anastrozole 10 mg (n = 129)	Megestrol acetate (n = 128)
Whole body	Abdominal pain	12 (9.4)	12 (9.3)	13 (10.2)
	Asthenia	35 (27.3)	27 (20.9)	41 (32.0)
	Back pain	20 (15.6)	21 (16.3)	14 (10.9)
	Chest pain	8 (6.3)	14 (10.9)	8 (6.3)
	Headache	22 (17.2)	33 (25.6)	16 (12.5)
	Pain	20 (15.6)	28 (21.7)	19 (14.8)
	Pelvic pain	9 (7.0)	13 (10.1)	10 (7.8)
Cardiovascular	Hot flushes	28 (21.9)	20 (15.5)	15 (11.7)
Digestive	Anorexia	13 (10.2)	15 (11.6)	7 (5.5)
	Constipation	14 (10.9)	15 (11.6)	15 (11.7)
	Diarrhea	16 (12.5)	13 (10.1)	5 (3.9)
	Dry mouth	12 (9.4)	6 (4.7)	9 (7.0)
	Nausea	25 (19.5)	32 (24.8)	21 (16.4)
	Vomiting	18 (14.1)	17 (13.2)	9 (7.0)
	Increased appetite	0 (0)	1 (0.8)	12 (9.4)
Metabolic and nutritional	Peripheral edema	12 (9.4)	10 (7.8)	16 (12.5)
	Weight gain	1 (0.8)	6 (4.7)	20 (15.6)
Musculoskeletal	Arthralgia	6 (4.7)	7 (5.4)	5 (3.9)
	Bone pain	14 (10.9)	22 (17.1)	13 (10.2)
	Myalgia	7 (5.5)	3 (2.3)	4 (3.1)
Nervous system	Depression	13 (10.2)	5 (3.9)	4 (3.1)
	Dizziness	9 (7.0)	7 (5.4)	12 (9.4)
	Hypertonia	8 (6.3)	4 (3.1)	7 (5.5)
	Insomnia	5 (3.9)	7 (5.4)	7 (5.5)
	Paresthesia	8 (6.3)	11 (8.5)	8 (6.3)
Respiratory system	Cough increased	14 (10.9)	13 (10.1)	10 (7.8)
	Dyspnea	17 (13.3)	19 (14.7)	31 (24.2)
	Pharyngitis	14 (10.9)	18 (14.0)	12 (9.4)
	Sinusitis	5 (3.9)	7 (5.4)	6 (4.7)
Skin and appendages	Alopecia	9 (7.0)	7 (5.4)	2 (1.6)
	Pruritus	8 (6.3)	6 (4.7)	5 (3.9)
	Rash	7 (5.5)	10 (7.8)	13 (10.2)
	Sweating	4 (3.1)	3 (2.3)	13 (10.2)

TABLE 28 Adverse events occurring in more than 5% of patients in any treatment group (Trial 0005)

Body System	COSTART-preferred term	Number of patients (%)		
		Anastrozole 1 mg (n = 134)	Anastrozole 10 mg (n = 117)	Megestrol acetate (n = 125)
Whole body	Aggravation reaction*	11 (8.2)	8 (6.8)	7 (5.6)
	Asthenia	7 (5.2)	6 (5.1)	6 (4.8)
	Back pain	8 (6.0)	5 (4.3)	5 (4.0)
	Headache	12 (9.0)	11 (9.4)	8 (6.4)
	Infection	2 (1.5)	6 (5.1)	7 (5.6)
	Pain	8 (6.0)	10 (8.5)	10 (8.0)
Cardiovascular	Hot flushes	4 (3.0)	6 (5.1)	6 (4.8)
	Hypertension	3 (2.2)	1 (0.9)	8 (6.4)
Digestive	GGT increased	3 (2.2)	7 (6.0)	4 (3.2)
	Nausea	16 (11.9)	16 (13.7)	7 (5.6)
	Vomiting	6 (4.5)	9 (7.7)	7 (5.6)
Hemic and lymphatic	Anemia	0 (0.0)	6 (5.1)	3 (2.4)
Metabolic and nutritional	Alkaline phosphatase increased	5 (3.7)	6 (5.1)	3 (2.4)
	Peripheral edema	2 (1.5)	11 (9.4)	12 (9.6)
	Weight gain	3 (2.2)	3 (2.6)	10 (8.0)
Musculoskeletal	Bone pain	3 (2.2)	7 (6.0)	6 (4.8)
Nervous system	Dizziness	7 (5.2)	5 (4.3)	3 (2.4)
	Somnolence	7 (5.2)	4 (3.4)	1 (0.8)
Respiratory system	Cough increased	8 (6.0)	5 (4.3)	9 (7.2)
	Dyspnea	7 (5.2)	8 (6.8)	22 (17.6)
Skin and appendages	Rash	8 (6.0)	5 (4.3)	6 (4.8)

* Exacerbation of any pre-existing condition
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms
GGT Gamma glutanyl transferase

(f) Conclusions

Anastrozole was found to be efficacious in the treatment of women with advanced breast cancer. There was no statistically significant difference between the effect of either anastrozole 1 mg daily or anastrozole 10 mg daily and megestrol acetate 40 mg four times daily on time to disease progression, objective response rate, or time to treatment failure. Approximately one third of patients in each treatment group had either an objective response (CR + PR) or stabilization of disease for greater than 24 weeks. These results are clinically significant given the disease and population being treated and consistent with what has been previously reported with megestrol acetate and aminoglutethimide.

The data are not yet mature enough to allow comparisons of overall survival.

There was no difference between either dose of anastrozole and megestrol acetate in the physical and functional dimensions of quality-of-life score. There were transient differences between treatments in other quality-of-life assessments; megestrol acetate was associated with

Statistical Review and Evaluation

DATE: DEC 4 1995

NDA#: 20 541

APPLICANT: Zeneca Pharm.

NAME OF DRUG: Arimidex (anastrozole) 1 mg Tablets

DOCUMENTS REVIEWED: Desk Copy Dated 09/22/95, Xeroxed Pages of Attachment G, pp. 187 304, and Two Diskettes.

I. Background

Dr. Sung K. Kim (HFD 150) requested the Division of Biometrics to review the sponsor's stability submission in support of a 30 months expiration dating period. He requested an analysis of the appearance information as the sponsor had not done one. The sponsor had provided all data on diskette in two different formats

II. Sponsor's Results

The sponsor's primary results were given in the 9/22/95 Desk Copy. The sponsor used the stability program of the Division of Biometrics to analyze active agent content, water content, and dissolution data obtained at storage temperatures of 25 and 30 degrees Celsius. The product was packaged into 30 and 100 count HDPE bottles and into PVC blister packs.

A total of four batches packaged into bottles were studied. The active ingredient data obtained at each of the two temperatures regressed only to individual lines. The estimated expiration dating periods ranged from 28 to 72 months. The lone estimated expiration dating period below 30 months was from batch 9112N stored at 25 degrees C in 100 count bottles. This batch, as do two others, had only 12 months data. Only batch PH/7862/88 has 18 months stability data Three of the four batches were also packaged into PVC blister packs. These data also regressed to individual lines and estimated expiration dating periods of at least 38 months.

The sponsor analyzed the water content only for the product stored in bottles. With an upper limit of 7.0% w/w the data estimated extrapolated expiration dating periods of at least 45 months

The dissolution data were also analyzed for only the bottled product. These data estimated that the product can be expected to show at least 80% dissolution at 30 minutes for at least 71 months.

In Attachment G the sponsor presents the individual data for the primary, the supporting and the bulk tablet studies as well as a discussion of the data. This discussion is based on fewer observations then the findings above and is therefore superceded.

III. Reviewer's Results

The sponsor used the Division of Biometrics stability program in his analyses. He provided the data on two diskettes. This reviewer used the set of four batches packaged into 30 count bottles and stored at 25 degrees Celsius for up to 18 months for verification of the sponsor's results. Her findings were identical to those of the sponsor and she therefore accepted his findings on the active ingredient, the water content and the dissolution results submitted in the 9/22/95 submission. The single low expiration dating estimate of 28 months is based on one of the batches with 12 months actual data. If the product's current degradation pattern does not change materially this batch may be expected to estimate improved expiration dating periods as more data become available.

The sponsor analyzed the water content for only the bottled product. These data estimated an extrapolated expiration dating period of at least 45 months. This reviewer also analyzed the water content of the PVC blister packs. When stored at 25 degrees C the data support an extrapolated expiration dating period of 41 months. The data obtained at 30 degrees C are very sparse; three data points for batch 7862/88 and two data points each for batches 9093N and 9111N. This data set estimated expiration dating periods of 26 to 33 months.

The dissolution results were obtained at 30 minutes. The bottled data estimated at least 71 months of expiration dating period when the product was stored at 25 or at 30 degrees Celsius. This reviewer also analyzed the dissolution data of the PVC blister packs. Whether stored at 25 degrees C or at 30 degrees C the data

estimated an extrapolated expiration dating period of at 72 months.

Dr. Kim also requested an analysis of the appearance data. This measurement was coded as NT=not tested, NC=no change, SD=slight darkening, and YD=yellow discoloration. These measurements do not lend themselves to numeric coding and therefore not to any statistical analysis. The slight darkening of some tablets which was observed occasionally cannot be interpreted statistically and no expiration dating period can be set based on these observations.

IV Summary and Conclusion

The primary stability data for this product are four batches bottled into 30 and 100 HDPE bottles. One batch was stored for 18 months, the other three for 12 months. The sponsor analyzed the active ingredient, dissolution, and water content data obtained at 25 and at 30 degrees Celsius. The shortest estimated expiration dating period was 28 months based on the active ingredient data of batch 9112N when stored at 25 degrees C for 12 months in 100 count bottles. As all other batches estimated extrapolated expiration dating periods over 30 months, it may be expected from a statistical point of view that this batch will also estimated a longer expiration dating period as more data become available. However, at this point the statistics support only a 28 months expiration dating period for the active ingredient of the bottled product.

The data from water content and from dissolution estimated extrapolated expiraton dating periods well beyond the requested 30 months for the product packaged into bottles.

There was also stability data of three of the batches packaged in PVC blister packs listed by the sponsor as supporting evidence. The extrapolated estimated expiration dating period based on the data of the active ingredient is at least 38 months. Water content was not analyzed by the sponsor. This reviewer's analyses calculated estimated expiration dating periods of 41 months when stored at 25 degrees C and of only 26-33 months when stored at 30 degrees C. For the later estimates the data were very sparse and are therefore not very reliable The dissolution data of the PVC blister packs estimated an extrapolated expiration dating period of 72 months.

As mentioned above, the appearance data cannot be coded numerically in a rational way and are therefore not ameanable to statistical analysis.

Roswitha E. Kelly

Concur: 12/4/95

George Chi, Ph.D.

cc: Archival NDA 20-541 Arimidex (anastrozole) 1 mg Tablets
HFD-701/Dr. Anello
HFD-150/Dr. De Lap
HFD-150/Dr. Wood
HFD-150/Dr. Kim
HFD-710/Chron
HFD-710/Dr. G. Chi
HFD-710/R. Kelly
HFD-710/RKELLY/11/22/95/wp-arimidex.rev

Bio

DEC 8

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-541 Submission Dates: December 6, 1995

Drug Name, Dose and Formulation: Arimidex® (Anastrozole, ZD1033) Tablets, 1 mg

Sponsor: Zeneca Pharmaceuticals, Wilmington, Delaware 19897

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: Response to comment

INTRODUCTION:

In the Biopharmaceutics' review of the Arimidex NDA, the Human Pharmacokinetics and Biopharmaceutics portion of the application was found acceptable. In the review, several comments were made and sent to the sponsor. Comment #4 specifically requests the sponsor to provide information on patient compliance to cimetidine in study # 0013. This was a drug interaction study to study the effect of cimetidine on pharmacokinetics of arimidex. Subjects took the cimetidine therapy at home. Since plasma levels of cimetidine were not determined, there was a question of compliance monitoring for cimetidine. Note that this study results showed no drug interaction between cimetidine and arimidex. The study was carried out in 12 post menopausal female volunteers. Assuming that all patients were compliant, there is no safety concern with co-administration of cimetidine and arimidex. However, patient compliance is in question and needs to be addressed before a statement of no drug interaction can be placed in arimidex label.

SPONSOR'S RESPONSE:

Monitoring of patient compliance was done through drug accountability. On day 19, the subjects were given cimetidine to cover the dosing for days 20 to 23. Cimetidine was packaged in separate bottles for each day. Each subject also was given an extra bottle of spare tablets (4 cimetidine tablets). When the subjects reported to the clinical research center on day 23, the bottles were returned and the tablet counts were recorded on case report forms.

REVIEWER'S COMMENTS:

The sponsor's drug accountability information is useful to address the question of patient compliance to some extent. However, at least a single plasma level of cimetidine would have been useful to determine levels of cimetidine at the end of cimetidine therapy. Assuming patients' compliance to cimetidine, there is no safety concern. However, in order to have a 'no drug interaction with cimetidine statement on arimidex label', more definitive study will be necessary. Such a study is not required, however, sponsor can choose to do the study to make a claim on the label. If the sponsor still has blood samples from study # 0013, plasma levels of cimetidine can be determined and submitted for agency's review.

RECOMMENDATION:

Sponsor's response to comment #4 of Biopharmaceutics' review has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The statement regarding no drug interaction between cimetidine and arimidex should be removed from the label at this time. Please forward the above comments to the sponsor.

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation - II

FT Initialed by Atik Rahman, Ph.D. 12/8/95

CC list:

HFD-150: NDA 20-541;
HFD-150: Division file;
HFD-150: CSO\Leslie Vaccari;
HFD-150: Medical Reviewer\Julie Beitz;
HFD-860: Biopharm\Atik Rahman;
HFD-870: Biopharm\Dale Conner;
HFD-870: Biopharm\John Hunt;
HFD-870: Biopharm\Mei Ling Chen;
HFD-860: Biopharm\Hank Malinowski;
HFD-880: Biopharm\Nick Fleischer;
HFD-850: Biopharm\Larry Lesko;
HFD-850: Biopharm\Chron;
HFD-850: Biopharm\Drug;
HFD-850: Biopharm\Venkata Ramana S. Uppoor;
HFD-340: Viswanathan;
HFD-205: FOI.

DEC 8 1995

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-541 Submission Dates: October 19, 1995
November 16, 1995

Drug Name, Dose and Formulation: Arimidex® (Anastrozole, ZD1033) Tablets, 1 mg

Sponsor: Zeneca Pharmaceuticals, Wilmington, Delaware 19897

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: Revised labeling

INTRODUCTION:

In the Biopharmaceutics' review of the Arimidex NDA, the Human Pharmacokinetics and Biopharmaceutics portion of the application was found to be acceptable. The reviewer's labeling comments were faxed to the sponsor by the CSO on October 4, 1995. A revised label (revision of the Pharmacokinetics portion of the label) was faxed to the agency by the sponsor on October 20, 1995 (letter date: October 19, 1995) and was provided on computer diskette on November 16, 1995.

In the attached label, the sponsor-provided revised draft label is modified to show the recommendations from this reviewer. Deletions from the sponsor's draft are marked with a ~~strikeout~~ while additions are in redline (appears as shadow upon printing).

COMMENTS:

1. In table 1, the sponsor should include C_{max} information following single dose in females and also multiple dose data in female volunteers and patients with advanced breast cancer ($t_{1/2}$ and $C_{SS(min)}$).

2. The sponsor should address comment #4 of Biopharmaceutics' review. The comment deals with patient compliance to cimetidine in the drug interaction study of cimetidine and arimidex (study # 0013) before the statement '*Administration of cimetidine had no effect on anastrozole pharmacokinetics*' can be placed in the label.

3. The sponsor should modify the label appropriately to incorporate the additions and deletions suggested by the reviewer (see attached label).

RECOMMENDATION:

This draft label has been reviewed by the Office of Clinical Pharmacology and

Biopharmaceutics and has been found to be acceptable provided the comments made in the label are addressed by the sponsor. Please forward the modified draft label and above comments to the sponsor at an appropriate time.

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation - II

FT Initialed by Atik Rahman, Ph.D. 12/8/95

CC list:

HFD-150: NDA 20-541;
HFD-150: Division file;
HFD-150: CSO\Leslie Vaccari;
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HFD-850: Biopharm\Larry Lesko;
HFD-850: Biopharm\Chron;
HFD-850: Biopharm\Drug;
HFD-850: Biopharm\Venkata Ramana S. Uppoor;
HFD-340: Viswanathan;
HFD-205: FOI.

SEP 2 8 1995 SEP 28 1995

BIOPHARMACEUTICS / PHARMACOKINETICS' REVIEW

NDA 20-541 Submission Dates: March 28, 1995
May 3, 1995
June 30, 1995

Drug Name, Dose and Formulation: Arimidex® (Anastrozole, ZD1033) Tablets, 1 mg

Sponsor: Zeneca Pharmaceuticals, Wilmington, Delaware 19897

Reviewer: Venkata Ramana K. Sista, Ph.D.

Type of Submission: New Drug Application, NME, 1S

SYNOPSIS: Arimidex, a new aromatase inhibitor is developed by the sponsor as a treatment of advanced breast cancer in postmenopausal women who have progressed following tamoxifen therapy. This drug inhibits the formation of estrogen and produces beneficial effect in women with breast cancer by reducing serum oestradiol concentrations. The proposed dose of Arimidex is one 1 mg tablet to be taken once a day. The NDA contains several pharmacokinetic (17 in vivo studies including 3 clinical studies) studies. Two dose strengths 1 and 10 mg were studied during the drug development process, however only the 1 mg tablet strength is proposed for marketing.

15 in-vivo studies and 4 in-vitro studies have been reviewed. Two studies have not been reviewed because those doses and formulations were not relevant to the ones used in the study and / or proposed for marketing.

The sponsor has adequately validated the gas chromatographic assay for arimidex. The sponsor also adequately characterized the pharmacokinetics (single and multiple dose) of arimidex in healthy volunteers, hepatically impaired patients and renally impaired patients. Pharmacokinetics were also studied in advanced breast cancer patients. Effect of age and gender although not studied as a specific study; comparisons across study were made. Metabolic enzymes (cytochrome P450 isozymes) responsible for arimidex metabolism have not been identified. About 75% of the arimidex dose administered is excreted in urine (mostly as metabolites) and about 10% in feces. About 5 - 10% of unchanged drug is found in urine. Arimidex is metabolized by N-dealkylation, hydroxylation and direct glucuronidation. All metabolites of arimidex found in human plasma and urine were found to be inactive. Arimidex is highly soluble in water, which helps explain almost 100% bioavailability of arimidex relative to oral solution. Absolute bioavailability information on the tablets is not available. Arimidex is absorbed rapidly with a t_{max} of about 1 - 2 hours. The drug has a long half-life of about 40 hours in males and about 45 - 50 hours in postmenopausal females. It is moderately protein bound (40%). The pharmacokinetics of arimidex appear to be linear over a dose range of mg studied in the dose escalation study. Dose-proportionality is clear with respect to AUC and C_{max} which was seen in the dose range of mg in a single study. At steady state, plasma concentrations of arimidex increased 3 - 4 fold as compared to single dose. Intrasubject variability in arimidex pharmacokinetics was found to be less than 5% for AUC and less than 10% for C_{max}, Cl/F and $t_{1/2}$. Food decreased the C_{max} of arimidex by 16% and delayed the absorption with an increase

in T_{max} to 5 hours. In severe hepatic impairment, arimidex AUC and C_{max} increased by % following administration of 10 mg single dose. In renal impairment, there was no change in apparent total body clearance, however, mean renal clearance was approximately 50% lower in renally impaired patients following administration of single dose of 10 mg of arimidex. Pharmacokinetics of arimidex were similar in advanced breast cancer patients and normal volunteers. The PK-PD relationship of arimidex has not been studied by the sponsor. However, PK and PD data across several groups correlated to the pharmacodynamic marker (% oestradiol suppression) using a sigmoid E_{max} model.

Several doses were tested during arimidex drug development. However, 1 mg is the dose that has been selected for use. The to-be marketed formulation is different from the tablet used in both biostudies and clinical studies. This to-be marketed formulation has been linked to the clinical formulation with a bioequivalence study. These 2 formulations (to-be marketed and clinical formulation) are bioequivalent to each other (C.I. on AUC = 88-100%, C.I. on C_{max} = 97-123%). Several pharmacokinetic studies were conducted using the 10 mg tablets and not with 1 mg tablet. However, since the dose has been reduced to 1 mg, these studies are adequate to address the safety concerns.

When administered concomitantly with arimidex, no notable changes in clearance of antipyrine were observed. Administration of cimetidine with arimidex did not result in any changes in pharmacokinetics of arimidex. In vitro inhibition studies carried out using human liver microsomes indicate that arimidex inhibits metabolic reactions catalyzed by cytochrome P450 1A2, 2C8/9 and 3A4 with Ki values which are approximately 30 fold higher than expected steady state plasma concentrations following 1 mg dose.

RECOMMENDATION: The present submission (NDA 20-541) has been reviewed by the Division of Biopharmaceutics. The submission is acceptable provided that labeling comments # 1 - 4 and comment # 4 are adequately addressed by the sponsor. The dissolution specifications set by the agency as provided in comment # 3 should be used.

TABLE OF CONTENTS:

IN VITRO STUDIES

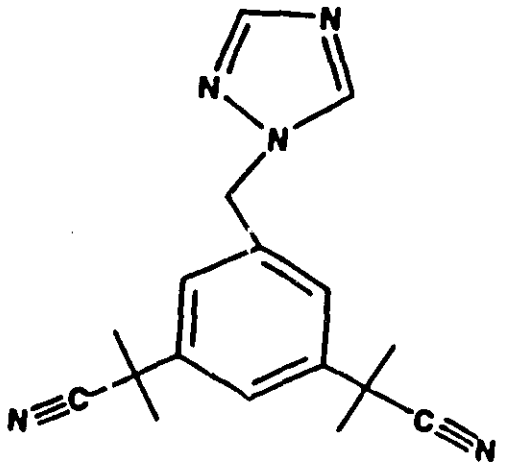
I. BACKGROUND

Arimidex® Tablet contains anastrozole (ZD1033) which is a nonsteroidal aromatase inhibitor. This drug is a triazole derivative, is achiral and exists as a single polymorph. The aromatase enzyme complex catalyses the synthesis of estrogens from androgens. Since estrogens promote growth of certain breast tumors, inhibition of estrogen synthesis by aromatase enzyme inhibition is an effective treatment for hormone-dependent breast cancer. The sponsor has proposed to market the Arimidex tablets at a dose strength of 1 mg. The proposed indication for Arimidex is for the treatment of advanced breast cancer in postmenopausal women who have progressed following tamoxifen therapy. The proposed dose is 1 mg tablet to be taken once a day. Arimidex tablet is a white film coated biconvex tablet.

The sponsor met with the agency on 08/11/1994 (pre-NDA meeting) where various issues and aspects to be included in the NDA were identified.

STRUCTURE OF DRUG ENTITY: Arimidex is chemically 2,2'[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropiononitrile) with a molecular weight of 293.4. Arimidex is achiral with the structure shown in figure below.

FIGURE 1:



SOLUBILITY CHARACTERISTICS: Arimidex is moderately soluble in water (0.53 mg/ml at 25°C). The solubility of arimidex is independent of pH.

II. FORMULATION: During the course of drug development, the sponsor changed formulations after clinical studies. The to-be marketed tablet formulation has not been studied in pivotal clinical studies. It has been linked to the clinical tablet through a bioequivalence study. The details of the final tablet formulation and the clinical tablet formulation are given below.

ARIMIDEX FINAL AND CLINICAL TABLET FORMULATION

Table (1)

INGREDIENT	Clinical tablet mg/tablet	To-be marketed tablet, mg/tablet
Arimidex (anastrozole) Lactose Povidone Sodium starch glycolate Magnesium stearate	1.0	1.0
COATING Hydroxypropylmethylcellulose Polyethylene glycol 300 Titanium dioxide		

III. . STUDIES THAT WERE NOT REVIEWED

Several studies have been submitted as part of the NDA, however, studies that are not pivotal will not be included in this review. List of studies not reviewed with reasons are provided below.

1. Bioequivalence study comparing the 10 mg clinical tablet to the 10 mg to-be marketed tablet: This study was not reviewed because the sponsor dropped their plan of developing the 10 mg tablet.
2. Bioequivalence study on Zeneca reprocessed Megestrol acetate capsule and Bristol Myers Squibb MEGACE tablet: This study was not reviewed as the reprocessed capsule was not used in any study and this BE study does not have any impact on any study carried out during the drug development process of Arimidex. This was confirmed upon discussion with the medical reviewer. The active control used in pivotal clinical trial is MEGACE tablet and not the reprocessed capsule.

IV. PHARMACOKINETICS:

The summary of pharmacokinetics of the drug obtained from tablets (including 1 and 10 mg) is provided here.

a. ABSOLUTE BIOAVAILABILITY (and RELATIVE BIOAVAILABILITY): Pharmacokinetics of the drug have not been determined following intravenous route of administration. Hence, information on absolute bioavailability is not available. However, information from mass balance study where radiolabeled drug was administered indicates that at least 75% of administered drug crossed the gastrointestinal barrier. Information on relative bioavailability can be obtained from food effect and relative bioavailability study where a solution arm was included. It was found that bioavailability of the tablets relative to solution was 100% based on AUC and C_{max} (study # 0011).

b. ABSORPTION: Following oral doses up to 60 mg (either via single or multiple administration) in healthy volunteers, arimidex was absorbed rapidly. The mean T_{max} across all formulations ranged from hours. Mean C_{max} following 1 mg single dose in postmenopausal female volunteers ranged from ng/ml. $AUC_{0-\infty}$ could not be calculated for 1 mg single dose because of assay limitations in terminal phase. $AUC_{0-\infty}$ at 10 mg single dose ranged from ng.hr/ml in postmenopausal female volunteers. Plasma concentrations were at least 3-fold higher at steady state compared to single dose. Absolute bioavailability was not determined during the drug development process. Relative to oral solution, the estimated bioavailability of the 10 mg arimidex tablet formulation is about 100%. Intrasubject variability in ZD1033 pharmacokinetics was found to be less than 5% for AUC and less than 10% for C_{max}, Cl/F and $t_{1/2}$.

c. DISTRIBUTION: **Apparent steady state volume of distribution** of arimidex (Vd_{ss}/F) obtained by modeling methods was found to be in the range of L (mean 74.3 L).
Plasma protein binding: Arimidex is 40% bound to plasma proteins as shown by determination of protein binding in-vitro by ultrafiltration technique at concentrations of µg/ml. Arimidex binds to both albumin and α_1-acid glycoprotein.

d. ELIMINATION (METABOLISM AND EXCRETION):

Terminal phase half-life: Half-life of arimidex is approximately 50 hours in postmenopausal female volunteers. Mean Cl/F was found to be 19 ml/min.
Metabolism: Arimidex is highly metabolized as indicated by about 9% unchanged drug found in urine upon oral administration. Arimidex is metabolized by N-dealkylation, hydroxylation and glucuronidation. Major metabolites of arimidex are triazole, ZD1033 glucuronide and hydroxy ZD1033 glucuronide. None of these metabolites are active.

Enzymes responsible for metabolism of arimidex have not been identified. In vitro studies to characterize cytochrome P450 isozymes responsible for metabolism were stopped because of difficulties in conducting the study due to long half-life of the drug. Based on the results from the radiolabeled study (mass-balance study), the metabolic pathway for arimidex in humans and preclinical species is shown below:

IMPN – 3,5-bis -(2-methyl-propiononitrile)

Excretion: Upon administration of 10 mg single oral dose of radiolabeled arimidex, mean cumulative urinary and fecal recoveries of total radioactivity were 74.6 and 8.7% respectively after administration of ^{14}C-triazole-ZD1033, and were 71.2 and 13.6% after administration of ^{14}C-cyano-ZD1033. About 5% of unchanged drug was found in urine. This indicates that most of arimidex is renally excreted as metabolites.

e. DOSE PROPORTIONALITY: When studied at four dose levels of 1, 5, 10 and 20 mg arimidex administered as tablets of different strengths, the dispositional pharmacokinetics are linear. Linearity in AUCs could be determined only at doses of 5, 10 and 20 mg since AUC could not be estimated due to assay limitations at 1 mg dose. AUCs and C_{max}s were dose-proportional (AUC = ng-hr/ml and C_{max} = ng/ml at 5, 10 and 20 mg dose levels respectively). This data indicates that total plasma clearance, half-life and bioavailability (or at least Cl/F) are dose-independent.

f. FOOD EFFECT: Food decreased arimidex C_{max} by 16% (statistically significant difference) and had no effect on AUC when arimidex 10 mg tablet formulation was administered within 0.5 hours after high fat breakfast. Food also delayed the absorption of arimidex, the median t_{max} increased from 2.0 (fasting) to 5.0 (fed state) hours. The 90% confidence interval for ratio of C_{max} between fed and fasted was within the 80 - 125% range (%). Hence food is unlikely to have a significant effect on plasma concentrations of the drug. However, note that the food effect study was not conducted on the 1 mg final tablet. The results obtained with the 10 mg tablet provide comfort since there was no food effect on this product studied. Also, the two tablet strengths (1 and 10 mg) when studied in the dose proportionality study were found to be dose proportional. These results indicate no food effect on safety and efficacy.

g. SPECIAL POPULATIONS:

Age: No specific studies to study the effect of age on pharmacokinetics of arimidex were carried out. Since the clinical pharmacokinetic trials were conducted in postmenopausal volunteers or patients of age >50 years, no separate trial to evaluate the PK in elderly is necessary. Age-related effects when analyzed by stratification of C_{min} data from the clinical trial showed that C_{min} values were comparable across the age groups (<50, 50-65, 65-80 and >80 years) and did not indicate any age-related effects on pharmacokinetics.

Gender: This drug is specifically indicated for postmenopausal females and hence specific studies to evaluate gender effect were not carried out. However, comparison across studies indicate that mean ZD1033 C_{max} values were slightly higher in females (144 - 225 ng/ml) than in males (124 - 155 ng/ml) after 10 mg single dose. Half life also appears to be longer in females (41-53 hours) compared to males (30 - 47 hours). These results indicate that clearance of ZD1033 is higher in men than in women.

Hepatic impairment: Pharmacokinetics of arimidex was studied after administration of 10 mg single dose to subjects with normal hepatic function and patients with stable hepatic cirrhosis. Mean C_{max} and AUC were approximately 25 - 30% higher in volunteers with hepatic cirrhosis than in the control group. Similar results were observed in patients with hepatic impairment having higher levels of ZD1033. Since higher AUC and C_{max} are observed, patients with hepatic impairment should be more closely monitored. Dose-adjustment may not be necessary as these levels seemed to be well tolerated and found to be safe.

Renal impairment: This study was carried out in subjects with normal renal function and in subjects with renal impairment (Cl_{Cr} < 30 ml/min). Mean C_{max} and AUC decreased by 17 and 7% in renal impairment. The mean renal clearance was about 50% lower in renally impaired patients. Despite this effect on renal clearance, there was no effect on total clearance (Cl/F) of ZD1033. Therefore, dose adjustment in renal insufficiency does not appear to be necessary. Subjects with mild and moderate impairment were to be studied as phase II only if significant effects in severe impairment were seen.

PK in patients: Pharmacokinetics of arimidex in healthy volunteers were found to be similar in patients with advanced breast cancer. Dose proportionality in pharmacokinetics of ZD1033 in patients was consistent with results from normal volunteers.

h. BIOEQUIVALENCE BETWEEN FORMULATIONS. All the studies (bio and clinical studies) evaluated the tablet formulation which was different from the to-be marketed formulation in that microcrystalline cellulose was removed in the to-be marketed tablet. These 2 tablets were linked via a bioequivalence study. 1 mg clinical tablet and the to-be marketed tablet are bioequivalent to each other. The 90% confidence interval for C_{max} was and for AUC was

V. DISSOLUTION: The proposed dissolution method for the arimidex tablet formulation is USP method II (paddle method) at a paddle speed of 50 rpm. The medium is 900 ml water at 37°C. The sponsor has proposed a dissolution specification of Q minutes. The dissolution data indicate that this is a highly soluble drug with a fast dissolution rate. Based on the dissolution data provided, the specification should be set at Q minutes. The dissolution method is acceptable.

VI. PHARMACODYNAMICS:

PK-PD: No specific attempts were made by the sponsor to develop a relationship between pharmacokinetics of ZD1033 and oestradiol suppression. At the proposed dose of 1 mg, oestradiol levels were reduced by about 70% within 24 hours and about 80% after 14 days of daily dosing. No significant effects of ZD1033 administration on cortisol and aldosterone secretion were observed. With the existing data from a parallel study, when attempts were made (by the reviewer), it was found that the PK (of ZD1033) - PD (% decrease in oestradiol) data fits to a sigmoid E_{max} model.

VII. DRUG INTERACTIONS:

Preclinical studies indicate that ZD1033 causes induction and inhibition of metabolism at doses of 20 - 60 mg (dose to humans). Results from studies described below confirm this in that at proposed dose of 1 mg, inhibition and induction are not seen, however, such a potential exists at higher doses.

a. In-vitro inhibition studies in human liver microsomes: These studies indicate that ZD1033 did not inhibit reactions catalyzed by human cytochrome P450 2A6 and 2D6. ZD1033 inhibited cytochrome P450 1A2, 2C8/9 and 3A4 with Ki values of 8, 10 and 10 μM (2.3, 2.9 and 2.9 μg/ml). These Ki values are at least 30 fold higher than the predicted steady state C_{max} concentrations (80 ng/ml) following 1 mg doses in breast cancer patients. Although based on the results, ZD1033 is a potent inhibitor, the proposed dose of arimidex is low (1 mg) and this may not result in any inhibition of clearance of drugs metabolized by these enzymes. Results of these studies also indicate that ZD1033 is less likely to produce drug interactions via inhibition of cytochrome P450 than ketoconazole or cimetidine (based on IC_{50} and achievable plasma concentrations at doses normally used).

b. In-vivo drug interaction studies:

Antipyrine: When antipyrine (500 mg i.v.) was co-administered with arimidex (single 30 mg dose and multiple 10 mg doses), no significant change in antipyrine clearance was observed. A 10% decrease in mean antipyrine clearance values after single dose ZD1033 and a 1.2% increase during the multiple dose was observed. No evidence for either inhibitory or inductive effect of ZD1033 on formation or clearance of antipyrine metabolites and clearance of antipyrine was seen.

Cimetidine: When arimidex (10 mg single dose) was administered after multiple dose of cimetidine (300 mg 4 times daily, 17 doses), no significant effects on pharmacokinetics of ZD1033 were seen. This indicates that cimetidine does not effect the pharmacokinetics of ZD1033. Effect of ZD1033 on cimetidine has not been evaluated in this study. Also, since cimetidine was taken by the subjects at home for 4 days (not in clinic), there is no way of knowing whether the subjects complied with taking the medication. Hence, these results although very positive, should be used with caution.

(10)

COMMENTS:

1. This NDA has been compiled well in terms of all the studies and flow of the material. Sponsor also provided information on dissolution and analytical data in a timely manner upon request from the reviewer.

2. In future submissions, the sponsor should attempt PK-PD model using the efficacy end-point as the PD measure. The sponsor is encouraged to provide this information in the NDA.

3. The dissolution method is acceptable. Based on the dissolution data provided, the specification should be set at Q % in minutes.

4. In the interaction study of ZD1033 with cimetidine, how was patient compliance to cimetidine monitored (note that cimetidine was taken by patients at home during the multiple dosing period)? The sponsor should provide this information in order for the study results to be valuable.

LABELING COMMENTS:

1. The sponsor should modify and submit the *Pharmacokinetics* section of the label as per the format recommended by Division of Biopharmaceutics. The CSO should forward this to the sponsor at appropriate time.

2. Please remove the following part of the sentence (in italics) from page 2 of the proposed label under food effect, '*and does not affect the plasma concentrations achieved at steady state*' since although conceivable, it is not supported by data.

3. In dosage recommendation for hepatic impairment, results of the study in hepatically impaired subjects should be included and suggestion for careful monitoring should be made since higher levels were observed in these subjects.

4. The label should also include information on intrasubject variability in pharmacokinetics of the drug.

08/22/95 (Biopharm. day 0 package)

Venkata Ramana K. Sista, Ph.D.
Pharmacokinetic Evaluation Branch I

Biopharm. Day 9/27/95 (Malinowski, Collins J, Fleischer N, Mei Ling Chen, Mehta M).

09/28/95 (Final review)

RD initialed by Mehul U. Mehta, Ph.D. 8/23/95
FT initialed by Mehul U. Mehta, Ph.D. 9/28/95

cc: HFD-150: NDA 20-541; HFD-150: Division file; HFD-150: Jbeitz; HFD-426: Nfleischer; HFD-426: Mmehta; HFD-426: Mchen; HFD-426: Chron; HFD-426: Drug; HFD-426: Reviewer (VRKSista); HFD-340: Viswanathan; HFD-19: FOI.

APPENDIX I

STUDY D1033IL/0010 & D1033IL/0020: (MASS BALANCE STUDIES)

STUDIES (2) TO ASSESS THE METABOLISM, EXCRETION AND PHARMACOKINETICS OF A SINGLE ORAL DOSE OF 10 MG [^{14}C]-ZENECA ZD1033 (ANASTROZOLE) IN HEALTHY, POST-MENOPAUSAL FEMALE VOLUNTEERS

Reference: Volumes 35 and 36
Investigator:
Study Location:

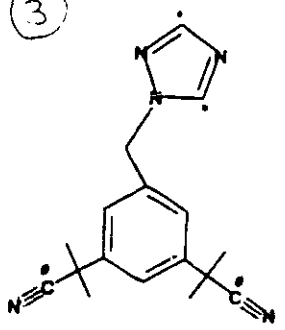
Objective:

To assess the metabolism, excretion and pharmacokinetics of a single oral dose of 10 mg [^{14}C]-Zeneca ZD1033 in healthy post-menopausal female volunteers.

Radiolabeled Forms:

^{14}C-ZD1033 given as 10 mg capsules filled with homogeneous powder of radiolabeled anastrozole containing 35 µCi of radioactivity. In the first study, the ^{14}C was on the triazole ring, while in the second study, the radiolabel was on the cyano group, as shown in the structure on the right:

Figure (3)



Study Design:

These were two open-label, non-randomized, single dose studies of the metabolism of ZD1033 radiolabeled with ^{14}C in either the triazole or cyano part of the molecule. 7 post-menopausal female volunteers of age 45 - 65 years participated in the study (only 6 completed the study). Three of the subjects received the first radiolabeled form and the other 3 received the 2nd form. After an overnight fast, subjects received one 10 mg capsule of the radiolabeled drug. Blood was drawn at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 192, 240, 288 and 336 hours after dosing for determination of plasma concentration of the drug and radioactivity in plasma. Urine and feces were collected at intervals upto 336 hours after dosing and radioactivity determined.

DETERMINATION OF TOTAL RADIOACTIVITY:

METABOLITE PROFILING, ISOLATION AND IDENTIFICATION: Carried out at

Metabolite profiling was done in plasma and urine by chromatographic and mass spectrometric technics.

Data Analysis:

Statistical analysis was limited to calculation of mean and standard deviation values of plasma concentrations of drug and radioactivity.

Results:

Recovery of radioactivity in urine and feces between 0 and 336 hours following administration

of the radiolabeled doses is shown in the table below. Approximately 75% of dose was eliminated in urine and about 10% in feces.

Table (2)

Label	Percentage (SD) of administered radioactivity		
	Urine	Feces	Total
[^{14}C]-triazole ZD1033	74.6 (8.9)	8.7 (1.6)	83.3 (10.3)
[^{14}C]-cyano ZD1033	71.2 (7.7)	13.6 (4.1)	84.8 (9.1)

Metabolites in plasma: Major plasma metabolites were (ZD1033 glucuronide). Upto 24 hours, ZD1033 was the most abundant component in plasma. By 72 hours, amounts of increased to levels approximately equal to ZD1033 and represented about 40% of the radioactivity present.

Metaboiites in urine: Table below shows the amounts of ZD1033 and radiolabeled metabolites in pooled urine upto 72 hours after dosing. Unchanged drug constituted about 5 - 6% of the administered radioactivity.

Table (3)

Profile of 0 to 72 hour urine pools

Compound	Percent of administered dose (SD)			
	Study 1033IL/0010 [14C]-triazole ZD1033		Study 1033IL/0020 [14C]-cyano ZD1033	
M2 (triazole)	8.4	(1.7)	ND	
M3*	1.2	(0.2)	1.0	(0.7)
M4 (hydroxy ZD1033 glucuronide)	12.1	(2.8)	17.5	(6.6)
M14 (ZD1033 glucuronide)	8.7	(2.2)	15.7	(4.7)
M9* (hydroxy ZD1033)	0.7	(0.1)	1.9	(0.6)
M15*	0.3	(0.1)	0.4	(0.2)
ZD1033	5.4	(2.2)	6.4	(2.2)
Total	36.7		45.2	
Total % dose in collection interval	39.0	(4.9)	46.8	(7.2)

* Less than 5% of the administered dose
ND = not detected

The proposed metabolic pathway for ZD1033 is shown in the figure below:

Figure 4

Hydroxy-ZD1033 glucuronide (M4)

Parent ZD1033 and total radioactivity in blood and plasma: These are presented in the following two figures:

Figure 5

Mean plasma ZD1033 concentrations and plasma and whole blood radioactivity concentrations after administration of [^{14}C]-triazole ZD1033

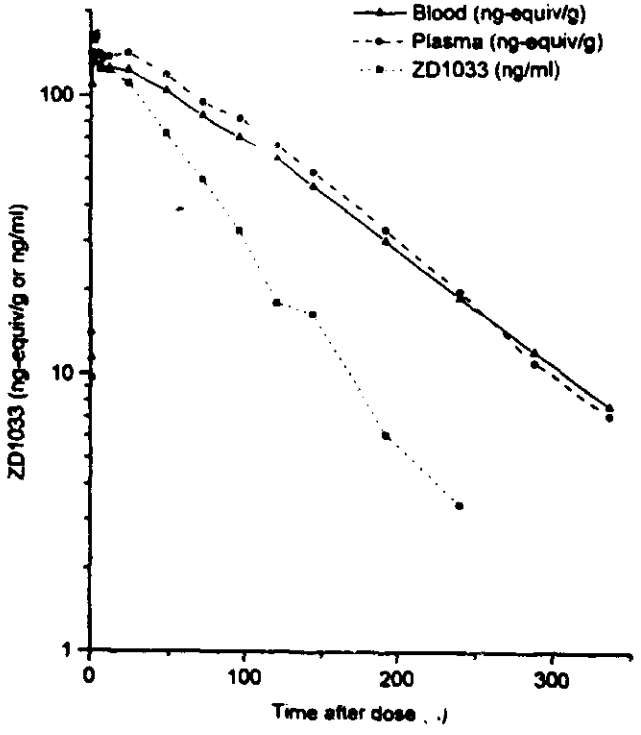
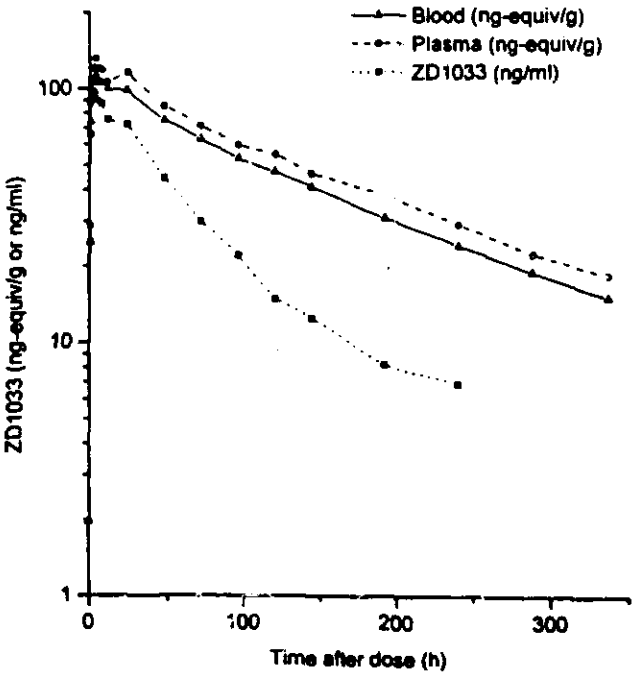


Figure 6

***Mean plasma* ZD1033 concentrations and plasma and whole blood radioactivity concentrations after administration of [^{14}C]-cyano ZD1033**



Summary of the pharmacokinetic parameters is shown in the table below:

Table (4)

Parameter	Radioactivity in Blood		Radioactivity in Plasma		ZD1033 in Plasma	
	Mean	SD	Mean	SD	Mean	SD
[14C]-triazole ZD1033						
C_{max}*	140	16	168	21	172	13
T_{max} (h)	2.3	0.6	3.3	1.2	3.7	0.6
$AUC_{0-\infty}$#	17600+	2900	19500+	3000	9549	920
t1/2 (h)	71.8	10.3	62.9	7.8	40.2	3.1
CL/F	NC		NC		17.6	1.7
[14C]-cyano ZD1033)						
C_{max}*	114	8	131	14	106	11
T_{max} (h)	3.7	0.6	3.7	0.6	3.0	1.0
$AUC_{0-\infty}$#	17600+	3300	20800+	3700	6517	1394
t1/2 (h)	132	35	138	35	50.0	20.3
CL/F	NC		NC		26.6	5.9

* C_{max} as ng-equiv/g for radioactivity and ng/ml for ZD1033
\# $AUC_{0-\infty}$ as ng-equiv.h/g for radioactivity and ng.h/ml for ZD1033
\+ $AUC_{0-\infty}$ values must be interpreted with caution, see Section 2.9
NC not calculated
SD standard deviation

ASSAY PERFORMANCE:

STUDY 0010:

Method: AD SOP 2.103
Range: ng/ml
Linearity: Linear within the range
QC sample levels: 3, 30 and 80 ng/ml
Precision: 27.4 % at 3 ng/ml, 3.8% at 30 ng/ml and 8.8% at 80 ng/ml
Accuracy: -12.5% at 3 ng/ml, 4.1% at 30 ng/ml and 15.2% at 80 ng/ml
Specificity: Chromatograms acceptable
Assay was found to be acceptable.

STUDY 0020:

Method: AD SOP 2.103
Range: ng/ml
Linearity: Linear in the range
QC sample levels: 3, 30 and 80 ng/ml
Precision: 6.9%, 6.2% and 7.2% at the 3 QC levels
Accuracy: -19.2%, -8.3%, -14.0% at the 3 QC levels
Specificity: Chromatograms acceptable

Conclusions:

Absorption of ZD1033 was found to be at least 70% based on the radioactivity in urine. Up to 24 hours after dosing, ZD1033 was the major component in plasma. Triazole was the major metabolite in plasma. About 70 - 75% of radioactivity was excreted in urine and about 10% in feces. ZD1033 is highly metabolized and only about 6% of the dose was excreted as unchanged drug in urine within 72 hours. Major urinary metabolites were triazole, hydroxy-ZD1033 glucuronide and ZD1033 glucuronide. One urinary metabolite, M14 (ZD1033 glucuronide) was not seen in any preclinical species.

Overall, it was found that this drug is metabolized by hydroxylation, N-dealkylation and glucuronidation.

STUDY D1033HQ/0001: (DOSE ESCALATION STUDY)

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE TOLERABILITY, PHARMACOKINETICS AND EFFECT ON SERUM CONCENTRATIONS OF OESTRADIOL AND OTHER HORMONES FOLLOWING ASCENDING SINGLE ORAL DOSES OF ICI D1033 (ANASTROZOLE) IN HEALTHY MALE VOLUNTEERS

Reference: Volumes 28 and 29
Investigator:
Study Location:

Objective:

1. To assess the tolerability of anastrozole in healthy male volunteers after single oral doses up to 60 mg, and
2. to assess any effect of these doses of anastrozole on serum concentrations of oestradiol and other hormones, and
3. to obtain preliminary information on pharmacokinetics of anastrozole.

Drug Dosage Forms:
0.1 mg dose: given as a solution
Other doses: given as tablets

0.5 mg tablet: formulation # F6897, batch # 49169/90
5.0 mg tablet: formulation # F6898, batch # 49170/90
Matching placebos for 0.5 and 5.0 mg tablet: formulation # F6896, batch # 49168/90

Study Design:

This study consisted of 2 phases, a parallel-group, ascending-dose phase up to single doses of 30 mg, and a second crossover phase. Both phases of the study were randomized, double-blind and placebo-controlled. Both phases included healthy male volunteers (18-50 years old).

In the first parallel group phase, the starting dose given was 0.1 mg orally. Tolerability was assessed. An interval of 48 hours was left between dosing days before higher doses were administered to other subjects. If no unacceptable effects were observed at previous dose levels, increasing doses were given up to 30 mg (ascending doses of 0.1, 0.5, 1.5, 3, 7.5, 15 and 30 mg). At each dose level, 4 volunteers received the drug and 2 received placebo.

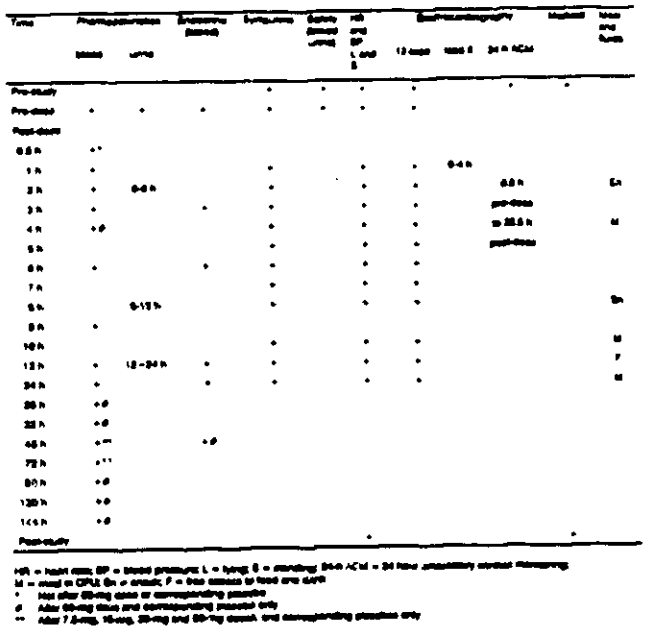
In the crossover phase, 6 volunteers received matching placebo and 60 mg anastrozole given on two study days with a washout period of 3 weeks.

Totally 30 volunteers were recruited for the study, out of which 29 volunteers entered the study, and 28 volunteers completed the study. Once subject dropped out for personal reasons.

Study procedures (blood sampling for ZD1033 and endocrine levels etc.) are shown in the table below:

Table 5

Summary of study procedures on each study day



Data Analysis:
No formal analysis was performed on data from the parallel group phase. For the crossover phase (60 mg dose), ZD1033 and placebo data were compared using ANOVA. Pharmacokinetic parameters were determined by model-independent methods. % reduction in various hormone levels were calculated on baseline-scaled data.

Results:
ASSAY PERFORMANCE:
I. High sensitivity curve:
Method used: 32P-02
Range: ng/ml
Linearity: Quadratic fit (with second degree polynomial coefficient being very small)
QC sample levels: 2 ng/ml and 75 ng/ml
Accuracy: -10.5% and -6.9% at 2 and 75 ng/ml respectively
Precision: 17.3% and 6.8% at 2 and 75 ng/ml respectively
Specificity: Chromatograms found acceptable

Assay was found to be acceptable.

II. Low sensitivity curve:
Method used: 32P-02
Range: ng/ml
Linearity: Quadratic fit (with 2nd deg. polynomial coefficient being extremely small)
QC sample levels: 75 and 2500 ng/ml
Accuracy: -8.5 and -10.44% at low and high QC levels
Precision: 1.5 and 1.8% at low and high QC levels
Specificity: Chromatograms found to be acceptable

Assay was found to be acceptable.

III. Analysis in urine:
Method used: 32U-03
Range: ng/ml
Linearity: Quadratic fit (with 2nd deg. polynomial coefficient being extremely small)
QC sample levels: 10, 100 and 400 ng/ml
Accuracy: -6.2%, 3%, 3% at low, medium and high QC levels
Precision: 3.8%, 7.5% and 2.9% at low, medium and high QC levels
Specificity: Chromatograms found to be acceptable with well resolved peaks
Assay was found to be acceptable.

Plasma concentration-time profiles following single doses of 0.1 to 60 mg ZD1033 are shown in the figures below:

Figure (7)

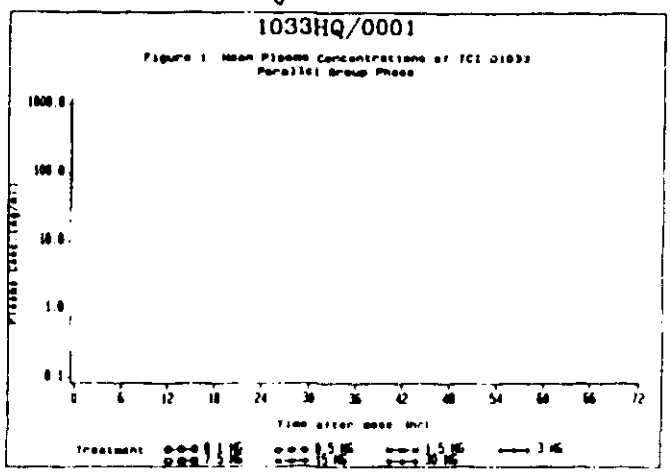
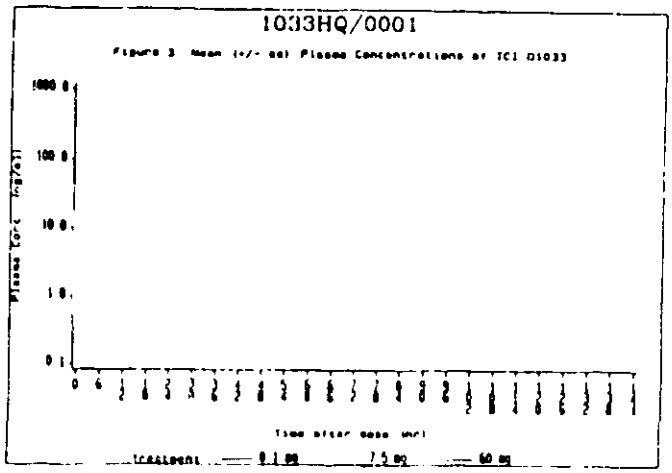


Figure (8)



Mean PK parameters following single doses of ZD1033 are shown in the following table:

TABLE (6)

Parameter	Mean (SD) PK parameters after single doses of ZD1033 (only median for t_{max})							
	0.1 mg	0.5 mg	1.5 mg	3 mg	7.5 mg	15 mg	30 mg	60 mg
AUC_{0-24}, ng.hr/ml	19.7 (4.7)	93.1 (36.6)	267.2 (35.7)	589.0 (117.0)	1295.0 (21.2)	2715.0 (372.9)	6125.0 (849.2)	13808.3 (1630.5)
C_{max}, ng/ml	1.8 (0.6)	10.4 (9.3)	18.0 (5.0)	36.5 (9.1)	75.7 (8.0)	191.5 (57.2)	361.0 (27.1)	845.1 (132.0)
T_{max}, hr	1.50	1.07	2.49	2.00	12.58	2.00	1.51	2.00
$AUC_{0-\infty}$, ng.hr/ml	-	-	-	-	-	-	-	36255.0 (6872.1)
$t_{1/2}$, hr	-	-	-	-	-	-	-	32.2 (7.0)

Average urinary excretion of ZD1033 over the first 24 hours after dosing ranged from % of the administered dose, and appeared to be independent of dose.

Following figures show the % reduction in oestrone and oestradiol levels.

Figure (9)

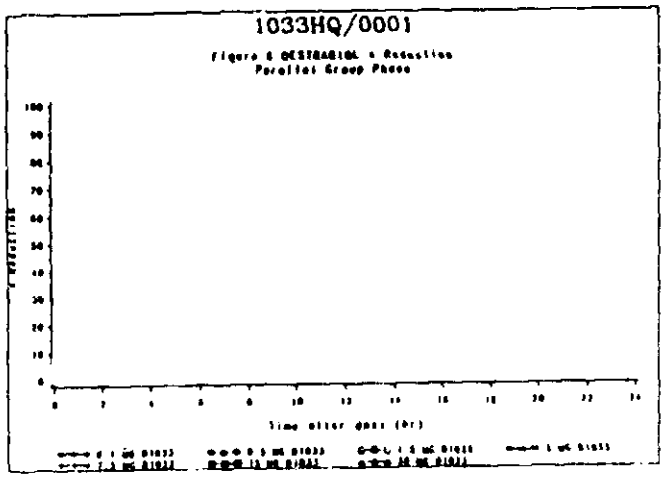
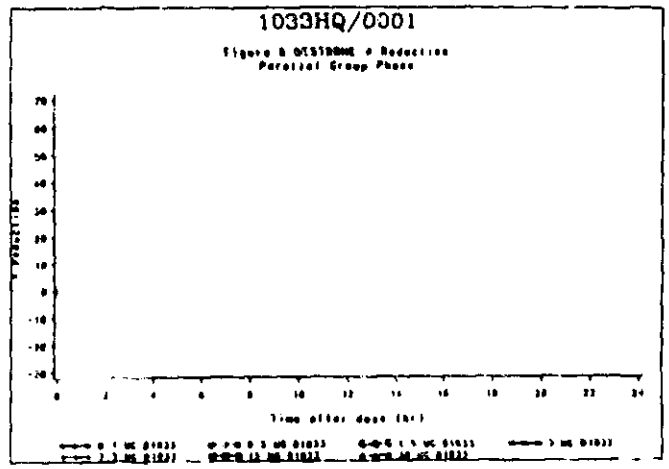
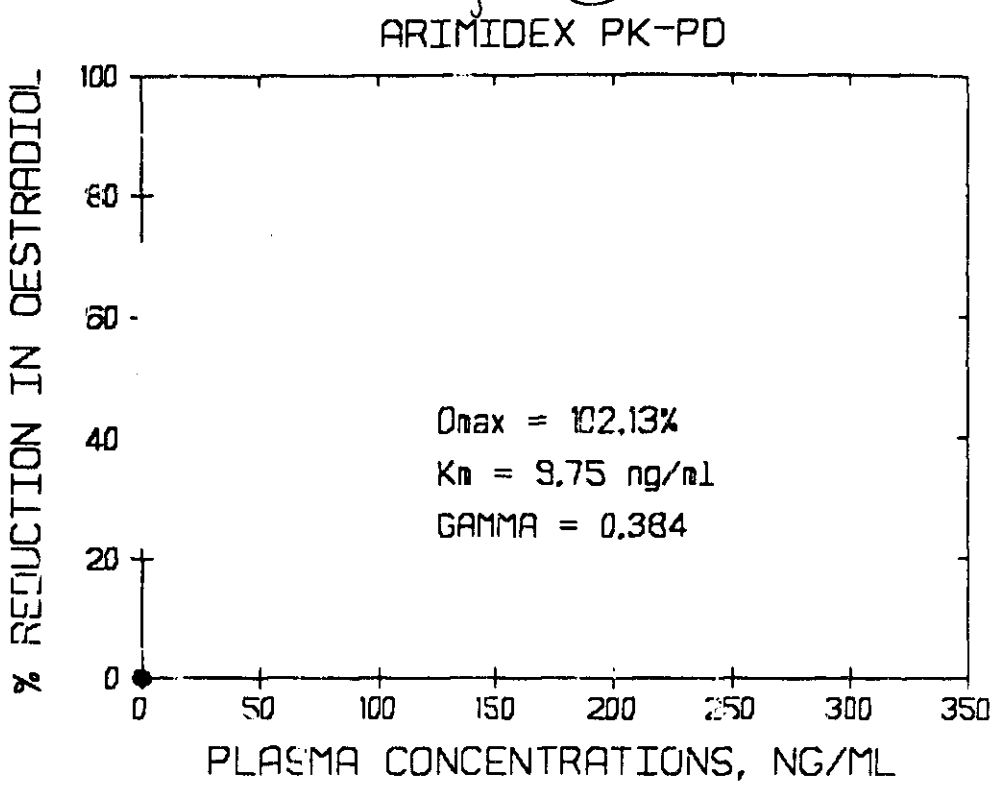


Figure (10)



% reduction in oestradiol correlated well with plasma concentration of ZD1033 and fit well to a sigmoid E_{max} model (calculated and fitted by the reviewer) (Note that data was from different subjects of the parallel group phase). The figure below shows the data fit and various parameter values.

Figure (11)



Conclusions:

ZD1033 was well tolerated by healthy male volunteers. Cmax and AUC increased with increasing doses upto 60 mg dose range tested. ZD1033 produced a reduction in serum oestradiol levels (>70%) for longer than 48 hours. Similar but smaller effect was found on serum oestrone levels. Rise in serum LH and FSH was found. No significant effect on plasma cortisol (not studied after ACTH stimulation) and ACTH levels were found.

STUDY D1033IL/0009: (SAFETY STUDY WITH 0.5 AND 1 MG DOSE IN POST-MENOPAUSAL FEMALE VOLUNTEERS)

A STUDY TO ASSESS THE PHARMACOKINETICS AND PHARMACODYNAMIC EFFECTS OF 14 DAYS DOSING WITH 0.5 AND 1 MG DOSES OF ZD1033 ON SERUM OESTRADIOL CONCENTRATIONS IN POST-MENOPAUSAL FEMALE VOLUNTEERS

Reference: Volumes 43 and 44
Investigator:
Study Location:

Objective:
1. To assess the effect of 14 daily doses of 0.5 mg and 1 mg ZD1033 on serum oestradiol concentrations.
2. To obtain multiple dose pharmacokinetic data on ZD1033 in healthy, post-menopausal female volunteers during 14 days of dosing with 0.5 and 1 mg ZD1033 daily.
3. To determine the tolerability by healthy post-menopausal female volunteers of 14 daily doses of 0.5 and 1 mg ZD1033.

Drug Dosage Forms:
Dosage: 0.5 or 1 mg once daily for 14 days.
Batch #s: ICI D1033 0.5 mg tablet (F6897): ADM 49169/90
ICI D1033 0.5 mg placebo tablet (F6896): ADM 49168/90.

Study Design:
This is a randomized, double-blind, parallel-group study in 14 healthy post-menopausal female volunteers aged 45 to 64 years. Seven subjects received one 0.5 mg tablet and a placebo tablet (0.5 mg dose) and the other 7 subjects received two 0.5 mg tablets (1 mg dose) per day for 14 days. Blood samples were collected at 0, 1, 2, 3, 6, 9, 12 and 24 hours on day 1 and at 0 hours on days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 and at 0, 12, 24, 48, 72, 96 and 144 hours after dosing on day 14 for determination of plasma concentrations of ZD1033. For determination of serum oestradiol concentrations, blood samples were drawn at 0 and 12 hours on day 1 and at 0 (pre-dose) on days 2, 3, 4, 6, 8, 10, and 14 and at 24, 48, 72, 96 and 144 hours after dosing on day 14.

Pharmacokinetic parameters were determined by model-independent methods. Ratios of C_{mun} values on days 5 - 14 relative to day 8 were calculated. The primary endpoint for analysis of oestradiol was the mean baseline-scaled oestradiol concentrations 24 hours postdose on days 13 and 14. The secondary endpoint was the area under the baseline scaled oestradiol concentration-time curve (AUC). Both these endpoints were analyzed using ANOVA allowing for effects of treatments.

Results:
ASSAY PERFORMANCE:

Method used: 32P-02
Range: ng/ml
Linearity: Quadratic fit with very low second degree polynomial coefficient
QC sample levels: 2, 40 and 75 ng/ml
Accuracy: -7.0, 9.75, 3.87% at low, medium and high QC levels
Precision: 8.6, 5.2 and 5.3% at low, medium and high QC levels

Specificity: Chromatograms found to be acceptable

Assay was found to be acceptable.

Assay validation data for oestradiol assay was not provided.

Following figures show the mean ZD1033 concentration-time profiles upto 24 hours and 14 days respectively. Mean plasma concentrations following administration of 1 mg dose were approximately twice the concentrations after the 0.5 mg dose.

Figure 12

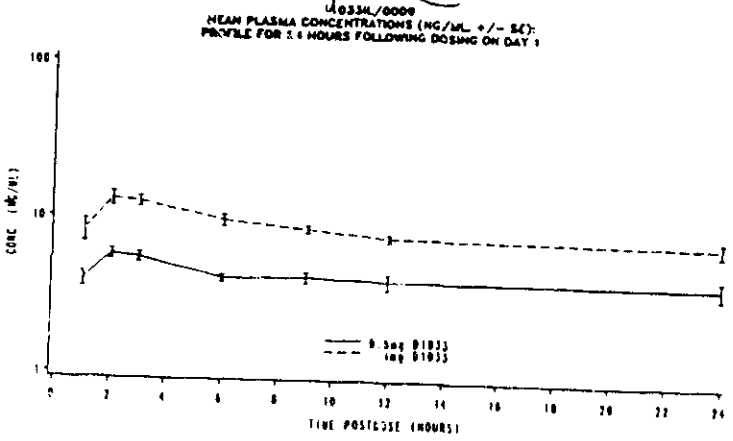
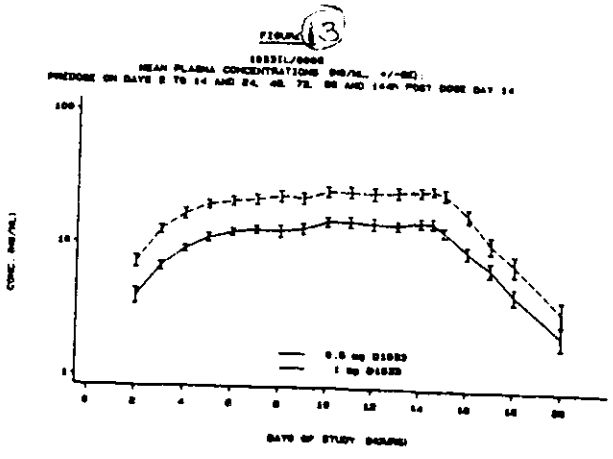


Figure 13



On day 1, mean ZD1033 C_{max} values were 5.97 and 13.7 ng/ml for 0.5 mg and 1.0 mg doses respectively. Median T_{max} was 2 hours for both doses. Mean half life was 45.7 hours and 40.6 hours after 0.5 mg and 1 mg doses. Plasma ZD1033 concentrations during repeated dosing were evaluated to determine time to steady state and degree of accumulation when administered one a day. Steady state concentrations were reached by day 9 as shown by the mean ratios of C_{min} (see table below). Even though steady state based on mean ratios appears to have been achieved by day 5, the range (min - max) was wide with minimum being as low as 0.65. Based on these results and the results obtained from study 0002 (see figure 17), steady state is achieved by day 9.

TABLE 7 RATIOS OF CMIN (NG/ML) VALUES FOLLOWING DOSES 5 TO 14 RELATIVE TO CMIN FOLLOWING DOSE 8

		DOSE 5 : DOSE 8	DOSE 6 : DOSE 8	DOSE 7 : DOSE 8	DOSE 8 : DOSE 8	DOSE 9 : DOSE 8	DOSE 10 : DOSE 8	DOSE 11 : DOSE 8
0.5mg ZD1033	MEAN	0.943	0.992	0.947	1.000	1.139	1.137	1.097
	SD	0.178	0.139	0.132	0.000	0.151	0.075	0.121
	MIN	0.65	0.83	0.72	1.00	0.97	1.07	0.93
	MAX	1.16	1.24	1.13	1.00	1.37	1.29	1.34
	N	7	7	7	7	7	7	7
1mg ZD1033	MEAN	0.940	0.975	1.025	1.000	1.121	1.124	1.091
	SD	0.117	0.056	039	0.000	0.034	0.066	0.123
	MIN	0.76	0.91	0.99	1.00	1.08	1.01	0.89
	MAX	1.10	1.04	1.07	1.00	1.18	1.20	1.22
	N	6	6	6	6	6	6	6

After once daily administration of ZD1033, C_{min} values at steady state were approximately 3.5 fold greater than C_{min} after single dose (indicative of extent of accumulation).

OESTRADIOL DATA:

At both dose levels, mean serum oestradiol levels decreased to less than 20% of baseline values after 1st dose and remained until days 3 - 6 after the final dose. Mean oestradiol concentrations and baseline-scaled values are shown in figures below:

Figure 14

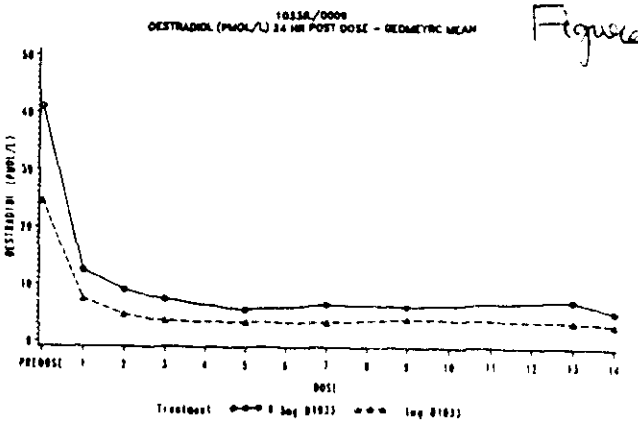


FIGURE 15

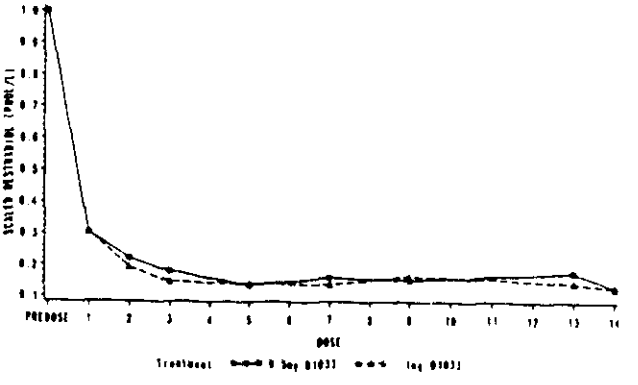


Table below summarizes the results of analysis of mean baseline-scaled oestradiol concentrations 24 hours after dosing on days 13 and 14.

Table (8)

Statistical analysis of oestradiol concentrations 24 hours after dosing on Study Days 13 and 14

ICI D1033 dose	No. of evaluable volunteers	Mean baseline-scaled post-dose oestradiol values	Treatment effect (ratio 0.5 : 1.0 mg)	95% confidence limits	p-value	Mean oestradiol suppression
0.5 mg	6	0.156	1.13	(0.55, 2.33)	0.713	84%
1.0 mg	7	0.138				86%

This analysis showed no significant difference between doses. However, in subjects given 1 mg dose, there were more subjects with no detectable post-dose oestradiol levels than in subjects given 0.5 mg dose.

Conclusions:

Both 0.5 and 1 mg ZD1033 doses for 14 days were well tolerated by post-menopausal female volunteers. Steady state was achieved within 9 days. Daily dosing with ZD1033 suppressed oestradiol concentrations to less than 20% of baseline values. This data confirms that ZD1033 is a potent aromatase inhibitor which inhibits oestradiol formation.

STUDY D1033HQ/0002: (SAFETY STUDY WITH 3 MG DOSE IN POST-MENOPAUSAL FEMALE VOLUNTEERS)

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERANCE, PHARMACOKINETICS AND EFFECTS ON ENDOCRINOLOGY OF DAILY ORAL DOSING WITH 3 MG ZD1033 GIVEN FOR 10 DAYS TO HEALTHY POST-MENOPAUSAL VOLUNTEERS

Reference: Volumes 45 and 46
Investigator:
Study Location:

Objective:

1. To study the safety and tolerability of ZD1033 in healthy post-menopausal female volunteers.
2. To assess the effect of 3 mg QD for 10 days, on serum oestradiol and other hormonal concentrations.
3. To obtain multiple dose pharmacokinetic data on ZD1033.

Drug Dosage Forms:

Dosage: 3 mg once daily for 10 days.
Batch #s: *ICI D1033 0.5 mg tablet (F6897): ADM 49169/90*
ICI D1033 0.5 mg placebo tablet (F6896): ADM 49168/90.

Study Design:

This is a randomized, double-blind, placebo-controlled crossover study in 8 healthy post-menopausal female volunteers (7 completed the study) aged 45 to 62 years. Subjects received eight single daily doses of 3 mg ZD1033 and placebo, each given on study day 1 and study days 4 to 10 of each treatment period. There was a washout period of at least 9 days between the two periods. Blood samples were collected at 0, 1, 2, 3, 6, 9, 12, 24, 48 and 72 hours on day 1 and 10; at 96 hours on day 10; and at '0' hours on days 4, 5, 6, 7, 8 and 9 for determination of plasma concentrations of ZD1033. For determination of serum oestradiol, oestrone and androstenedione concentrations, blood samples were drawn at 0, 6, 12, 24, 48 and 72 hours on day 1, at 0 hours on day 4, 6, 8 and 10 and at 24, 48, 72 and 96 hours on day 10. Blood samples were taken at 0 and 3 hours after dosing on days 1 and 10 for determination of levels of serum aldosterone, cortisol, 17-hydroxyprogesterone, dehydroepiandrosterone sulphate, luteinising hormone, ACTH, FSH and sex hormone-binding globulin. Samples for cortisol assay were also taken at 0 hours on days 3, 5, 7 and 9. ACTH stimulation test (250 µg tetracosactrin I.M., samples drawn at 0, 30 and 60 minutes after injection) was performed 3 hours after dosing on day 10 of each treatment period.

Pharmacokinetic parameters were determined by model-independent methods. Ratios of $AUC_{0\text{-}24}$ on day 10 and AUC_{0-} on day 1 were calculated. The primary endpoint for analysis of hormones was the mean baseline-scaled oestradiol, oestrone and androstenedione concentrations at 6, 12, 24, 48 and 72 hours postdose on day 1 and at 0, 24, 48, 72 and 96 hours on day 10. For cortisol and 17-hydroxyprogesterone, increase in baseline-scaled values at 30 and 60 minutes post ACTH stimulation were used. The secondary endpoints were baseline scaled values of other hormones. These endpoints were analyzed using ANOVA allowing for effects of treatments, volunteers and periods.

Results:
ASSAY PERFORMANCE:

Method used: 32P-02
Range: ng/ml
Linearity: Quadratic with very small 2nd degree polynomial coefficient
QC sample levels: 2, 40 and 75 ng/ml
Accuracy: -6.0, 0, 0% at low, medium and high QC levels
Precision: 13.7, 2.9 and 2.5% at low, medium and high QC levels
Specificity: Chromatograms found to be acceptable

Assay was found to be acceptable.

Following figures show the mean ZD1033 concentration-time profiles after the first dose (day 1) and eighth dose (day 10). C_{max} averaged 46.2 ng/ml and 113.7 ng/ml (approximately 3 fold higher on day 10) on days 1 and 10 respectively. Mean ± SD value for $AUC_{0-\infty}$ on day 1 was 2995 ± 1055 ng/ml and AUC_{0-24} on day 10 was 2220 ± 328 ng/ml.

Figure (16)

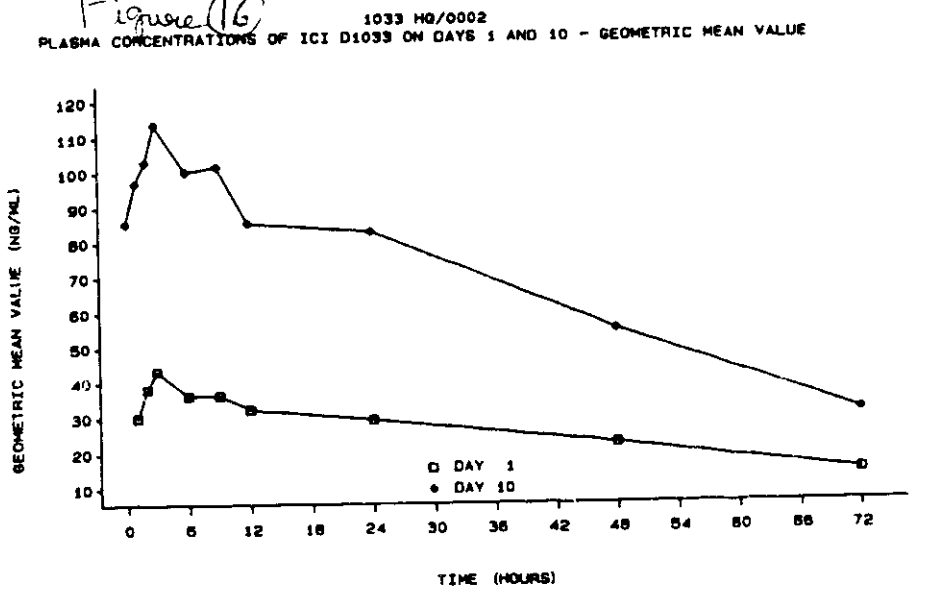
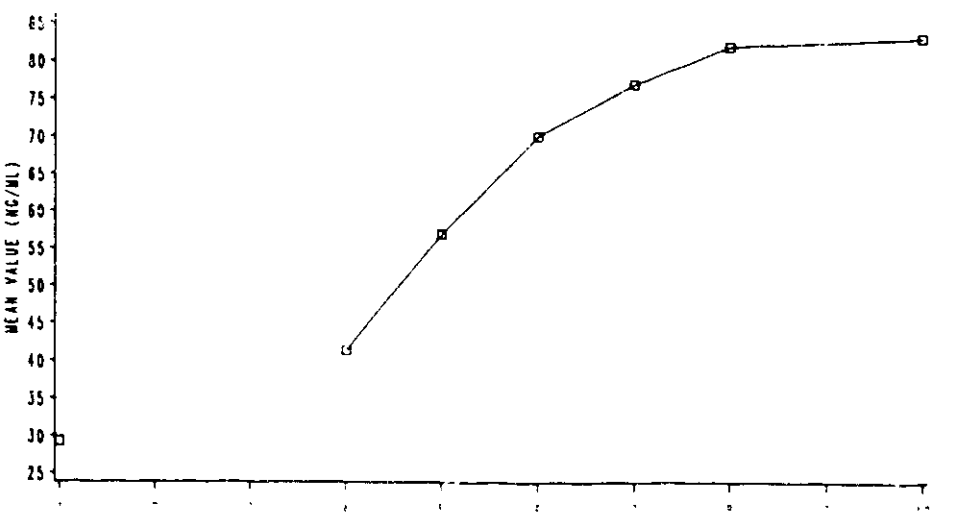


Figure (17)



% reduction in oestrone and oestradiol levels is shown in the figures shown below:

Figure (18)

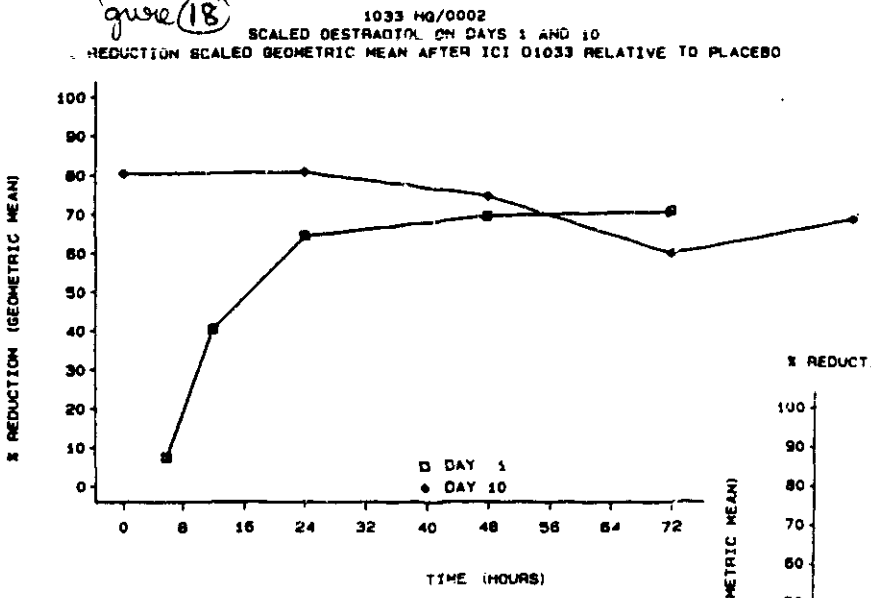
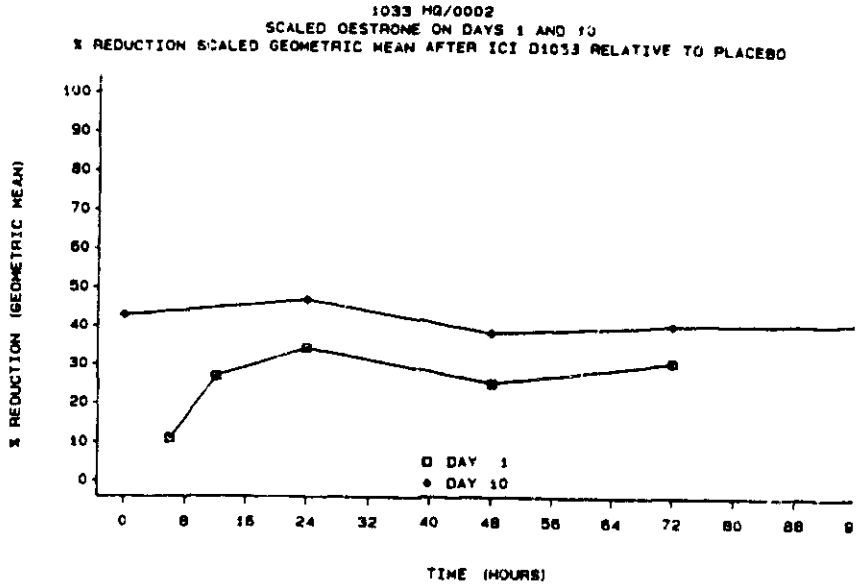


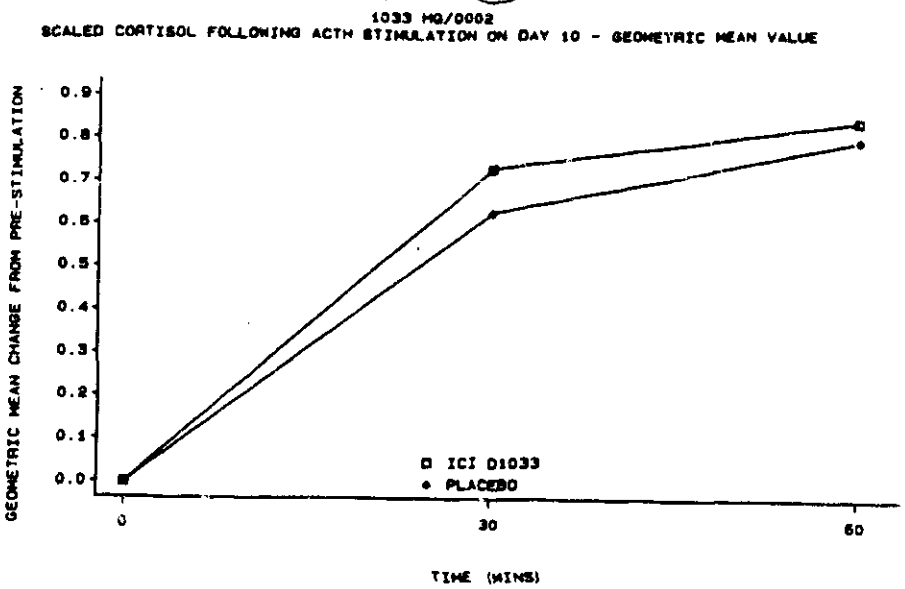
Figure (19)



Compared to corresponding values during placebo treatment, mean serum oestradiol concentration decreased progressively after dosing to about 30% after 1st dose and 20% after dosing on day 10. A similar pattern of decrease in mean serum oestrone concentrations occurred, however maximal decreases occurred only upto about 60% of placebo values.

ADRENAL HORMONES: Mean serum cortisol levels were found to be lower (39%) after first dose but not different from placebo on days 3 to 10. On day 10, mean cortisol response to ACTH stimulation were not statistically significantly different from those receiving placebo (see figure below).

Figure (20)



Conclusions:

ZD1033 seems to be tolerated by healthy post-menopausal volunteers. Plasma ZD1033 concentrations increased with multiple dosing with approximately 3-fold higher levels at steady state. Daily dosing with 3 mg ZD1033 achieved an 80% fall in oestradiol and a 40% fall in oestrone levels which was largely sustained for about 96 hours after the final dose on day 10. ZD1033 did not show any significant effect on cortisol levels and on levels of gonadotrophins. This confirms that ZD1033 is a potent aromatase inhibitor and does not have a significant effect on enzymes that regulate adrenocorticoid biosynthesis.

Comments:

Calculation of $AUC_{0-\infty}$ from 0-72 hour plasma concentration data after the first dose leads to errors because of problems in calculation of terminal slope (as the half life of this drug is about 45 - 50 hours). This must have led to high variability in calculation of AUC after the first dose. Although this study gives an idea of accumulation, because of the problem stated here, time to steady state and extent of accumulation are better assessed from the previous study # 1033IL/0009.

STUDY 1033IL/0019: (DOSE PROPORTIONALITY STUDY)

DOSE PROPORTIONALITY STUDY OF ZENECA ZD1033 IN POSTMENOPAUSAL WOMEN

Reference: Volumes 33 and 34
Investigator:
Study Location:
Objective:

To evaluate the dose proportionality of ZD1033 in postmenopausal women following administration of 1, 5, 10 and 20 mg doses.

Study design:

This is a randomized, open-label, 3 period trial, with a balanced incomplete block design. 20 healthy postmenopausal women participated in this study (19 completed the study). Each subject took single doses of 3 of the 4 ZD1033 doses studied (1, 5, 10 and 20 (2 x 10 mg tablets) mg) as per the sequence to which the subjects were randomly assigned. Thus, each of the doses were given to 15 subjects. Dose was taken with 240 ml of water. Subjects fasted for 8 hours before and 4 hours after dosing in each period. There was a 3 week washout period between doses.

BATCH #S:
ZD1033 10 mg tablets (F11137, lot # 93-3070): ADM 49323/92
ZD1033 5 mg tablets (F6898, lot # 92-3170): ADM 49170/90
ZD1033 1 mg tablets (F11133, lot # 93-3069): ADM 49322/92.

Blood was drawn from the subjects at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192 and 216 hours after dosing on day 2 for each period. Plasma samples were kept frozen until analyzed for ZD1033 concentrations. Urine samples were collected but were to be analyzed only in cases of unusual plasma levels. Pharmacokinetic parameters were determined by model-independent methods. Statistical analyses were conducted on dose-normalized C_{max} and AUC by ANOVA and linearity was assessed.

Results:

ASSAY PERFORMANCE:

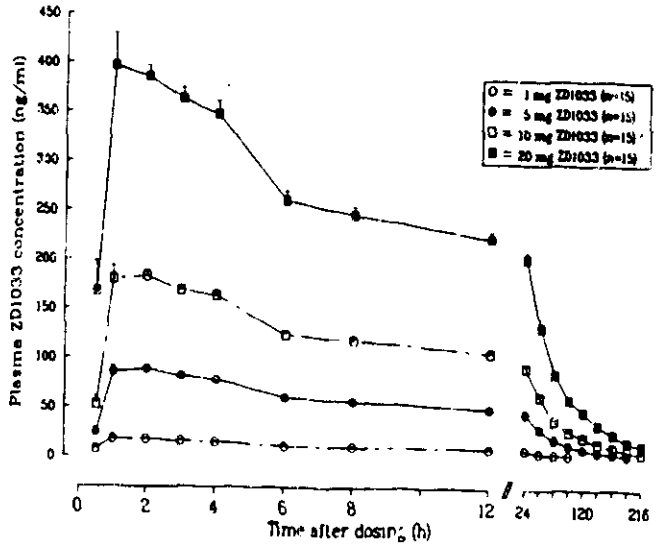
Method used: 32-02R1
Range: ng/ml
Linearity: Linear in the range with coefficient of determination of 0.998
QC sample levels: 7.5, 15.0, 40.0 and 75.0 ng/ml
Accuracy: 1.2, 0.67, 6.5, 4.26% at 7.5, 15, 40 and 75 ng/ml
Precision: 3.2, 3.0, 2.4 and 2.6% at 7.5, 15, 40 and 75 ng/ml
Specificity: Chromatograms acceptable

Assay was found to be acceptable.

Pharmacokinetic results from the 1 mg dose were limited because of assay limitations and hence dose proportionality assessment was based on parameters obtained for 5, 10 and 20 mg ZD1033 doses.

Mean plasma concentration-time profiles following 1, 5, 10 and 20 mg ZD1033 single doses are shown in the figure below:

Figure (21)



The table below shows the least square means for the ZD1033 PK parameters (for t_{max}, it is the median) and range. No dose-dependent changes in C_{max}, t_{max}, clearance and half-life were observed.

Table (9)

Parameter	1 mg ZD1033	5 mg ZD1033	10 mg ZD1033	20 mg ZD1033
		Least square means (range)		
C_{max}, ng/ml	17.5 (15.9 - 25.1)	93.0 (73.9 - 122.0)	201.7 (151.0 - 258.0)	434.7 (351.0 - 674.0)
AUC_{0-t}, ng.hr/ml	548 (342 - 1247)	4349 (3011 - 5267)	8318 (5922 - 12029)	18330 (14810 - 27742)
$AUC_{0-\infty}$, ng.hr/ml	-	4825 (3298 - 5797)	9079 (6124 - 14269)	18905 (15036 - 22109)
$t_{1/2}$, hr	-	56.3 (39.7 - 72.9)	50.7 (36.9 - 76.9)	50.8 (34.1 - 78.0)
Cl/F, ml/min	-	18.7 (14.4 - 25.3)	19.0 (11.7 - 27.2)	17.9 (15.1 - 22.2)
		Median (range)		
T_{max}, hr	1 (1 - 2)	2 (1 - 4)	1 (1 - 3)	1 (1 - 3)

Plasma concentrations after 1 mg dose were only quantifiable for 2 elimination half-lives and hence, $AUC_{0-\infty}$, $t_{1/2}$ and Cl/F could not be calculated. Plots to show dose proportionality in pharmacokinetics of ZD1033 are shown in figures below (for AUC and C_{max}).

Figure (22)

Dose proportionality of Anastrozole (ARIMIDEX)

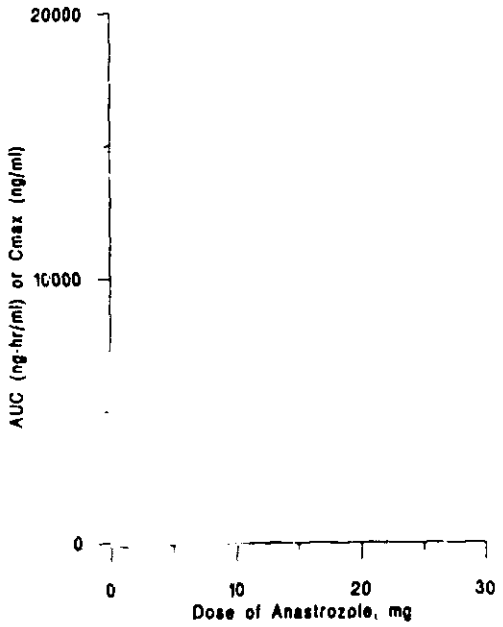
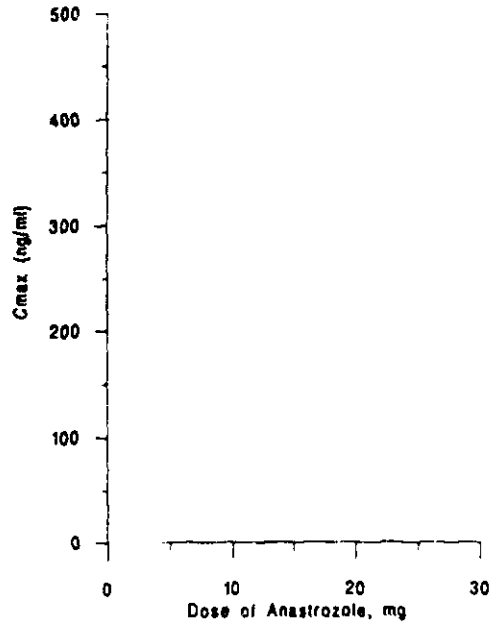


Figure (23)

Dose proportionality of Anastrozole (ARIMIDEX)



Dose proportionality assessment was based on parameters obtained for 5, 10 and 20 mg doses. The dose-normalized parameter values are shown in the table below:

Table (10)

Parameter	Least square means		
	5 mg ZD1033	10 mg ZD1033	20 mg ZD1033
C_{max}/dose (10^{-6}/ml)	18.5	20.2	21.8
AUC_{0-} (10^{-6} hr/ml)	918	910	957

No significant differences were observed in dose-normalized AUC values, however, a significant difference in C_{max} was seen with dose-normalized C_{max} values for 10 and 20 mg being 109 and 118% of the value obtained from the 5 mg dose.

Conclusions:

Plasma ZD1033 AUC values were dose-proportional. There appears to be some difference in C_{max} values but that could be due to different strengths employed in the study.

Comments:

This is not a true dose-proportionality study. Ideally, one should carry out this study at a range of doses obtained using multiple units of the same dose strength. Inspite of this problem in this study, overall, the results from this study do not show any non-linearity in pharmacokinetics of ZD1033 in the dose range of 1 - 20 mg.

STUDY 1033IL/0011: (FOOD EFFECT AND RELATIVE BIOAVAILABILITY STUDY)

STUDY TO DETERMINE THE EFFECTS OF FOOD ON THE BIOAVAILABILITY OF ZD1033 TABLETS AND THE BIOAVAILABILITY OF ZD1033 TABLETS RELATIVE TO AN ORAL SOLUTION

Reference: Volume 30
Investigator:
Study Location:

Objective:

To determine the effects of food on the bioavailability of ZD1033 tablets, and to determine the bioavailability of ZD1033 relative to an oral solution.

Study design:

This is a randomized open-label three-way crossover design study in 9 healthy male volunteers (7 received ZD1033 under fed conditions and 9 received ZD1033 solution and tablet under fasting condition) of age 18-62 years of age. The first arm of the study included a single 10 mg ZD1033 tablet administered under fasting conditions, the second arm consisted of the same formulation given under fed conditions within 30 minutes after standard heavy breakfast, while the third arm consisted of a solution (dose 10 mg) given under fasting conditions. Each dosing was separated by a 3 week washout period.

Composition of standard heavy breakfast is given in the table below:

TABLE (11)

Food	Amount	Protein (g)	Fat (g)	Carbohydrate (g)	Kcals
Whole milk for cereal	150 ml	4.9	5.7	10	98
Cereal (corn flakes)	30 g	2.6	0.5	10	110
Fried white bread	20 g	1.5	10.3	10	111
Fried bacon	60 g	19.7	13.4	0	199
Eggs	2 (120 g)	16.9	22.4	0	278
White toast	30 g	2.3	0.5	10	70
Butter	10 g	0	0.5	0	70
Decaffeinated coffee or tea with milk	200 ml	0.3	0.4	1	7
Total	NA	48.2	53.7	41	943

Batch #s: ZD1033 10 mg tablet (F11137): ADM 49323/92
ZD1033 0.5 mg/ml solution (F11214): ADM 59440/93

Blood sample were drawn for determination of plasma concentration of ZD1033 at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 216, 264, 312 and 360 hours after each dose. Safety was also monitored during this period. Pharmacokinetic parameters were determined by model-independent methods. These log-transformed parameters from fasted and fed , and from fasted tablet and solution were compared by the sponsor using ANOVA model consisting of subject, treatment and period as factors. 95% confidence intervals were computed. The reviewer calculated the same way for fasted vs. fed conditions using ANOVA model consisting of subject, sequence, treatment and period as factors. 90% confidence interval was computed using a two one-sided t-test.

Results:

ASSAY PERFORMANCE:

Method used: AD SOP 2.103
Range: ng/ml
Linearity: Linear within the range
QC sample levels: 3, 30 and 80 ng/ml
Accuracy: 4.96, 3.07, 2.03% at low, medium and high QC levels
Precision: 16.3%, 7.0% and 5.7% at low, medium and high QC levels
Specificity: Chromatograms presented are acceptable

Assay was found to be acceptable.

Geometric mean parameters and their confidence intervals are provided in the following table:

Table (12)

	$AUC_{0-\infty}$ (ng.hr/ml) geometric means	C_{max} (ng/ml) geometric means	$t_{1/2}$, hrs lsmeans
Tablet (fed)	6681	104	47.1
Tablet (fasted)	6383	124	41.1
Oral solution	6373	120	42.3
Food effect*	105%	84%	6.0
95% C.I.	96 - 114%	74 - 94%	1.1 - 10.8
90% C.I.	93 - 114%	82 - 92%	
p-value	0.286	0.007	0.019
Formulation effect*	100%	104%	-1.1
95% C.I.	92 - 109%	93 - 117%	-5.8 - 3.5
p-value	0.970	0.475	0.603

* Ratios for AUC and C_{max}, differences for $t_{1/2}$

Mean plasma concentration profiles are shown in figures shown below:

Figure 24

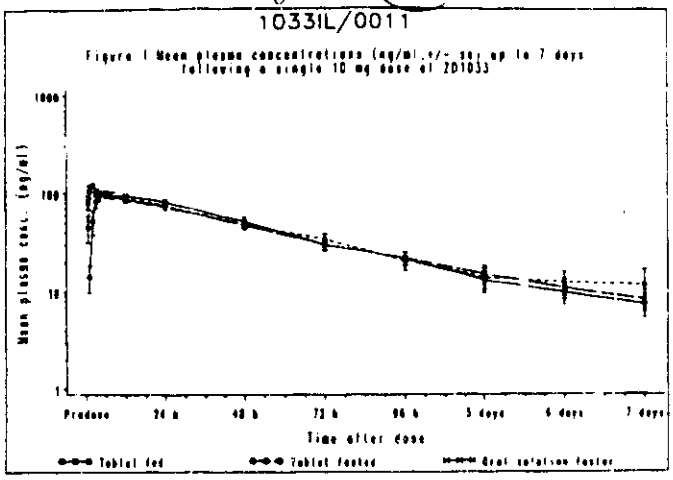
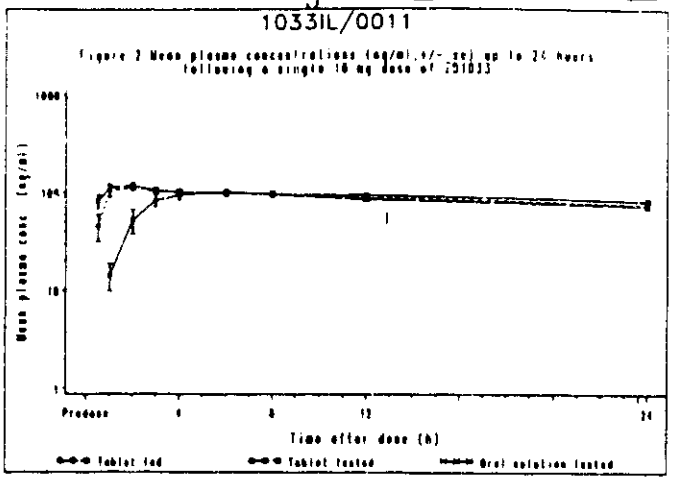


Figure 25



The absorption of ZD1033 from the tablet formulation was delayed in presence of food with median t_{max} being 2 hours in fasted state and 5 hours when the tablet was taken after food.

Conclusions:

1. Food had no effect on the AUC while there was small decrease in C_{max}, however the 90% confidence intervals are within the % range. This suggests that food is unlikely to have a significant effect on the plasma concentrations of ZD1033. However, there is an effect on t_{max}.

2. The oral bioavailability of the clinical trial tablet was 100% relative to a solution of ZD1033.

Comments:

1. Food effect was not studied on 1 mg final tablet. However, the results obtained above gives comfort in the sense that there was no food effect on the 10 mg tablet. This tablet strength when compared with the 1 mg clinical trial tablet in the dose proportionality study were found to be dose proportional. Also, this is an immediate release tablet with the to-be marketed tablet being bioequivalent to the clinical trial tablet.

2. The oral bioavailability is shown to be 100%. This is relative to solution and is not absolute bioavailability.

STUDY D1033US/0003: (PHARMACOKINETIC STUDY IN PATIENTS)

A SAFETY AND PHARMACOKINETICS STUDY OF 5 AND 10 MG ZD1033 IN POST MENOPAUSAL WOMEN WITH CANCER

Reference: Volumes 47
Investigator:
Study Location:
Objective:

To evaluate the safety and tolerability, pharmacokinetics and the effects of 5 and 10 mg doses of ZD1033 on estradiol, cortisol (following ACTH stimulation) and androstenedione levels.

Study design:

This is an open-label sequential design study carried out in 4 centers. 19 female patients with advanced breast cancer were enrolled. An oral dose of 5 mg of ZD1033 was taken by the patients once daily for 14 days, followed by 10 mg (two 5 mg tablets) of ZD1033 once daily for 14 consecutive days.

Batch #: 5 mg tablet (F6898, lot # 92-3170) ADM 49170/90.

Blood samples were obtained for trough plasma concentrations of ZD1033 from all patients at 0 (pre-dose) hours on days 0, 1, 2, 4, 11, 14, 15, 16, 18, 25, 28 and at 24, 48 and 72 after dosing on day 28. A 24 hours pharmacokinetic assessment was conducted on one patient on the final day of both the 5 mg and 10 mg dosing periods (days 14 and 28). Samples were drawn at 0, 1, 2, 3, 5, 6, 12, 18 and 24 hours on those 2 days in addition to the trough samples. Serum levels of estrogens and androstenedione were measured at screening, at the end of the two dosing periods and during the follow-up period after dosing. An ACTH stimulation test (250µg synthetic ACTH (cortrosyn) injection I.M.) was performed at screening and at the end of the 5 and 10 mg treatment periods to assess the effects of ZD1033 on adrenal function.

Pharmacokinetic parameters were determined by non-compartmental methods. Attainment of steady state and extent of accumulation were determined from the Cmin values after doses 10, 13 and 14 relative to dose 1 in both periods. Since there is no washout period between the 2 dosing periods, extent of accumulation for 10 mg dose was not estimated.

Results:

ASSAY PERFORMANCE:

Method used: 32P-02
Range: ng/ml
Linearity: Quadratic with negligible 2nd degree polynomial coefficient
QC sample levels: 75, 1200 and 2500 ng/ml
Accuracy: 0.4, -3.42, 5.32% at low, medium and high QC levels
Precision: 5.1%, 6.2% and 9.5% at low, medium and high QC levels
Specificity: Chromatograms presented were well resolved

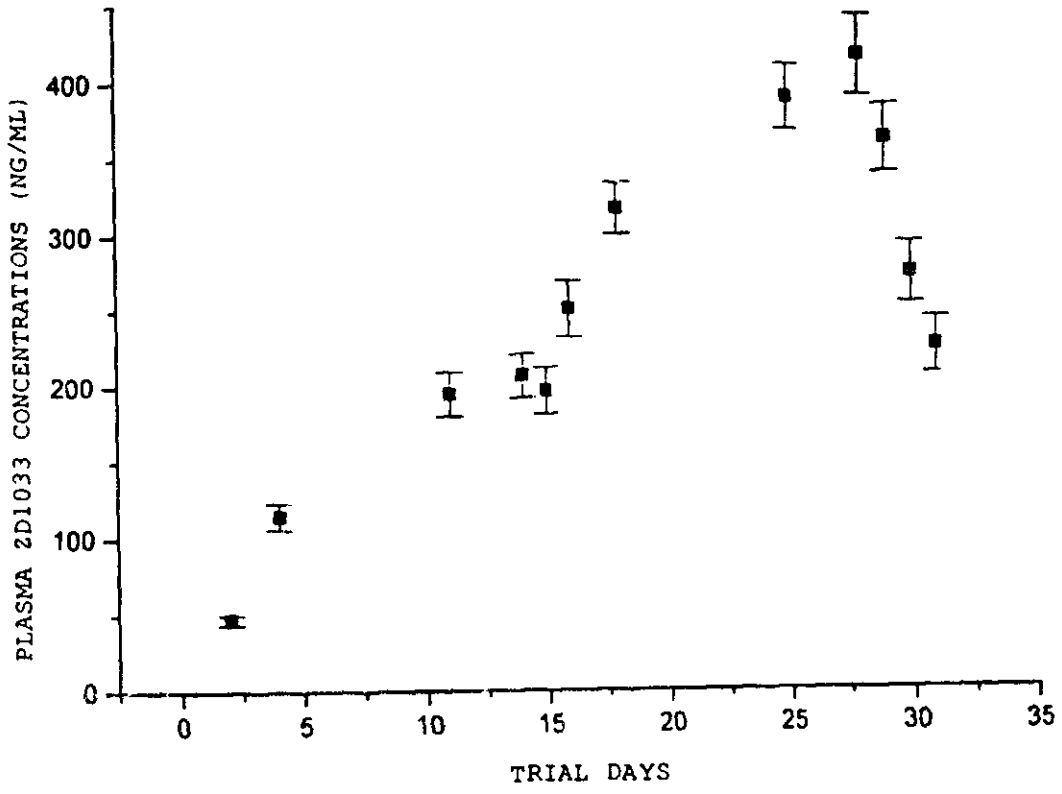
Assay was found to be acceptable.

Plasma samples for trough drug levels were collected between 21 - 26.5 hours after previous dose from the patients. Due to the long elimination half-life of the drug, this range may not have a

major impact on determination of steady state pharmacokinetics. Mean plasma Cmin values after administration of 5 mg and 10 mg ZD1033 doses are presented in the figure below. These levels exhibited a dose-proportionate increase.

Figure 26

Mean (+/– SE) plasma ZD1033 concentrations obtained following administration of 5-mg (Days 1–14) and 10-mg (Days 15–28) ZD1033 doses



Comparison of ZD1033 Cmin ratios ± SD for time to steady state is shown in the table below:

Table 13

Dose	Cmin 13/Cmin 10	Cmin 14/Cmin 10
5 mg	1.07 ± 0.25 (n = 16)	1.03 ± 0.23 (n = 17)
10 mg	1.06 ± 0.15 (n = 15)	0.94 ± 0.11 (n = 16)

Based on the above results, steady state seemed to have been achieved at least by day 10.

EXTENT OF ACCUMULATION:

After 5 mg dosing:

Cmin 10/Cmin 1 = 4.38 ± 1.41 (n = 17)

Cmin 13/Cmin 1 = 4.55 ± 1.35 (n = 17)

Cmin 14/Cmin 1 = 4.35 ± 1.52 (n = 18)

Pharmacokinetic parameters obtained from the patient that underwent the 24 hour PK assessment are shown in the following table and the plasma concentration-time profile is presented in the figure.

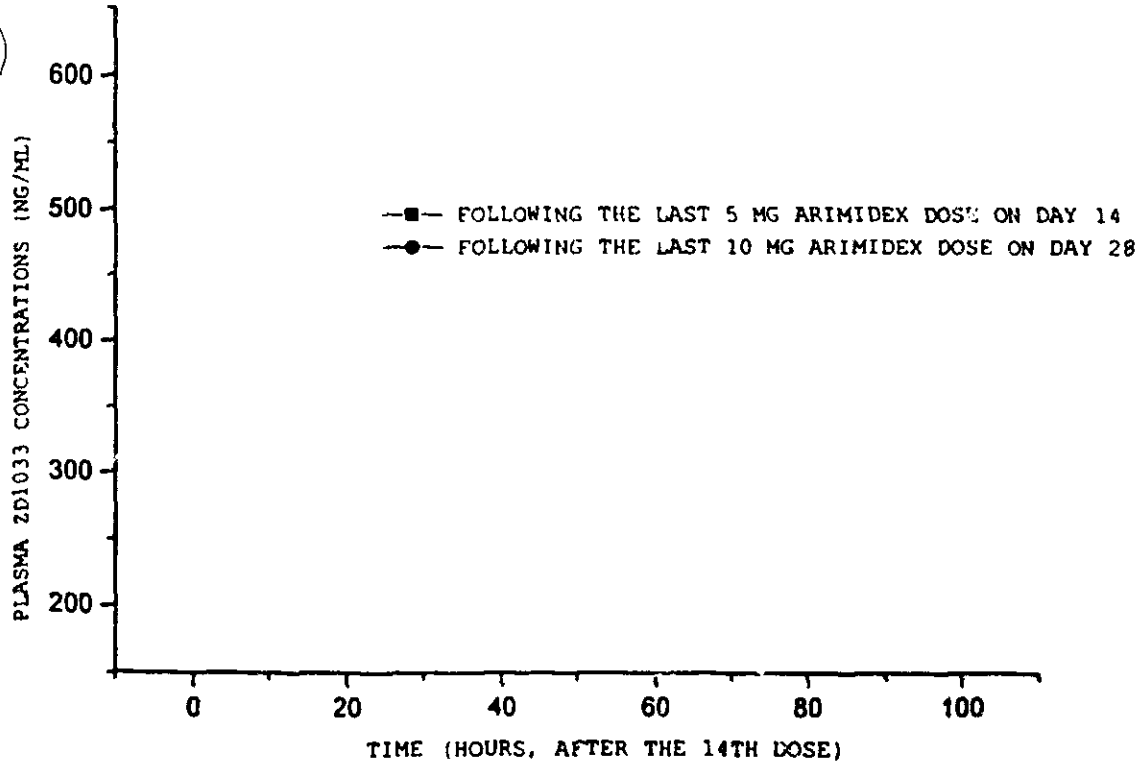
TABLE #(14)

Summary of ZD1033 steady state pharmacokinetic parameters for Patient 1/1

Parameter	ZD1033 5 mg	ZD1033 10 mg
C_{max} (ng/ml)	275	611
T_{max} (h)	2	2
$AUC_{(0-24)}$ (ng x h/ml)	5,280	10,200

Plasma ZD1033 concentrations obtained following administration of the last ARIMIDEX dose, Patient 1/1

FIGURE #(27)

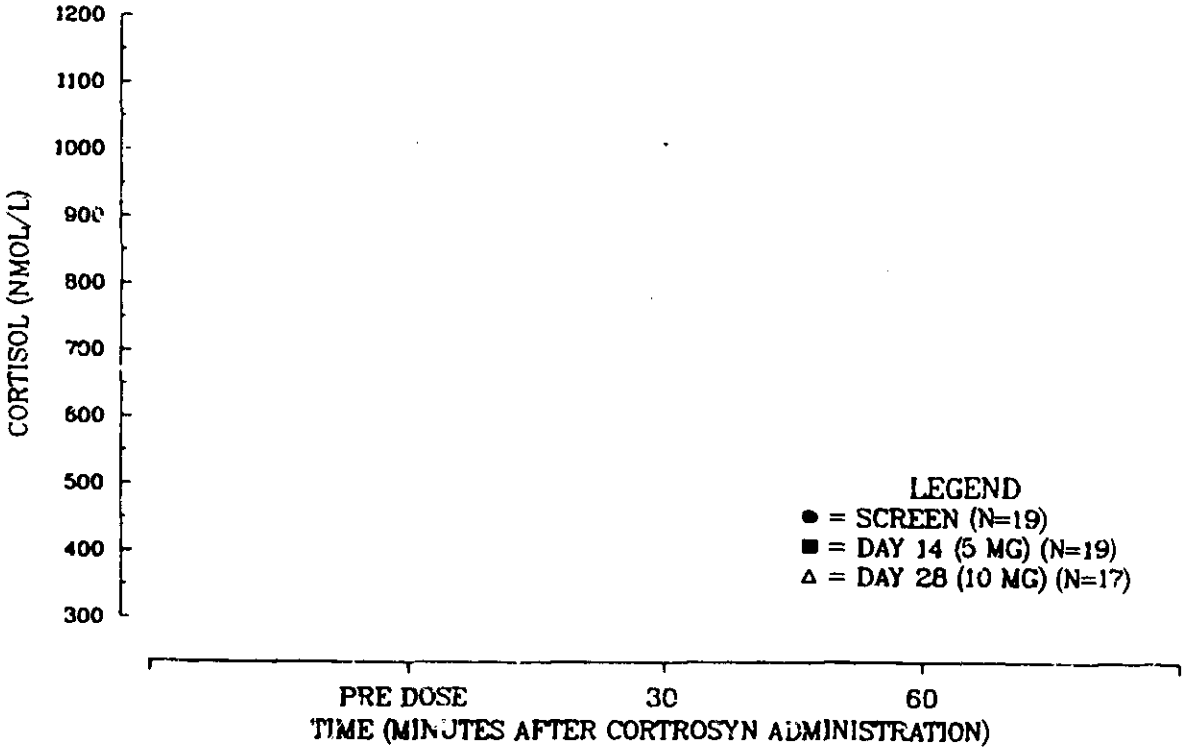


This data further confirms dose-proportionality in the patient. These pharmacokinetics in the patients are similar to those found in normal healthy volunteers.

Results of ACTH stimulation test are shown in the graph below. No statistically significant differences in cortisol and aldosterone levels were found following administration of both 5 and 10 mg doses for 14 days each.

Figure 28

ACTH stimulation results after administration of 5 and 10 mg of ZD1033 – cortisol



Conclusions:

Dose proportionality in pharmacokinetics was observed. Steady state was achieved by about the 10th dose and extent of accumulation was 4-fold. ACTH stimulation test results indicate no impairment of adrenal secretion of cortisol or aldosterone. Significant suppression of oestradiol and oestrone levels were observed. Doses of 5 and 10 mg ZD1033 administered for 14 consecutive days each were well tolerated in advanced breast cancer patients.

STUDY D1033US/0007: (EXTENSION STUDY IN PATIENTS - COMPASSIONATE USE TRIAL)

AN OPEN-EXTENSION STUDY FOR THE USE OF 10 MG ZD1033 IN POST MENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER WHO WERE RESPONDING TO TREATMENT

Reference: Volume 48
Investigator:
Study Location:
Objective:

To evaluate the effects of extended oral treatment with 10 mg ZD1033 administered once daily on the safety, tolerance, estrogen levels and plasma concentrations of the drug in postmenopausal women with advanced breast cancer (who participated in study 0003).

Study design:

This is a multicenter (4 centers), open-label compassionate-use trial involving 17 post-menopausal female advanced breast cancer patients who participated in study 0003 above in whom there was no evidence of progression of advanced breast cancer during treatment with ZD1033. Subjects were given 10 mg ZD1033 orally once daily as one 10 mg tablet (F11005, lot #s 92-3171 and 93-3082, batch # ADM 49388/91). This study lasted for about 84 weeks. Blood samples were drawn for trough plasma concentrations of ZD1033 and endocrine measurements at predose time at weeks 2, 4, 8 and 12 and later every 2 months while the patients received treatment. ACTH stimulation tests were performed at weeks 4 and 12 for measurement of any HPA axis suppression (cortisol suppression).

Results:

ASSAY PERFORMANCE:

Method used: 32-02R1
Range: ng/ml
Linearity: Linear within the range
QC sample levels: 7.5, 15, 40 and 75 ng/ml
Accuracy: -0.27, -6.67, 4.25, 4.93% at 7.5, 15, 40 and 75 ng/ml
Precision: 8.0, 16.8, 3.9 and 0.7% at 7.5, 15, 40 and 75 ng/ml
Specificity: Chromatograms acceptable

Assay was found to be acceptable.

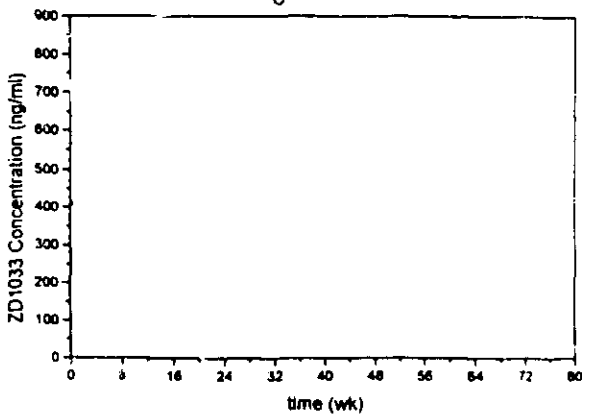
Following daily administration of 10 mg oral dose of ZD1033 for up to 84 weeks, mean Cmin values ranged from 408 to 536 ng/ml (see table below).

TABLE # 15

Trial week	n	Mean (SD) ng/ml
2	12	453 (116)
4	10	408 (112)
8	10	438 (131)
12	7	418 (151)
20	4	519 (100)
28	1	439
36	4	515 (90.8)
44	2	516 (84.9)
52	1	474
60	1	476
68	1	448
76	1	536

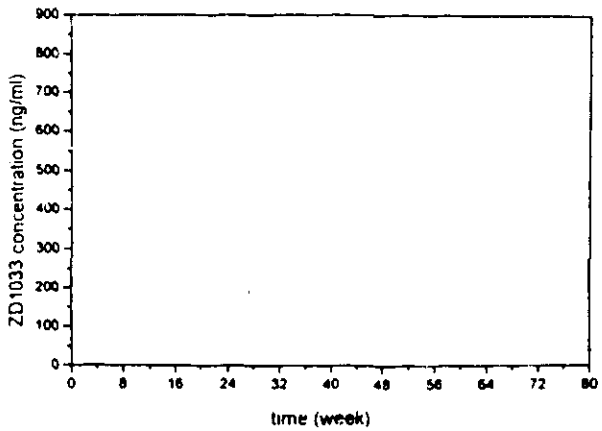
These results indicate no apparent time-dependent changes in ZD1033 pharmacokinetics. Effects of age and weight on pharmacokinetics were explored graphically as shown in figures below. In the range studied, clear trends in pharmacokinetics with age and weight were not seen.

Figure 29



Patient age and plasma concentrations of ZD1033

Figure 30



Patient weight and plasma concentrations of ZD1033

ACTH STIMULATION RESULTS: Results from the following table indicate no evidence of HPA axis suppression by ZD1033.

Table 16

Cortisol and aldosterone mean concentrations

Parameter	Time sequence	Day 59			Day 115		
		n	Mean	SD	n	Mean	SD
Cortisol (nmol/l)	Before cosyntropin	15	353.2	117.5	9	397.9	146.8
	30 min after cosyntropin	15	786.9	185.1	9	908.0	187.8
	60 min after cosyntropin	15	926.1	210.6	9	1008.3	221.0
Aldosterone (pmol/l)	Before cosyntropin	16	313.8	207.8	10	382.8	141.9
	30 min after cosyntropin	16	726.4	278.7	9	844.5	421.9
	60 min after cosyntropin	16	788.9	387.2	10	859.9	532.1

SD Standard deviation

Suppression of oestrogens and effects of androstenedione are shown in the table below:

Table 17

Absolute estrogen and androstenedione mean serum concentrations

Trial day	Estradiol* (pmol/l)			Estrone# (pmol/l)			Estrone sulfate^ (pmol/l)			Androstenedione** (nmol/l)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Baseline##	17	6.9	5.1	17	90.3	32.7	17	785.9	542.7	17	2.6	1.1
45	16	4.9	1.9	16	21.3	12.2	14	99.1	84.0	16	3.2	1.6
59	16	3.7	0.2	16	21.7	14.3	16	100.8	68.1	16	2.9	1.5
87	13	3.9	0.5	13	23.8	16.3	13	84.7	45.5	13	3.0	1.0
115	11	4.4	1.4	11	22.4	10.7	11	72.0	30.6	11	3.1	1.1
171	7	4.4	0.7	7	30.4	16.3	7	71.9	26.0	7	3.2	0.9
227	5	4.5	1.6	5	47.3	11.8	5	95.4	47.3	5	3.2	1.0
283	4	3.7	0.0	4	40.7	9.1	4	102.6	45.4	4	3.0	0.9
339	5	3.7	0.0	5	56.2	12.4	5	313.7	459.7	5	3.7	1.8
395	4	3.9	0.4	4	94.3	86.1	4	113.7	69.7	4	3.1	1.4
451	3	68.3	111.9	3	102.3	93.9	3	94.9	40.6	3	3.0	0.9
507	2	3.7	0.0	2	19.4	14.4	2	68.4	34.0	2	2.8	3.5

*Limit of quantitation = 3.67 pmol/l.
#Limit of quantitation = 9.25 pmol/l.
^Limit of quantitation = 9.25 pmol/l.
**Limit of quantitation = 0.35 nmol/l.
##From Trial 1033US/0003.
SD Standard deviation

Conclusions:

Mean steady state minimum concentrations of ZD1033 ranged from 408 - 536 ng/ml and indicated no time-dependent changes in pharmacokinetics. From exploratory analysis, no effects of age and weight on pharmacokinetics of ZD1033 were apparent. Estradiol suppression was maintained during the trial. ZD1033 did not inhibit adrenal cortisol secretion. ZD1033 was well tolerated.

STUDY 1033IL/0004: (PHASE III EFFICACY AND SAFETY STUDY)

A RANDOMIZED, MULTICENTER, EFFICACY AND SAFETY STUDY TO EVALUATE ARIMIDEX (ZD1033 1 AND 10 MG) DOUBLE-BLIND, COMPARED WITH OPEN-LABEL MEGESTROL ACETATE IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER

Reference: Volumes 49 to 64
Investigator:
Study Location:
Objective:

The primary objectives of this trial were to compare two dosages of ZD1033 (1 mg once daily and 10 mg once daily) with megestrol acetate (MEGACE of Bristol-Myers) (40 mg four times daily) on the following parameters: a) time to progression of disease; b) tumor response; and c) safety and tolerability. The secondary objectives of this trial were to compare the treatment groups with respect to time to treatment failure, duration of response, quality of life in the first year of treatment, and survival.

Study Design:

This is a randomized, double-blind trial for 1 and 10 mg ZD1033 and open-label for megestrol acetate, parallel group, multicenter trial (49 centers) in 386 postmenopausal patients with advanced breast cancer who have progressed on tamoxifen treatment. 128 of these patients were randomized to receive 1 mg ZD1033, 130 to receive 10 mg ZD1033 and 128 to receive megestrol acetate. ZD1033 was administered as 1 or 10 mg dose once daily while megestrol acetate was given at 40 mg 4 times daily.

Batch #s:

ZD1033 1 mg: ADM49240/92, ADM49322/92 and ADM59002/93 (F11133, lot #s 92-3207, 93-3002, 93-3020, 93-3069, 93-3111T and 94-3008).

ZD1033 10 mg: ADM49243/92, ADM49323/92 and ADM59003/93 (F11137, lot #s 92-3208, 93-3003, 93-3019, 93-3112T, and 94-3009)

Megestrol acetate: H3K29B, MCE41, MCE42, A4J76C, B4J34B, MCE43 and MCE40 (F10099).

Treatment was continued until disease progression or until patient withdrew treatment. There were several efficacy and safety measures that were determined in this study. Serum levels of oestradiol and estrone were measured at 0, every 4 weeks up to week 24 and every 12 weeks thereafter. Blood samples for determination of ZD1033 concentrations were drawn from only those patients randomized to ZD1033 treatment at predose on week 0, 4, 8, 12, 16, 20, 24, 36 and 48.

Results:

ASSAY PERFORMANCE:

Method used: 32-02R1
Range: ng/ml
Linearity: Linear within the range with a coefficient of determination of 0.998
QC sample levels: 7.5, 15, 40 and 75 ng/ml
Accuracy: -0.8, -4.0, 1.0, 1.6% at 7.5, 15, 40 and 75 ng/ml
Precision: 3.5, 5.7, 4.2 and 2.5% at 7.5, 15, 40 and 75 ng/ml

Specificity: Chromatograms acceptable

Assay was found to be acceptable.

The median duration of follow-up for all randomized patients was about 180 days.

Plasma concentrations (C_{min}) obtained from patients after administration of 1 and 10 mg doses of ZD1033 are shown in the figures below:

Figure (31)

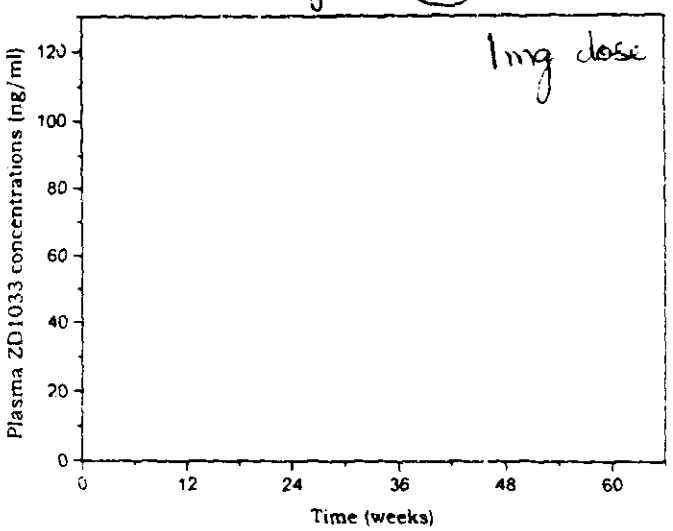
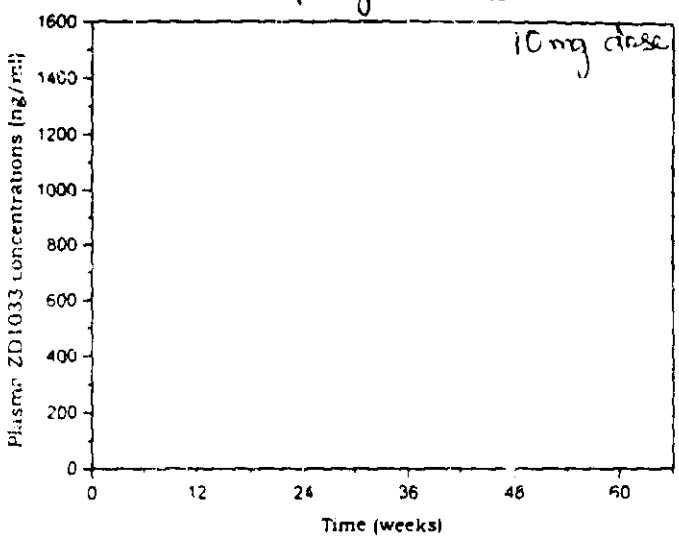


Figure (32)



After administration of 1 mg ZD1033 daily, plasma steady state concentrations ranged mostly between 20 and 60 ng/ml, and that after 10 mg dose ranged between 200 and 600 ng/ml indicating consistent dose-proportionality of ZD1033.

For detecting any effect of age on pharmacokinetics of ZD1033, patients were categorized into 4 age groups of <50 years, 50 - 65, 65 - 80 and >80 years. Mean C_{min} values in these age groups are shown in the table below. No apparent age related differences in pharmacokinetics of ZD1033 are seen.

Table (18)

Z[illegible] ues obtained within a 2-hour interval of the scheduled sample [illegible]s following daily dosing of 1 and 10 mg of ZD1033

Week	Mean C_{min} (ng/ml) (n)			
	Age group (years)			
	50 or less	> 50 to 65*	> 65 to 80*	Over 80
ZD1033 1 mg				
4	33.3 (3)	35.9 (13)	44.3 (10)	43.3 (2)
8	36.5 (1)	45.5 (10)	33.5 (6)	41.5 (2)
12	34.0 (3)	38.1 (10)	37.6 (9)	17.4 (1)
16	43.0 (1)	34.4 (8)	35.8 (6)	21.8 (1)
20	43.1 (1)	26.6 (4)	39.9 (8)	21.0 (1)
24	44.9 (1)	33.1 (6)	43.4 (7)	44.3 (2)
36	NA	33.1 (2)	46.2 (4)	33.0 (1)
48	NA	21.5 (1)	NA	32.3 (1)
60	NA	24.3 (1)	NA	NA
ZD1033 10 mg				
4	275 (2)	384 (10)	430 (13)	354 (3)
8	NA	420 (8)	437 (11)	634 (2)
12	NA	352 (9)	419 (9)	NA
16	458 (1)	335 (12)	256 (2)	272 (1)
20	NA	365 (6)	403 (5)	274 (2)
24	NA	374 (6)	384 (7)	NA
36	NA	603 (5)	484 (2)	NA
48	NA	464 (1)	NA	NA
60	NA	349 (1)	NA	NA

*Inclusive of upper age limit.
C_{min} Minimum concentration
n Number of patients
NA Not applicable

Several patients with renal and hepatic impairment entered the study. C_{min} values when categorized for these patients, show slightly higher levels as compared to the patients without renal and hepatic impairment. Tables below show the C_{min} values in various patients (samples taken within 2 hours of the sampling time are shown in the first table and samples taken at least 12 hours after the last dose was presented in the second table).

Table (19)

ZD1033 C_{min} values obtained within a 2-hour interval of the scheduled sample collection times during daily dosing of 1 and 10 mg of ZD1033

Week	Mean C_{min} (ng/ml) (n)	
	Patients without hepatic impairment	Patients with hepatic impairment
ZD1033 1 mg		
4	38.4 (27)	57.4 (1)
8	40.8 (19)	NA
12	35.4 (22)	60.5 (1)
16	34.0 (15)	44.1 (1)
20	33.2 (13)	57.9 (1)
24	39.9 (15)	37.3 (1)
36	40.8 (6)	39.2 (1)
48	26.9 (2)	NA
60	24.3 (1)	NA
ZD1033 10 mg		
4	394 (28)	NA
8	434 (20)	721 (1)
12	385 (18)	NA
16	328 (16)	NA
20	365 (13)	NA
24	379 (13)	NA
36	569 (7)	NA
48	464 (1)	NA
60	349 (1)	NA

C_{min} Minimum concentration
n Number of patients
NA Not applicable

Table 20

Range of ZD1033 steady-state concentrations obtained during daily dosing with 1 and 10 mg of ZD1033

Week	Range of steady-state concentrations (ng/ml) (n)		
	Patients without hepatic or renal impairment	Patients with hepatic impairment	Patients with renal impairment
ZD1033 1 mg*			
4			
8			
12			
16			
20			
24			
36			
48			
60			
ZD1033 10 mg#			
4			
8			
12			
16			
20			
24			
36			
48			
60			

*Represents all data from samples collected 14 to 38 hours after the last dose.
#Represents all data from samples collected 13 to 34 hours after the last dose.
n Number of patients
NA Not applicable

Conclusions:

Dose proportionality in pharmacokinetics between 1 and 10 mg doses is seen in patients also. No apparent age-related trends in pharmacokinetics of ZD1033 is observed. Slightly higher plasma concentrations were observed in patients with hepatic and renal impairment although these differences could not be quantitated due to variability in patients and also few numbers of patients with hepatic and renal impairment.

STUDY 1033IL/0016: (1 MG TABLET BIOEQUIVALENCE STUDY)

A STUDY TO ASSESS THE BIOEQUIVALENCE OF THE PHASE III CLINICAL TRIALS FORMULATION AND THE COMMERCIAL FORMULATION OF ZD1033 (3 X 1 MG TABLETS) IN FASTED, HEALTHY MALE VOLUNTEERS

Reference: Volume 31
Investigator:
Study Location:

Objective:

To assess the bioequivalence of the phase III clinical trials formulation and the commercial formulation of ZD1033 (three 1 mg tablets) in healthy, male volunteers.

Study design:

This is a randomized, double-blind, 2-way crossover study of single doses (3 mg, i.e., three 1 mg tablets) of the clinical and to-be marketed formulations of ZD1033. 12 healthy male volunteers between 18 and 62 years of age participated in the study (only 11 completed the entire study). The two assessment periods were separated by a 3 week washout period. The tablets were taken by the subjects after an overnight fast, with 150 ml of water. A snack was given after 2 hours and standard meal was allowed 4 hours after dosing.

Batch numbers:
ZD1033 clinical phase III formulation (formulation # F11133): ADM59002/93
ZD1033 commercial (to-be marketed) formulation (# F11292): ADM34034/94

Blood was collected for determination of plasma concentrations of ZD1033 at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 216, 264, 312 and 360 hours after each dose. Pharmacokinetic analysis of data was performed using model-independent technics. AUC and C_{max} were log transformed before analysis. These endpoints were analyzed using an ANOVA model allowing for effects of subjects, sequence, period and treatments as factors in the model. Bioequivalence was assessed using the 90% confidence interval on AUC and C_{max} for the ratio of commercial formulation to the clinical formulation.

Results:

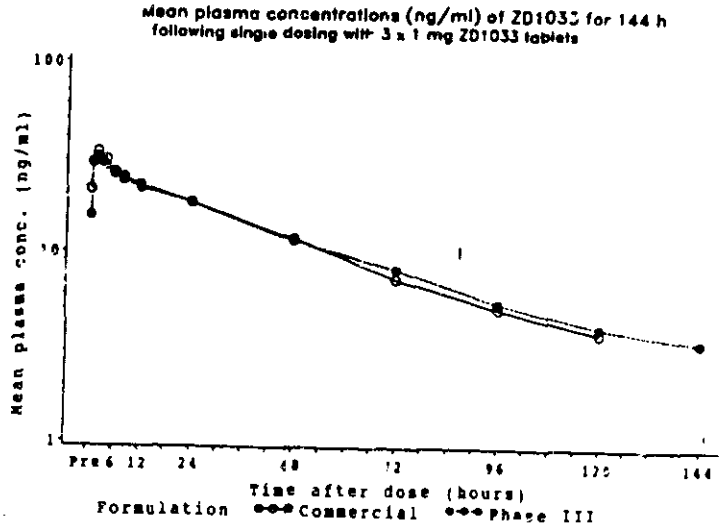
ASSAY PERFORMANCE:

Method used: AD SOP 2.103
Range: ng/ml
Linearity: Linear within the range
QC sample levels: 3, 30 and 80 ng/ml
Accuracy: 2.68 - 19.27 % at low QC, -4.15 to -3% at medium QC and -5.20 to -2.53% at high QC
Precision: 3.1 - 3.8% at low QC, 2.9 - 3.9% at medium QC and 3.9 - 4.8% at high QC levels
Specificity: Chromatograms acceptable

Assay was found to be acceptable.

Mean plasma concentration profiles following 3 mg dose of clinical and to-be marketed tablets are shown in the figure below:

Figure 33



The mean plasma ZD1033 concentration profiles were similar between the 2 formulations, with t_{max} occurring within 1 - 2 hours after dosing. C_{max} and AUC were similar for both formulations. Mean half-life was found to be 40.0 and 45.4 hours after administration of the commercial tablet and clinical tablet respectively.

Results of the pharmacokinetic analysis (on log transformed parameters) are summarized in the following table:

TABLE 21

Parameter	N	Commercial tablet (ls mean)	Phase III tablet (ls mean)	Ratio	90% confidence interval
$AUC_{0\text{-last}}$, ng.hr/ml	11	1331.0	1461.3	0.91	0.84 - 0.98
$AUC_{0-\infty}$, ng.hr/ml	11	1575.1	1682.1	0.94	0.88 - 1.00
C_{max}, ng/ml	11	35.8	32.7	1.09	0.97 - 1.23

Calculation of confidence intervals for AUC and C_{max} is shown below:

ARIMIDEX 3 X 1 MG AUC

STD ERROR OF ESTIMATE 3.613198E-02
ESTIMATE (B.L.U.E.). . -6.573328E-02

POWER ANALYSIS

POWER FOR .2 M(r)= 98.94718 %

REFERENCE MEAN 7.4278
TEST MEAN 7.362067
NUMBER OF SUBJECTS . . 11
DEGREES OF FREEDOM . . 9
NUMBER OF TREATMENTS . 2
DELTA 2

POWER FOR -.2 M(r)= 99.83553 %

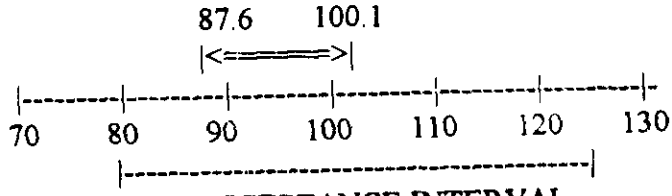
DETECTABLE DIFFERENCE: 11.36423 %

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 87.63701
UPPER CI (% OF REF MEAN): 100.05
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: 0.00092
p> 120 % REF MEAN: <0.00013
CONCLUSION: PASS



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 87.6% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 100.1% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS -0.88% OF THE REFERENCE MEAN.

ARIMIDEX 3 X 1 MG CMAX

STD ERROR OF ESTIMATE 6.335636E-02
ESTIMATE (B.L.U.E.). . 9.071271E-02
REFERENCE MEAN 3.478636
TEST MEAN 3.572115
NUMBER OF SUBJECTS . . 11
DEGREES OF FREEDOM . . 9
NUMBER OF TREATMENTS . 2
DELTA 2

POWER ANALYSIS

POWER FOR .2 M(r)= 72.34416 %
POWER FOR -.2 M(r)= 88.02389 %

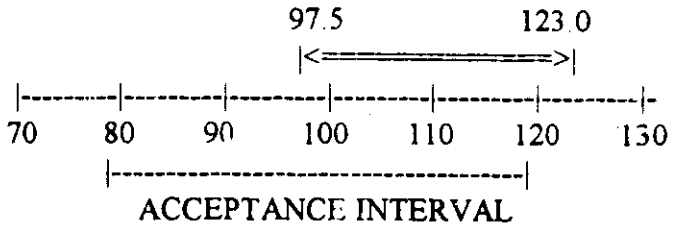
DETECTABLE DIFFERENCE: 19.92684 %

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 97.48947
UPPER CI (% OF REF MEAN): 122.98
CONCLUSION: PASS

P VALUES OF TWO ONE-SIDED TEST

p< 80 % REF MEAN: 0.00040
p> 120 % REF MEAN: 0.09127
CONCLUSION: FAIL



EQUIVALENCE WOULD BE DECLARED (ALPHA = .05) IF IT IS ACCEPTABLE FOR THE RATIO OF THESE PARAMETER MEANS TO BE AS LOW AS 97.5% OF THE OBSERVED REFERENCE MEAN, AND IT IS ACCEPTABLE FOR THE RATIO OF THEIR MEANS TO BE AS HIGH AS 123.0% OF THE OBSERVED REFERENCE MEAN. THE OBSERVED DIFFERENCE BETWEEN THE TEST AND REFERENCE MEANS IS +2.69% OF THE REFERENCE MEAN.

Conclusion:

The to-be marketed 1 mg tablet formulation is bioequivalent to the Phase III clinical tablet formulation.

(50)

STUDY D1033IL/0012: (EFFECT OF ZD1033 ON ANTIPYRINE METABOLISM)

EFFECT OF ZENECA ZD1033 ON ANTIPYRINE METABOLISM IN POSTMENOPAUSAL WOMEN

Reference: Volumes 39 and 40
Investigator:
Study Location:

Objective:

1. To determine the effect of single (30 mg) and multiple (10 mg) oral doses of ZD1033 on the metabolism of intravenously administered antipyrine (500 mg), and

2. To use antipyrine kinetics as a marker of both the inhibition and induction of hepatic oxidative activity.

Study design:

This is a randomized double-blind, parallel-group, placebo-controlled trial in 24 postmenopausal women (only 23 completed the trial) involving single and multiple oral doses of ZD1033 or placebo and single intravenous doses of antipyrine. The trial (both arms of parallel group) was divided into 4 periods (A, B, C and D). There was a one week interval between periods A and B and two week interval between periods B and D.

Period 'A' (days A-1 through A-5): On day A-2, each subject received a 5-minute infusion of antipyrine (500 mg).
Period 'B' (days B-1 through B-5): On day B-2, each subject received an antipyrine (500 mg) infusion and either an oral 30 mg dose of ZD1033 or a matching placebo. On the morning of day B-5, each subject received the first oral, 10 mg dose of ZD1033 or matching placebo of the multiple dosing regimen of period 'C'.
Period 'C' (days C-1 through C-10): Subjects took once daily 10 mg doses of ZD1033 or matching placebo on days C-1 to C-10 and day D-1.
Period 'D' (days D-1 through D-10): On the morning of day D-2, each subject received an infusion of antipyrine (500 mg) and a 10 mg dose of ZD1033 or matching placebo.

To summarize, comparison of PK of antipyrine in period B vs. period A, provides the effect of single dose ZD1033 on antipyrine pharmacokinetics in same subjects and comparison of data from 2 arms of period 'B' (ZD1033 vs. placebo) essentially gives the same information, although not the best comparison. Similarly comparison of data from period 'D' to period 'A' provides effect of multiple dose ZD1033 on antipyrine pharmacokinetics.

Batch #s: ZD1033 10 mg tablets (F11137, lot # 92-3208): ADM 49243/92
Placebo tablets (F6896, lot # 92-3209): ADM 49244/92
Antipyrine (lot # 3863541).

Blood samples were drawn at 0 and 24 hours on days B-2 and D-2 for determining plasma concentrations of ZD1033. For analysis of antipyrine, blood samples were collected at 0, 5, 15, 30 minutes and at 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours on days A-2, B-2 and D-2. Urine samples were

collected for determination of antipyrine and its metabolite levels during the intervals, 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hours on days A-2, B-2 and D-2.

The primary analysis parameters were plasma antipyrine clearance and cumulative urinary recoveries of antipyrine and its metabolites. T-tests were performed on log-transformed plasma antipyrine clearance and on the cumulative urinary recoveries of antipyrine and its metabolites to compare ZD1033 and placebo.

To evaluate inhibitory effect of ZD1033, values obtained after coadministration of antipyrine and ZD1033 (B-2) are compared with antipyrine alone (A-2). To evaluate combined inductive and inhibitory effect, parameters obtained after coadministration of antipyrine with ZD1033 (day D-2) were compared with antipyrine alone (A-2).

T-tests were performed to compare ZD1033 and placebo groups for safety in terms of laboratory and vital signs test results (changes from baseline were compared between 2 groups).

Results:

ASSAY PERFORMANCE:
ZD1033

Method used: 32-02R1
Range: ng/ml
Linearity: Linear in this range with a coefficient of determination of 0.999
QC sample levels: 7.5, 15, 40 and 75 ng/ml
Accuracy: -2.27, -2.0, 5.25 and 3.73% at 7.5, 15, 40 and 75 ng/ml
Precision: 2.0, 3.9, 1.7 and 0.9% at 7.5, 15, 40 and 75 ng/ml
Specificity: Chromatograms with well resolved peaks

Assay was found to be acceptable.

Antipyrine

1. Plasma
Method used: Reversed phase HPLC followed by UV detection
Range: µg/ml
Linearity: Linear with r-squared > 0.996
QC sample levels: 1.5, 10 and 75 µg/ml
Accuracy: -1.07 to - 3.38%
Precision: 2.03 to 3.41%
Specificity: Chromatograms not provided, although sponsor states that assay was specific.

Assay was found to be acceptable.

2. Urine
Method used: Reversed phase HPLC followed by UV detection
Range: µg/ml for antipyrine and 4 - 400 µg/ml for 3-HMA and 4-OHA.
Linearity: Linear with r-squared > 0.994

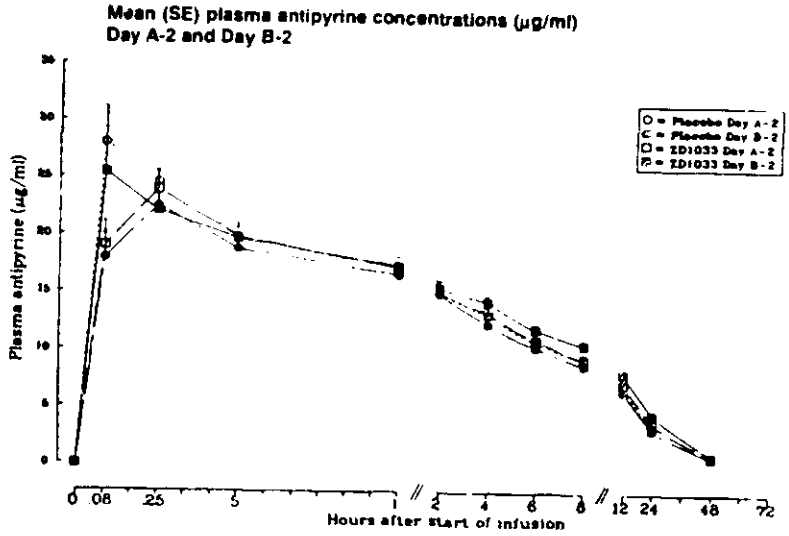
QC sample levels: 6, 40 and 200 µg/ml
Accuracy: <15.3%
Precision: <2.51%
Specificity: Chromatograms not provided.

Assay was found to be acceptable.

PHARMACOKINETIC RESULTS:

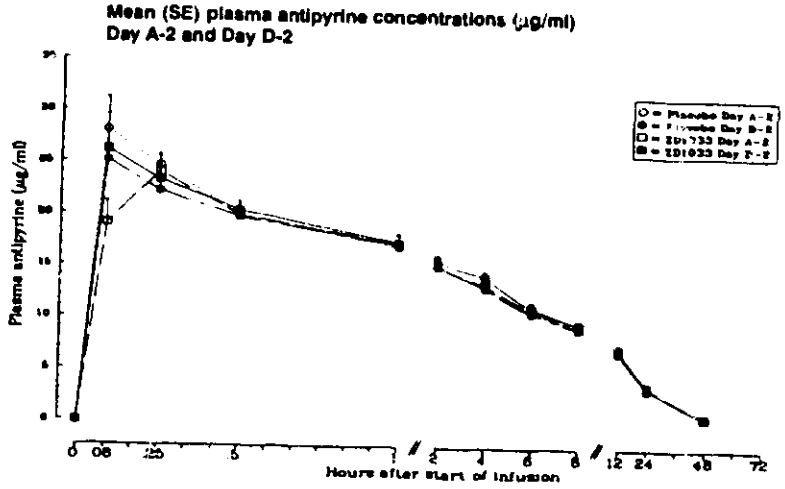
Mean plasma concentrations of antipyrine after period A and B (antipyrine infusion before and after single 30 mg dose of ZD1033 and placebo groups) is shown in the figure below:

Figure 34



Mean plasma concentrations of antipyrine after period A and D (antipyrine infusion before and after multiple 10 mg doses of ZD1033 and placebo groups) is shown in the figure below:

Figure 35



Mean PK parameters obtained for day A-2 dose (antipyrine alone), day B-2 dose (antipyrine with either 30 mg ZD1033 or placebo), and day D-2 dose (antipyrine following repeated dosing of either ZD1033 or placebo) are summarized in the following table:

TABLE 22

Parameter	Treatment gp.	Antipyrine alone (n = 12/gp.) (day A-2 dose)	Antipyrine + single dose of ZD1033 (n = 12/gp.) (day B-2 dose)	Antipyrine + multiple doses of ZD1033 (n = 12 for ZD gp. and 11 for placebo) (day D-2 dose)
		Arithmetic mean (SD) and ratio of ZD1033 : placebo gp.		
AUC_{0-} (µg.hr/ml)	ZD1033 Placebo	287 (73.4) 264 (69.2) 1.05	312 (62.1) 251 (68.0) 1.24	274 (63.4) 267 (83.0) 1.03
AUC_{0-t} (µg.hr/ml)	ZD1033 Placebo	264 (76.2) 239 (74.0) 1.07	285 (70.0) 232 (72.1) 1.23	253 (69.2) 234 (64.6) 1.08
C_{max} (µg/ml)	ZD1033 Placebo	25.1 (4.3) 29.5 (8.9) 0.82	28.0 (73.4) 24.0 (5.1) 1.17	30.0 (9.0) 29.4 (11.4) 1.02
Plasma clearance (ml/min)	ZD1033 Placebo	30.7 (7.5) 33.4 (8.0) 0.92	27.7 (5.8) 35.1 (7.8) 0.79	32.0 (7.6) 33.5 (8.5) 0.96
$t_{1/2}$ (hrs)	ZD1033 Placebo	11.3 (2.2) 10.7 (2.9) 1.06	11.7 (2.1) 10.8 (2.9) 1.08	10.5 (2.0) 11.0 (3.1) 0.95
Vd_z/F (l)	ZD1033 Placebo	27.0 (3.2) 28.0 (5.6) 0.96	26.4 (3.5) 29.2 (4.8) 0.90	26.3 (3.4) 28.4 (5.2) 0.93
		Median (Range)		
T_{max} (hrs)	ZD1033	0.25 (0.08 - 0.25)	0.08 (0.08 - 0.5)	0.165 (0.08 - 0.25)
	Placebo	0.08 (0.08 - 0.25)	0.25 (0.08 - 0.5)	0.25 (0.08 - 0.5)

Comparison of antipyrine clearance parameters is shown in the following table:

Table (23)

Comparison of antipyrine clearance parameters

Clearance ratios compared	Geometric mean (95% CI) of ratios		Ratio ZD1033 group: placebo group	90% CI of ratio
	ZD1033 group (n=12)	Placebo group (n=*)		
Day B-2 dose: Day A-2 dose#	0.91 (0.87 to 0.96)	1.05 (0.97 to 1.14)	0.87	0.80 to 0.93
Day D-2 dose: Day A-2 dose+	1.04 (0.99 to 1.10)	0.98 (0.95 to 1.01)	1.07	1.01 to 1.12

*n=12 for Day B-2 dose: Day A-2 dose, n=11 for Day D-2 dose: Day A-2 dose
#Antipyrine plus a single dose of trial treatment versus antipyrine alone
+Antipyrine after multiple doses of trial treatment versus antipyrine alone

Urinary recovery of antipyrine and its metabolites is shown in the following table:

Table (24)

Summary of 72-hour recovery of antipyrine and its metabolites

Parameter	Treatment group	Percentages of the antipyrine dose Mean (SD) and ratio*		
		Antipyrine alone (n=12 each group) (Day A-2 dose)	Antipyrine plus a single dose of trial treatment (n=12 each group) (Day B-2 dose)	Antipyrine after multiple doses of trial treatment (n=#) (Day D-2 dose)
Total antipyrine	ZD1033	4.55 (1.13)	6.46 (1.37)	6.17 (4.20)
	Placebo	4.75 (1.41)	4.63 (1.44)	6.48 (3.73)
		0.96	1.40	0.96
Free antipyrine	ZD1033	5.02 (1.82)	6.20 (1.87)	4.84 (1.23)
	Placebo	4.48 (1.51)	5.08 (1.21)	5.87 (2.11)
		1.12	1.22	0.84
Total 3-HMA	ZD1033	11.04 (1.86)	7.45 (1.95)	7.85 (2.19)
	Placebo	10.21 (2.15)	8.12 (2.28)	10.26 (2.15)
		1.08	0.92	0.76
Free 3-HMA	ZD1033	3.12 (1.34)	1.90 (1.20)	2.02 (1.20)
	Placebo	2.52 (1.60)	2.17 (1.62)	2.43 (1.50)
		1.24	0.88	0.83
Total 4-OHA	ZD1033	24.45 (4.87)	23.72 (4.75)	23.72 (5.28)
	Placebo	23.34 (6.18)	19.59 (3.30)	23.25 (5.96)
		1.05	1.21	1.02

*ZD1033 group: placebo group
#n=12 for ZD1033 group, n=11 for placebo group

Conclusions:

These results show no conclusive evidence that ZD1033 is an inducer or inhibitor of antipyrine metabolism (hepatic enzyme activity) at the doses tested.

Comments:

Concomitant administration of 30 mg single dose of ZD1033 and antipyrine led to a 20% increase in antipyrine AUC and C_{max} indicating that ZD1033 at higher doses might inhibit antipyrine metabolism. This was seen following the single dose administration but not after multiple dose (10 mg) administration although mean plasma concentrations of ZD1033 achieved at 24 hours were comparable (302, 315 and 306 ng/ml at 24 hours after A-2, 0 hours on D-2 and 24 hours on D-2 respectively). Since this approximately 20% increase is based on the ratio of treatment vs. placebo, this could be a result of variability. Since, the proposed dose of ZD1033 is 1 mg, the concern of inhibition of metabolism, if any, is minimized.

STUDY D1033IL/0013: (EFFECT OF CIMETIDINE ON PK OF ZD1033)

THE EFFECT OF MULTIPLE DOSES OF CIMETIDINE ON THE PHARMACOKINETICS OF ZENECA ZD1033 IN NORMAL POSTMENOPAUSAL WOMEN

Reference: Volumes 41 and 42
Investigator:
Study Location:
Objective:

To determine the effect of repeated doses of cimetidine on the pharmacokinetics of single doses of ZD1033 and to assess the intrasubject variability of ZD1033 pharmacokinetics.

Study design:

This is an open label, 3-period , pharmacokinetic and safety trial in 13 normal postmenopausal women (only 12 completed the study). On days 2, 11 and 24 of the trial, each subject took one 10 mg tablet of ZD1033 (these doses were taken with 240 ml water. The subjects fasted for 8 hours before and 4 hours after dosing). From day 20 to 24, each subject took 300 mg of cimetidine every 6 hours for a total of 17 doses.

Formulations: *ZD1033 10 mg tablets (F11137, lot # 92-3208): ADM 49243/92*

Cimetidine (Tagamet, SmithKline Beecham) 300 mg tablets (F10112): lot & batch # 242T13.

Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 and 192 hours after ZD1033 dosing on days 2, 11 and 24. An additional sample at 216 hours was drawn after dosing on days 11 and 24. These samples were analyzed for ZD1033 concentrations. Urine samples were collected at various intervals over a period of 96 hours, and would have been assayed only in cases of unusual plasma PK findings.

PK parameters were calculated by model-independent methods. For plasma-concentration data obtained after dosing on days 11 and 24, correction for residual ZD1033 concentrations from the previous dose (concentrations of 3 - 11 ng/ml at '0' time seen) was performed by subtracting the calculated residual ZD1033 concentrations from the observed concentrations at each sampling time point. Analysis of variance was performed on the pharmacokinetic parameters after each dose on days 2 and 11. ANOVA was also performed on PK parameters after doses on days 11 and 24.

Results:

ASSAY PERFORMANCE:

Method used: 32-02R1
Range: ng/ml
Linearity: Linear with a coefficient of determination of 0.998
QC sample levels: 7.5, 15, 40 and 75 ng/ml
Accuracy: 0.53, -0.8, 2.25, 5.33% at 7.5, 15, 40 and 75 ng/ml
Precision: 4.7, 4.9, 4.8 and 4.9% at 7.5, 15, 40 and 75 ng/ml
Specificity: Chromatographic peaks well resolved

Assay was found to be acceptable.

EFFECT OF CIMETIDINE:

Mean pharmacokinetic parameters obtained for single doses (10 mg) of ZD1033 given before

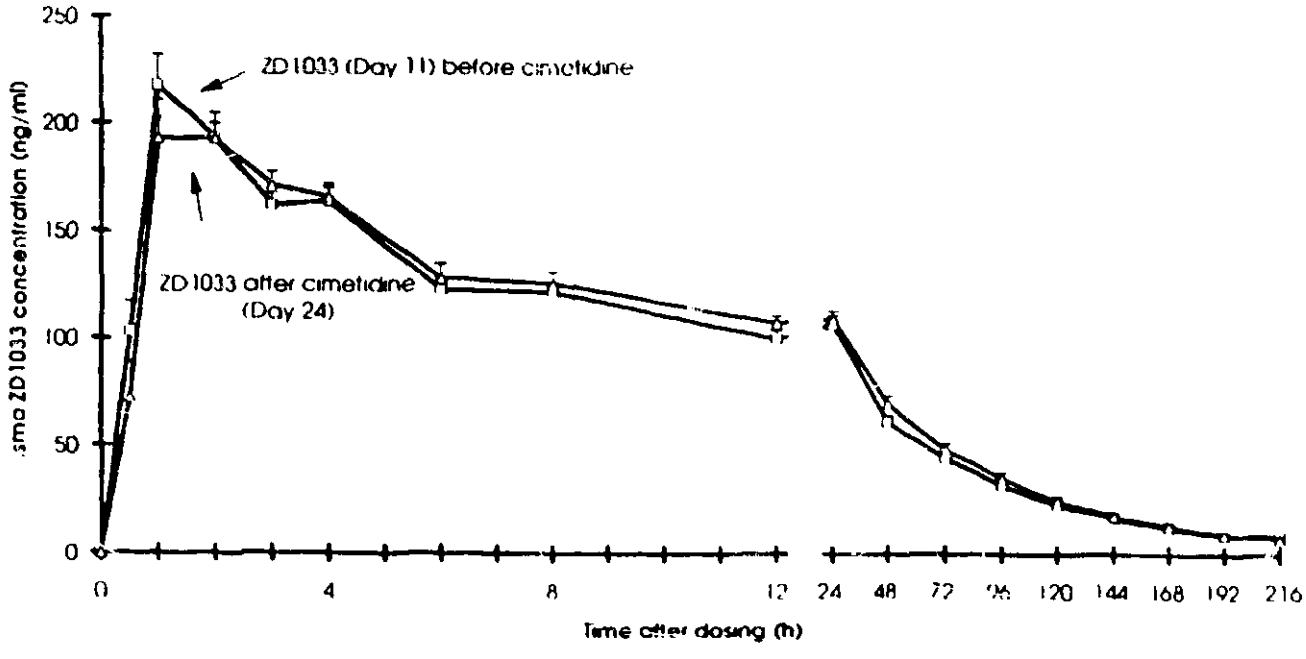
and after cimetidine treatment (days 11 and 24) are shown in the following table. The differences in PK parameters between days 11 and 24 were not found to be statistically significant.

TABLE 25

Parameter	ZD1033 before cimetidine (day 11)	ZD1033 after cimetidine (day 24)	Ratio or difference	90% C.I. on ratio or difference
Geometric mean (95% C.I.)				
AUC_{0-24}, ng.hr/ml	2846 (2645 - 3061)	2924 (2727 - 3136)	0.98	0.93 - 1.02
$AUC_{0-\infty}$, ng.hr/ml	9400 (8203 - 10771)	10035 (8901 - 11314)	1.03	0.98 - 1.08
C_{max}, ng/ml	214 (189 - 242)	209 (184 - 238)	1.07	1.02 - 1.12
Arithmetic mean (SD)				
$t_{1/2}$, hrs	48.7 (11.0)	49.2 (10.23)	0.54	-1.42 - 2.49
Cl/F, ml/min	18.1 (4.0)	16.9 (3.4)	-1.22	-2.22 - 0.21
Median (range)				
T_{max}, hrs	1 (1 - 2)	1 (1 - 6)		

The mean plasma profiles of ZD1033 before and after cimetidine doses are shown in the figure below:

Figure 36 **Mean (SE) plasma ZD1033 concentration for 10-mg doses (n=12)**



INTRASUBJECT VARIABILITY IN ZD1033 PHARMACOKINETICS:

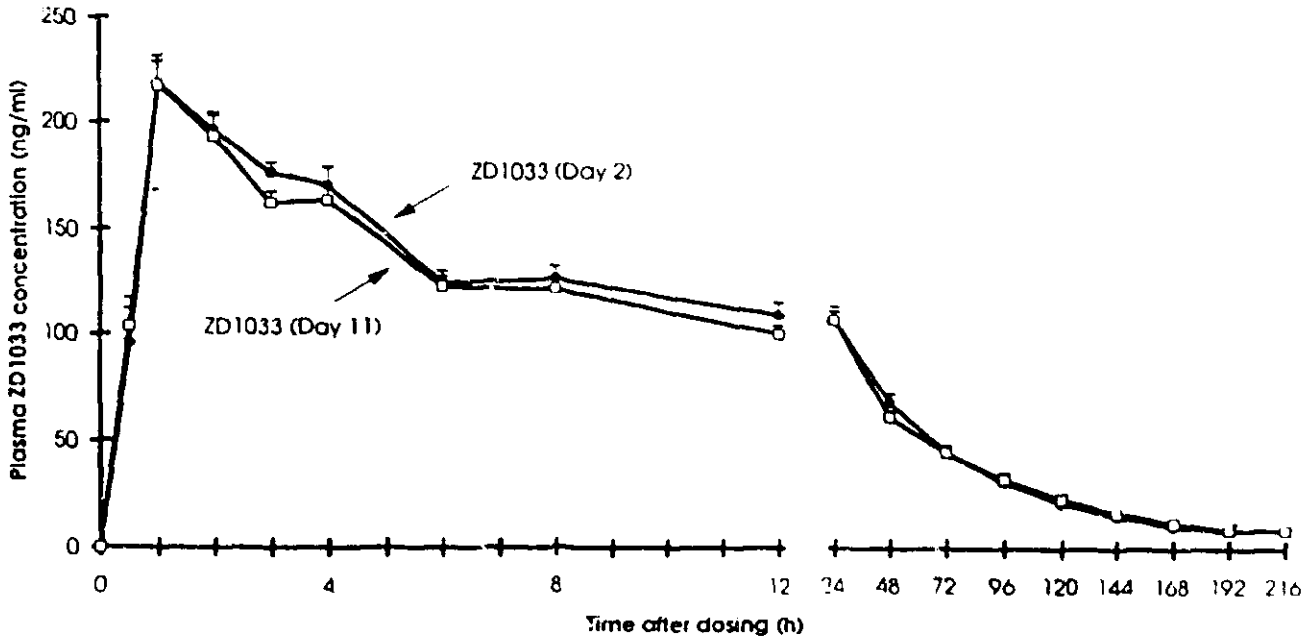
Mean pharmacokinetic parameters obtained for single doses (10 mg) of ZD1033 given on days 2 and 11 are shown in the following table.

TABLE 26

Parameter	First dose of ZD1033 (day 2)	Second dose of ZD1033 (day 11)	Ratio or difference	90% C.I. on ratio or difference
Geometric mean (95% C.I.)				
$AUC_{0-\infty}$, ng.hr/ml	9317 (8029 - 10811)	9400 (8203 - 10771)	0.96	0.89 - 1.03
C_{max}, ng/ml	223 (205 - 243)	214 (189 - 242)	1.01	0.97 - 1.05
Arithmetic mean (SD)				
$t_{1/2}$, hrs	44.5 (8.5)	48.7 (11)	4.15	2.48 - 5.81
Cl/F, ml/min	18.4 (4.5)	18.1 (4.0)	-0.26	-0.92 - 0.40
Median (range)				
T_{max}, hrs	1 (1 - 2)	1 (1 - 2)		

The mean plasma profiles of ZD1033 on days 2 and 11 are shown in the figure below:

Figure 37 **Mean (SE) plasma ZD1033 concentration for 10-mg doses (n=12)**



A comparison of inter and intrasubject C.V.s for AUC, C_{max}, Cl/F and $t_{1/2}$ are shown in the following table:

TABLE (27)

Parameter	Intersubject % CV	Intrasubject % CV
C_{max}	18	10.6
$AUC_{0-\infty}$	21	4.7
$t_{1/2}$	20	7.8
Cl/F	23	4.9

Conclusions:

Cimetidine pretreatment (300 mg q6hours for 4 days) did not affect the pharmacokinetics of single dose of ZD1033. The intrasubject coefficients of variation on various pharmacokinetic parameters indicate that this is not a highly variable drug. Single doses of ZD1033 given alone or following cimetidine treatment were well tolerated.

Comments:

1. This study has some deficiencies in the design in that a) this does not provide any information of the effect of ZD1033 on cimetidine pharmacokinetics, b) enough washout period was not allowed between doses to prevent carryover effect, and c) cimetidine was taken by the subjects at home and not when they were monitored, hence compliance is questionable.
2. Despite these problems, if we assume patient compliance, concomitant administration of cimetidine and ZD1033 was well tolerated and cimetidine did not influence the pharmacokinetics of ZD1033.

STUDY D1033IL/0014: (EFFECT OF HEPATIC IMPAIRMENT)

PHARMACOKINETICS AND SAFETY OF A SINGLE ORAL 10 MG ZD1033 DOSE IN SUBJECTS WITH LIVER DISEASE

Reference: Volume 37
Investigator:
Study Location:
Objective:

To investigate the effect of chronic liver disease on the pharmacokinetics and safety of single oral ZD1033 (10 mg) in patients with chronic liver disease (males and females)

Study design:

This is an open-label, single dose, parallel design pharmacokinetic trial in 8 subjects (4 male and 4 female) with liver disease (group I) and eight normal subjects (4 male and 4 female) matched to the subjects in group I (group II). Men and women between 18 and 70 years of age were included. Subjects in group I had a history of chronic hepatic disease related to alcohol abuse, documented by clinical or laboratory findings and confirmed by liver biopsy. Each subject in group II was sex, age, weight, race and smoking status matched to a subject in group I.

On study day 2, each subject took one 10 mg tablet (F11137, lot # 92-3208, batch # ADM 49243/92) of ZD1033. Blood was drawn periodically up to 264 hours (at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240 and 264 hours) after dosing to determine plasma concentrations of ZD1033. Pharmacokinetic parameters were analyzed by ANOVA. The ANOVA models included effects for paired subjects and groups (hepatically impaired and normal subjects).

Results

ASSAY PERFORMANCE:

Method used: AD SOP 2.103
Range: ng/ml
Linearity: Linear within the range
QC sample levels: 3, 30 and 75 ng/ml
Accuracy: 10.22, 4.19 and 6.23% at low, medium and high QC values
Precision: 29.1, 4.4 and 4.0% at low, medium and high QC levels
Specificity: Chromatographic peaks well resolved

Assay was found to be acceptable (although %CV at low QC was high, when unaccepted QC runs are removed, % CV is much less than 20%).

Pharmacokinetic parameters for hepatically impaired and normal subjects is shown in table below

TABLE 28

Parameter	Hepatically impaired (n = 8)	Normal subjects (n = 8)	Ratio or difference	90% C.I. on ratio or difference
Geometric mean (95% C.I.)				
$AUC_{0-\infty}$, ng.hr/ml	7870 (6830 - 9080)	6120 (4580 - 8180)	1.29	0.99 - 1.68
C_{max}, ng/ml	179 (153 - 209)	143 (130 - 157)	1.25	1.08 - 1.46
Arithmetic mean (SD)				
$t_{1/2}$, hrs	53 (15)	41 (16)	12	-6 - 29
Cl/F, L/hr	1.3 (0.2)	1.7 (0.6)	-0.4	-0.89 - 0.16
V_β/F, L	98 (28)	91 (14)	6.4	-17.30 - 30.09

The geometric mean AUC and C_{max} were 29% and 25% higher in the hepatically impaired group when compared with the normal group.

Plasma concentrations (ng/ml) following 10 mg dose of arimidex in both populations is shown in figures below:

Figure 38

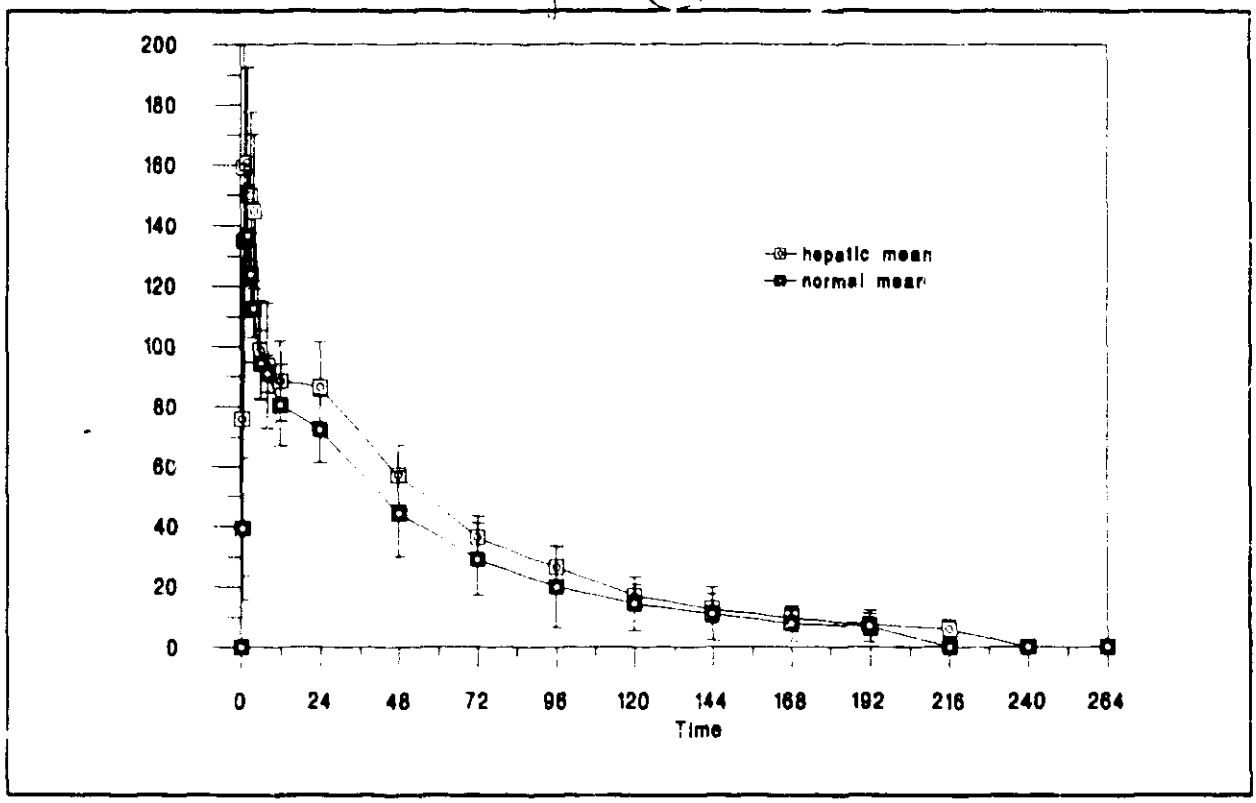
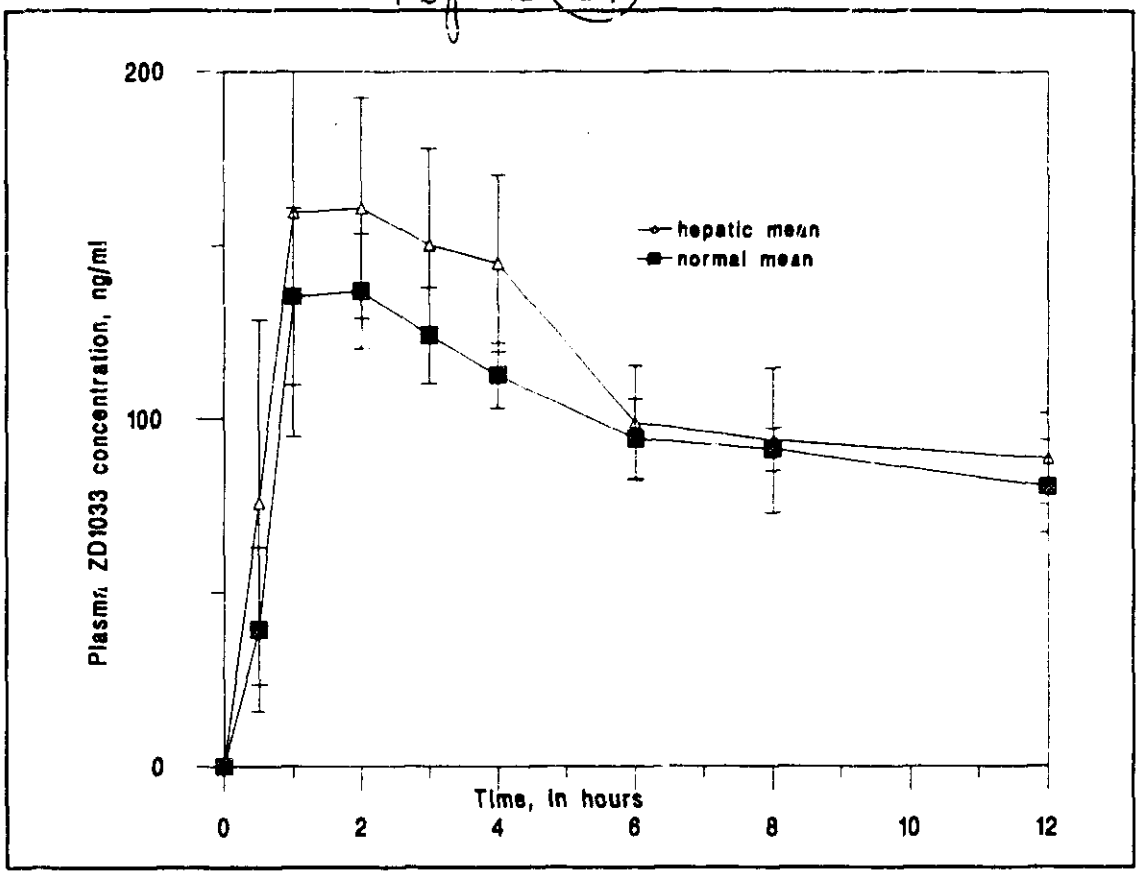


Figure 39



Conclusions:

C_{max} and AUC of ZD1033 in subjects with stable hepatic disease increased about 25-29% relative to normal subjects. However, this increase in levels did not lead to increased problems of toxicity. This dose was well tolerated in both groups of subjects.

Comments:

Since there was not more than 30% increase in pharmacokinetic parameters in hepatically impaired subjects and since this dose was well tolerated, adjustment of dosage in subjects with liver disease does not appear to be necessary, especially now that the proposed dose is 1 mg. Careful monitoring of these patients is recommended because of higher levels of ZD1033 found in these patients.

STUDY D1033IL/0018: (EFFECT OF RENAL IMPAIRMENT)

PHARMACOKINETICS AND SAFETY OF A SINGLE ORAL 10 MG ZD1033 DOSE IN SUBJECTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

Reference: Volumes 38
Investigator:
Study Location:
Objective:

To investigate the effect of severe renal disease on the pharmacokinetics and safety of oral ZD1033 (10 mg) in patients with severe renal impairment (males and females).

Study design:

This is a single dose, open label, pharmacokinetic study conducted in 7 severe renally impaired patients and 7 normal volunteers matched for age, weight, race, smoking status and gender (Phase II was planned to include mild and moderate renally impaired patients but was not carried out based on results of this study). The patients with renal impairment had a creatinine clearance between 10 - 30 ml/min/1.73 m^2 while the normal subjects' creatinine clearance was equal to or > 80 ml/min/1.73 m^2. Men and women between 18 and 70 years of age were included. Subjects in group I had a history of severe renal impairment. Each subject in group II was sex, age, weight, race and smoking status matched to a subject in group I.

On study day 2, each subject took one 10 mg tablet (F11137, lot # 92-3208, batch # ADM 49243/92) of ZD1033. Blood was drawn periodically up to 264 hours (at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240 and 264 hours) after dosing to determine plasma concentrations of ZD1033. Urine samples were collected at 0 - 4, 4 - 8, 8 - 12, 12 - 24, 24 - 48, 48 - 72, and 72 - 96 hours after dosing for determination of ZD1033 concentrations. Pharmacokinetic analysis of data was performed using model-independent technics. Paired T-tests were used to analyze the plasma PK parameters, renal clearance and % urinary recovery. Log-transformed data was used in the analysis of AUC and C_{max}.

Results:

ASSAY PERFORMANCE:

1. Plasma

Method used: AD SOP 2.103
Range: ng/ml
Linearity: Linear within the range
QC sample levels: 3, 30 and 80 ng/ml
Accuracy: -1.48 - 15.66% at low QC, -0.3 to -1.37% at medium QC and -2.73 to 3.8% at high QC
Precision: 4.3 - 14.5% at low QC, 3 - 4.5% at medium QC and 2.6 - 5.1% at high QC levels
Specificity: Chromatographic peaks well resolved

Assay was found to be acceptable.

2. Urine

Method used: 32-03R1
Range: ng/ml
Linearity: Quadratic with negligible 2nd degree polynomial coefficient

QC sample levels: 10, 100 and 400 ng/ml
Accuracy: 6.0, -0.5 and -6.75% at low, medium and high QC levels
Precision: 5.3, 2.5 and 2.9% at low, medium and high QC levels
Specificity: Chromatographic peaks well resolved

Assay was found to be acceptable.

ZD1033 IN PLASMA:

Table (29) Pharmacokinetic parameters for renally impaired and normal subjects is shown in table below:

Parameter	Renally impaired (n = 7)	Normal subjects (n = 7)	Ratio or difference	90% C.I. on ratio or difference
Geometric mean (95% C.I.)				
$AUC_{0-\infty}$, ng.hr/ml	7014 (5491 - 8960)	7512 (5995 - 9414)	0.93	0.73 - 1.20
C_{max}, ng/ml	131 (96 - 179)	158 (115 - 219)	0.83	0.53 - 1.29
Arithmetic mean (SD)				
$t_{1/2}$, hrs	45.8 (12.95)	48.7 (12.96)	-2.89	-12.81 - 7.03
Cl/F, ml/min	24.5 (6.15)	22.8 (5.53)	1.70	-4.17 - 7.57
V_β/F, L	94.2 (37.24)	89.4 (11.28)	4.86	-26.19 - 35.91

Plasma concentrations (ng/ml) and C_{max} and AUC following 10 mg dose of arimidex in both populations is shown in figures below. ZD1033 is absorbed rapidly in both populations with a t_{max} of about 2 hours after dosing. No statistically significant differences in any of the plasma PK parameters were found between the 2 populations.

FIGURE (40) **Plasma ZD1033 concentration following a 10-mg oral dose Mean + SE**

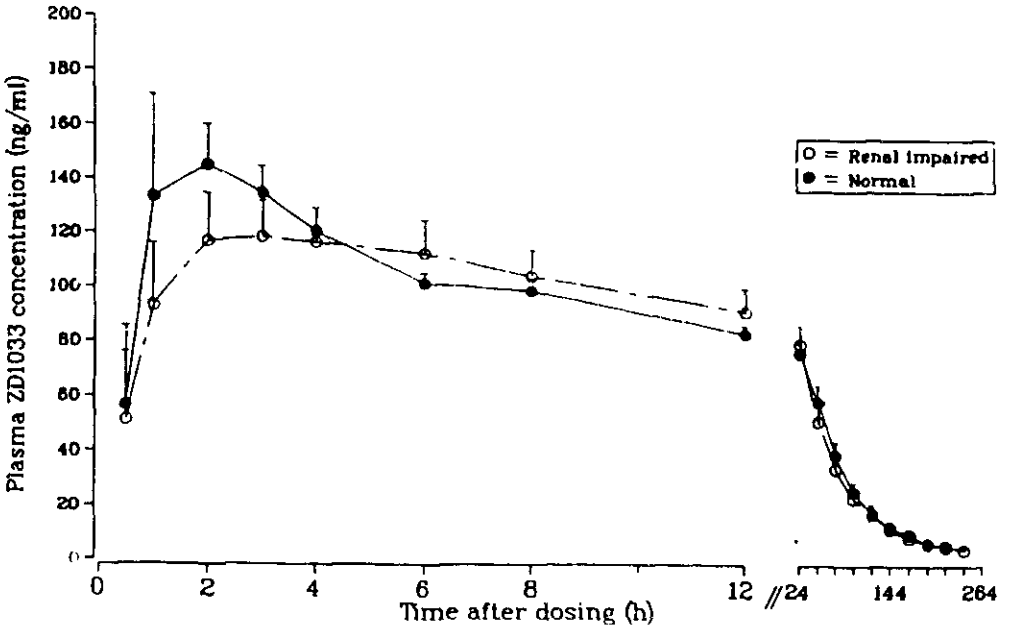


Figure 41

Individual AUC 0-inf values for matched subjects

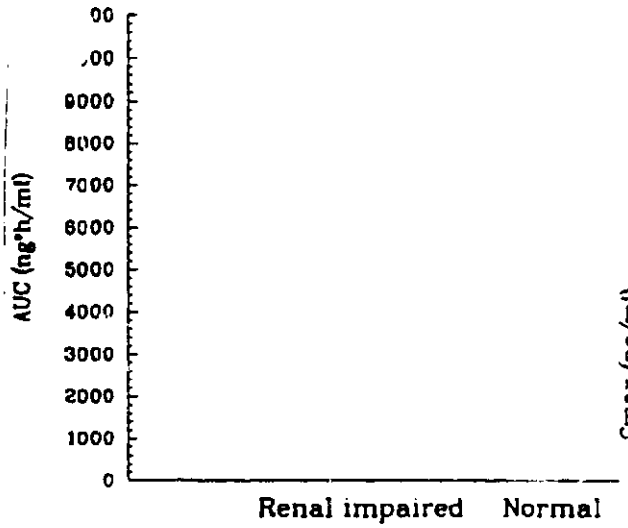
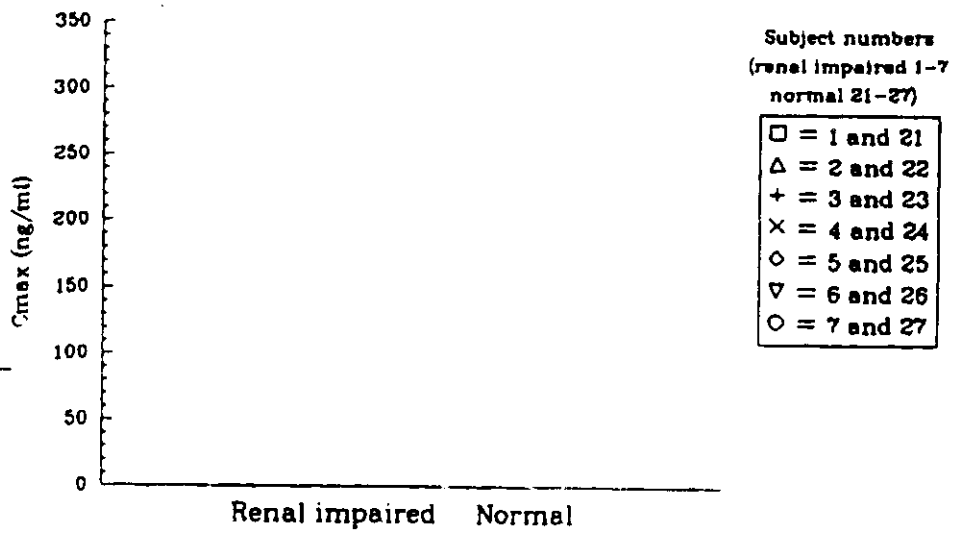


Figure 42

Individual Cmax values for matched subjects



ZD1033 IN URINE:

Following the 10 mg single oral dose of arimidex to severely renally impaired and normal subjects, the mean percent of dose excreted as unchanged drug in urine over the period of 0 - 96 hours was 5.65% and 11.00% respectively (see table below). This difference were found to be statistically significant.

Table 30

MEAN (and SD)URINARY DATA

Parameter	Renally impaired subjects (n = 7)	Normal subjects (n = 7)	Difference	90% C.I.
Renal clearance, ml/min	1.76 (0.47)	3.31 (1.23)	-1.54	-2.46 to -0.63
Recovery, %	5.65 (1.41)	11.00 (3.03)	-5.35	-7.76 to -2.94

Despite the decrease in renal clearance and urinary recovery in renally impaired subjects, this did not lead to significant changes in the plasma PK of the drug.

Conclusions:

C_{max} and AUC of ZD1033 in subjects with severe renal impairment were not statistically significantly different from normal subjects. This dose was well tolerated in both renally impaired and normal subjects. Hence, dosage adjustment in renally impaired patients seems unnecessary.

STUDY 1033DMX040 (IN VITRO ENZYME INHIBITION STUDY):

INHIBITORY EFFECTS OF ZD1033 ON CYTOCHROME P450 ACTIVITIES IN VITRO IN HUMAN HEPATIC MICROSOMES

Reference: Volume 66
Investigator: Scott W. Grimm, MS
Study Location: Zeneca Pharmaceuticals Group, Wilmington, DE 19897
Objective:

To investigate the effects of ZD1033 on human cytochrome P450 activities in vitro and to determine its potential to inhibit the metabolism of other drugs in man.

Study design:

Human liver microsomes obtained from 9 donor livers were incubated with various substrates (nifedipine: 10, 25 and 50 μM; tolbutamide: 100, 200 and 1000 μM; phenacetin: 50, 100 and 200 μM; etc.), reaction cofactors and a range of ZD1033 concentrations (1 - 500 μM). Quantitation of the specific metabolites formed by various isozymes (1A2, 2C8/9, 2D6 and 3A4) of cytochrome P450 were performed using reversed phase HPLC methods. Formation of hydroxycoumarin by P450 2A was monitored by fluorescence spectrometry.

Cimetidine and ketoconazole were used for comparing the inhibition potential of ZD1033 towards P450 3A4-mediated nifedipine metabolism.

IC_{50}s were determined graphically. K_is (inhibition constants) for ZD1033 were determined for different isozymes using Dixon plots.

Results:

The in vitro inhibition results (IC_{50}s and K_is) are shown in table below:

Table (31)

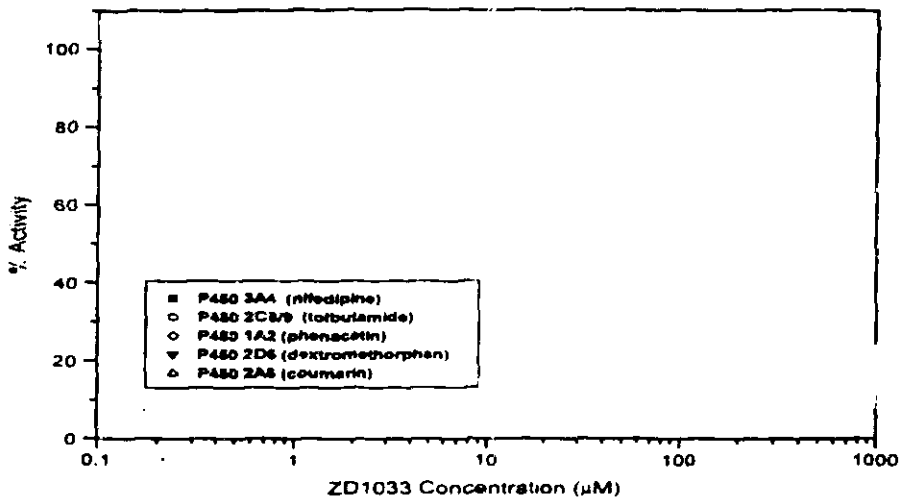
Human cytochrome P450	Test compound	Specific marker substrate	IC_{50} (μM)	K_i (μM)
1A2	ZD1033	Phenacetin	30	8
2A6	ZD1033	Coumarin	NI	---
2C	ZD1033	Tolbutamide	48	10
2D6	ZD1033	Dextromethorphan	NI	---
3A	ZD1033	Nifedipine	27	10
3A	Ketoconazole	Nifedipine	0.02	---
3A	Cimetidine	Nifedipine	650	---

NI = not inhibited at concentrations less than 500 μM.

ZD1033 did not inhibit P450 2D6 and 2A6 in hu nan liver microsomes. The inhibition curves for each cytochrome P450 activity are shown in figure below:

Figure 43

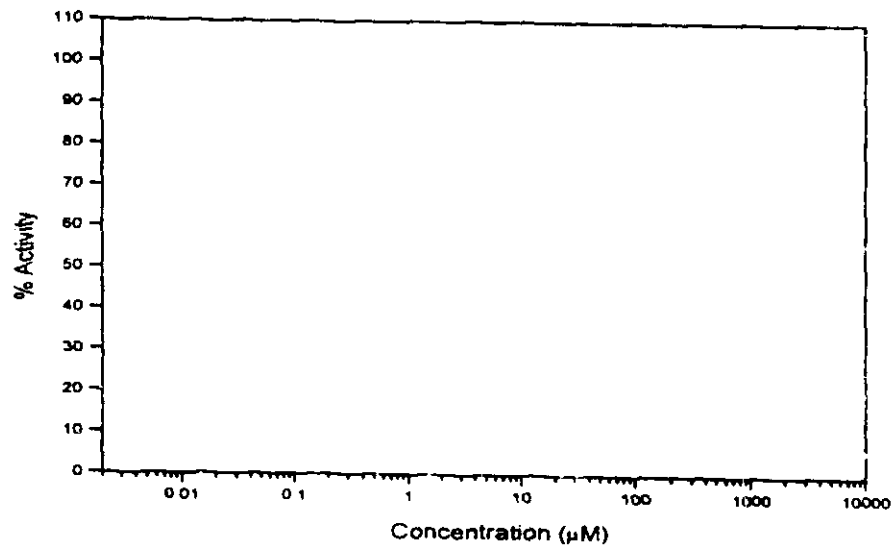
Concentration Response Curves for Inhibition of Human Cytochromes P450 1A2, 2A6, 2C8/9, 2D6 and 3A4 by ZD1033



Inhibition of P450 3A4 by ZD1033, ketoconazole and cimetidine is shown in figure below. Under identical conditions, the IC_{50} values for ZD1033, ketoconazole and cimetidine were 27 µM, 0.02 µM and 650 µM respectively.

Figure 44

Inhibition of Human Cytochrome P450 3A4 Activity by Ketoconazole, ZD1033 and Cimetidine (DMX040)



The K_i values determined for ZD1033 against cytochrome P450 1A2, 2C and 3A were found to be 8, 10 and 10 µM respectively (see Dixon plots shown below). Plots used to determine K_i for the inhibition of nifedipine metabolism exhibited nonlinearity indicating 2 inhibition sites. The second low affinity site had a K_i value of about 55 µM.

Figure 45

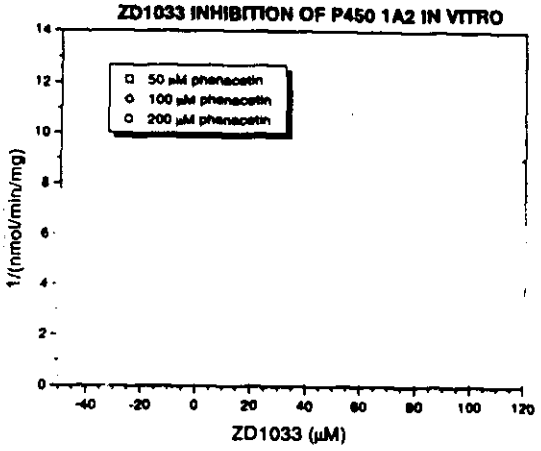


Figure 46

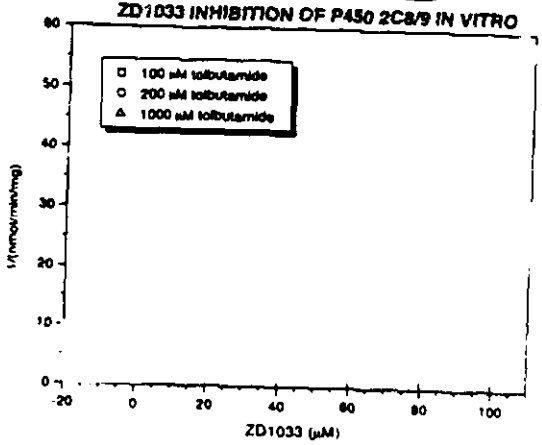
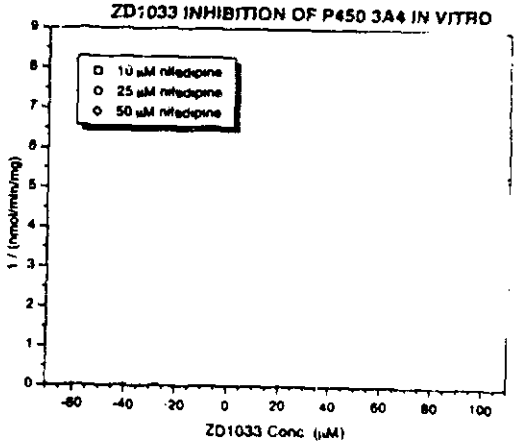


Figure 47



Conclusions:

ZD1033 inhibits cytochrome P450 1A2, 2C8/9 and 3A4 but not 2A6 and 2D6. ZD1033 was a less potent inhibitor of 3A4 than ketoconazole and is more potent than cimetidine.

Comment:

The K_i values (10 µM = 2.9 µg/ml) obtained for inhibition of various isozymes by ZD1033 are about 35 times higher than the anticipated plasma concentrations (in vivo) after administration of 1 mg arimidex tablets. Even though based on the K_i values, ZD1033 seems to be a potent inhibitor, when one takes the plasma concentrations achievable during normal clinical use into consideration, this may not be a potent inhibitor.

STUDY # 1033DMM021/01 (PROTEIN BINDING)

PROTEIN BINDING OF ZD1033 IN SELECTED SPECIES USING EQUILIBRIUM DIALYSIS

OBJECTIVE. To determine the extent of protein binding of ^{14}C-ZD1033 in mouse, rat, rabbit, dog, monkey, human plasma and human serum albumin, as determined by equilibrium dialysis.

METHODOLOGY: Mouse, rat, rabbit, dog, monkey, pooled male and female (normal) human plasma, human plasma from postmenopausal women, pooled male and female human serum, 4% human serum albumin solution and 0.08% α-1-acid glycoprotein solution were subjected to equilibrium dialysis to determine the protein binding of ^{14}C-ZD1033 (radiolabel on the triazole ring) in concentrations ranging from 0.02 - 100 µg/ml. Initial buffer, plasma, serum, albumin and α-1-acid glycoprotein solution and postequilibrium samples on both sides of dialysis membrane are assayed for total radioactivity. Radioactivity concentrations on each side of the membrane after overnight dialysis were used to calculate percent protein binding.

RESULTS: Mean % protein binding in plasma from various species is shown in the table below:

Table 32

Species	Concentration of ^{14}C-ZD1033 used, µg/ml										
	0.02	0.10	0.25	0.5	1.0	5.0	10	25	50	100	Mean
Dog	28.3	32.0	30.3	44.5	52.4	45.0	49.5	46.4	47.7	44.6	42.1
Rat	36.1	43.3	42.6	44.4	43.7	44.2	44.2	43.3	38.6	36.5	41.7
Mouse	31.4	28.7	29.8	25.1	25.4	24.0	22.0	24.1	22.9	21.0	25.4
Rabbit	25.2	22.7	24.9	24.5	23.2	20.9	20.9	21.8	20.6	19.1	22.4
Monkey	21.2	18.4	16.6	15.8	16.6	14.9	14.9	15.9	15.9	14.9	16.5
Human (normal)	33.9	35.2	37.2	38.3	31.6	34.8	30.9	31.4	32.3	25.8	33.1
Human (post-menopausal)	38.2	40.5	38.8	41.4	41.5	39.5	39.6	37.6	35.9	32.9	38.6
Human albumin (40 mg/ml)	22.3	26.1	24.4	21.6	23.1	24.0	23.4	22.6	20.4	19.7	22.8

ZD1033 is moderately bound (33 - 42%) to dog, rat and human plasma. Binding was constant throughout the concentration range (0.02 - 100 µg/ml) studied.

Binding to α-1-acid glycoprotein was determined at 0.1 and 100 µg/ml and was found to be 7.94% and 3.19% respectively.

Conclusions:

Protein binding to plasma from several species studied is moderate (33 - 42%).

DISSOLUTION METHOD DEVELOPMENT

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS:

Dosage form:	Arimidex tablet
Strength:	1 mg
Apparatus:	USP Type II apparatus, Paddle
Medium:	Distilled water
Volume:	1000 ml
Agitation speed:	50 rpm
Sampling time:	minutes
Analytical method:	HPLC with UV detector, at wavelength of 215 nm
Dissolution spec.:	Q % in minutes

Justification of dissolution method:

Solubility of the drug in water at 37°C is 1292 mg/liter. Due to this high aqueous solubility and low dose of arimidex, sink conditions are easily satisfied with water as the dissolution medium.

Dissolution characteristics of the tablet were determined under different dissolution conditions of dissolution media (pH 1 - 8 buffers) and different agitation speeds (25 - 100 rpm). More than 95% of the drug was released in about 10 minutes under all dissolution conditions tested. The only differences observed were at 5 minutes. Based on these results, selection of water as the dissolution medium is appropriate.

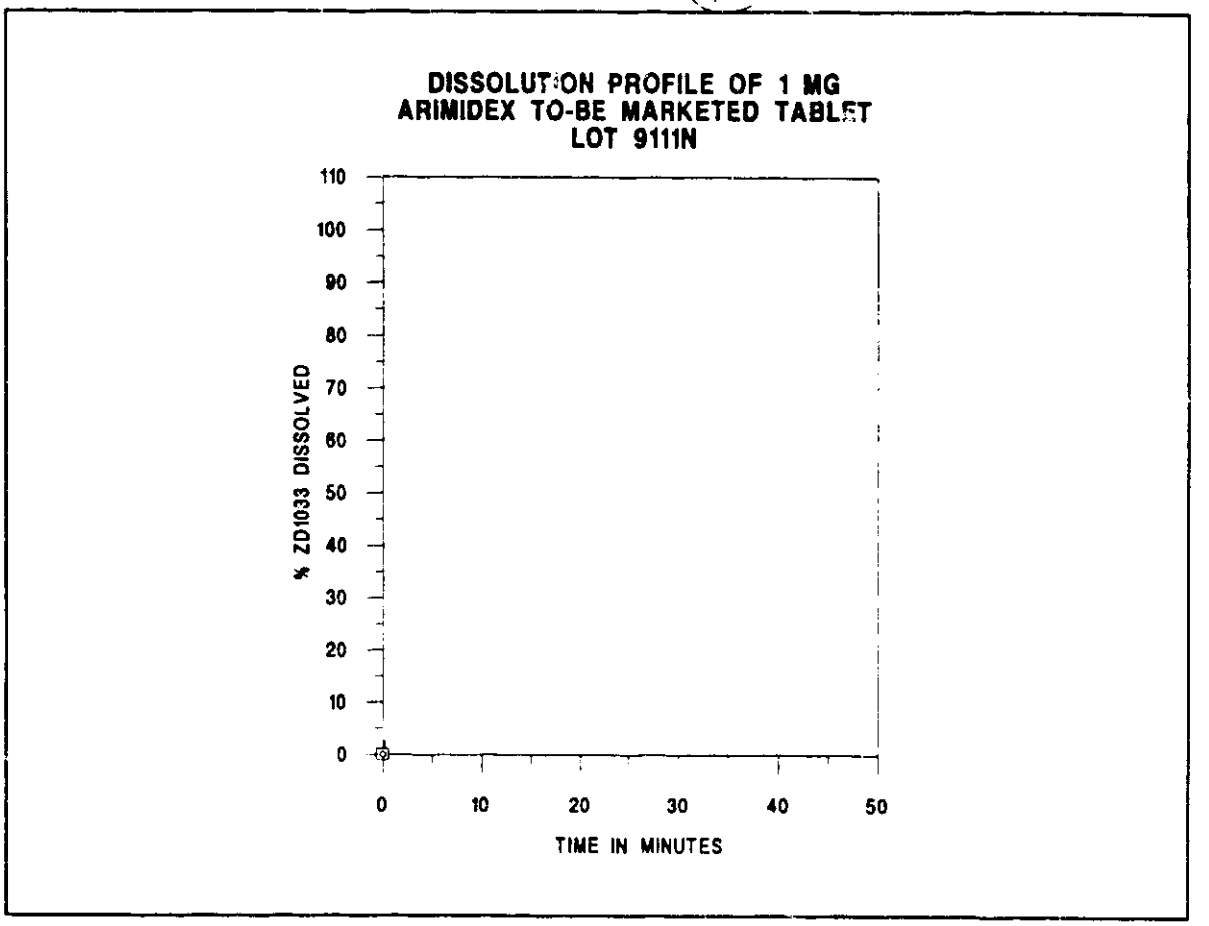
ZD1033 is rapidly released during dissolution (with water as dissolution medium, at 50 rpm, paddle method) as shown in the table below and also in the figure:

TABLE 33

DISSOLUTION DATA FOR ARIMIDEX 1 MG BIOEQUIVALENCE BATCH 9111N

Sample time (minutes)	% ZD1033 dissolved		
	Mean (n = 12)	% CV	Range
5	74	10.3	
10	98	1.2	
15	99	0.8	
30	99	0.8	
45	99	0.9	

FIGURE 48



COMMENTS:

1. Selection of water as the dissolution medium is appropriate after studying different dissolution media. Since the pH of the dissolution medium (water) seems to be unaffected during the course of dissolution, water can be used as the dissolution medium. The dissolution results indicate that this drug is highly soluble. Due to this, the selected dissolution method (as a matter of fact all other dissolution conditions tested) may not discriminate between different formulations of this drug. However, since this is an immediate release formulation of a highly soluble drug, such a method is acceptable.

2. Although only one to-be marketed bio-batch has been tested, all biobatches tested during the course of drug development also provided similar results.

3. Based on the results of dissolution testing, the selected dissolution specification for this product should be changed to Q % in minutes since more than 95% of the drug is released within that period.

ANALYTICAL METHODOLOGY (PRE-STUDY VALIDATION):

A) METHOD 32P-02: (This method was used in studies 0001, 0002, 0003 and 0009)

This method was developed for determination of ZD1033 in human plasma by capillary gas chromatography with electron capture detection. ZD1033 and the internal standard U33477 were separated from endogenous plasma components by an alkaline methyl-t-butyl ether extraction. ZD1033 and internal standard were quantitated by chromatography on a 50% phenyl-methyl silicone cross-linked capillary gas chromatography column, with Ni(63) electron capture detection.

ASSAY PERFORMANCE:

Assay specificity: No matrix interference in plasma and also no interference from aspirin, ibuprofen or acetaminophen.

HIGH SENSITIVITY CURVE:

Range: ng/ml
Standard curve r-squared: > 0.997
Standard curve precision: 5.5 - 19.6%
Standard curve accuracy: 88.8 - 109.7%
Recovery: Approximately 107%
Quality control sample performance:
Target concentration: 2.00 ng/ml
Mean measured concentration: 2.23 ng/ml
Mean accuracy: 112%
Intra-assay precision: 8.5%
Inter-assay precision: 2.2%
Target concentration: 75.0 ng/ml
Mean measured concentration: 75.7 ng/ml
Mean accuracy: 101%
Intra-assay precision: 5.3%
Inter-assay precision: 11.1%

LOW SENSITIVITY CURVE:

Range: ng/ml
Standard curve r-squared: > 0.999
Standard curve precision: 2.6 - 4.3%
Standard curve accuracy: 98.7 - 101.4%
Recovery: Approximately 107%
Quality control sample performance:
Target concentration: 75.0 ng/ml
Mean measured concentration: 75.2 ng/ml
Mean accuracy: 100%
Intra-assay precision: 2.7%
Inter-assay precision: 6.0%

Target concentration: 2500 ng/ml
Mean measured concentration: 2670 ng/ml
Mean accuracy: 107%
Intra-assay precision: 4.8%
Inter-assay precision: 7.1%

Stability of ZD1033 samples:

* Stable at room temperature for 3 hours
* Stable in methyl t-butyl ether after extraction for 2 hours
* Stable in injection solvent for 24 hours
* Stable up to 3 freeze-thaw cycles
* Stable for 9 months if frozen at approximately -70°C

CONCLUSION: This method is precise and accurate and validation results are found to be acceptable.

B) METHOD 32-02R1. (This method was used in studies 0004, 0007, 0012, 0013 and 0019)

This method is a modification of above method developed in order to reduce the sample volume required for analysis. The method is qualitatively same as described above except for changes in conditions such as temperature etc.

ASSAY PERFORMANCE:

Assay specificity: No matrix interference in plasma and also no interference from aspirin, ibuprofen, acetaminophen, aldactone, spironolactone, propranolol etc.

Range: ng/ml (range extended to ng/ml by sample dilution)
Standard curve r-squared: > 0.995
Standard curve precision: 2.2 - 7.2%
Standard curve accuracy: 93.0 - 105%
Recovery: Approximately 91 - 109%

Quality control sample performance:

Target concentration: 7.50 ng/ml	*Target concentration: 15.0 ng/ml*
Mean measured concentration: 7.08 ng/ml	Mean measured concentration: 14.7 ng/ml
Mean accuracy: 94.4%	Mean accuracy: 97.9%
Intra-assay precision: 0.4 - 12.7%	Intra-assay precision: 1.4 - 6.3%
Inter-assay precision: 7.8%	Inter-assay precision: 8.0%
Target concentration: 40.0 ng/ml	*Target concentration: 75.0 ng/ml*
Mean measured concentration: 38.1 ng/ml	Mean measured concentration: 78.1 ng/ml
Mean accuracy: 95.3%	Mean accuracy: 104%
Intra-assay precision: 0.5 - 16.1%	Intra-assay precision: 0.6 - 10.7%
Inter-assay precision: 8.1%	Inter-assay precision: 5.9%

Stability of ZD1033 samples:

* Stable in plasma at room temperature for 7 days
* Stable in methyl t-butyl ether after extraction for 3 hours
* Stable in injection solvent for 72 hours
* Stable up to 3 freeze-thaw cycles
* Stable for 15 months if frozen at approximately -70°C

CONCLUSION: This method and its validation results are found to be acceptable.

C) METHOD AD SOP 2.103 (Validation in UK of the method 32-02R1 developed in US): (This method was used in studies 0010, 0011, 0014, 0016, 0017, 0018 and 0020)

This method is same as 32-02R1 which was developed in US. Limited validation was performed to support the use of this method in UK. This method was also cross-validated with the method in US.

ASSAY PERFORMANCE:

Range: ng/ml (range extended to ng/ml by sample dilution)
Standard curve precision: 6.4 - 16.5%
Recovery: Approximately 94 - 110%

Quality control sample performance:

Target concentration: 3.00 ng/ml	*Target concentration: 30.0 ng/ml*
Mean measured concentration: 3.09 ng/ml	Mean measured concentration: 28.9 ng/ml
Mean accuracy: 97.0%	Mean accuracy: 96.3%
Intra-assay precision: 12.6%	Intra-assay precision: 6.9%
Inter-assay precision: 12.0%	Inter-assay precision: 3.6%

Target concentration: 80.0 ng/ml
Mean measured concentration: 81.1 ng/ml
Mean accuracy: 98.6%
Intra-assay precision: 6.0%
Inter-assay precision: 3.6%

CONCLUSION: The validation results are found to be acceptable

D) METHOD 32U-03:

This method was developed for determination of ZD1033 in human urine by capillary gas chromatography with electron capture detection. ZD1033 and the internal standard U33477 were separated from endogenous components in urine by an alkaline methyl-t-butyl ether extraction. ZD1033 and internal standard were quantitated by chromatography on a 50% phenyl-methyl silicone cross-linked capillary gas chromatography column, with Ni(63) electron capture detection.

ASSAY PERFORMANCE:

Assay specificity: No matrix interference in urine and also no interference from aspirin, ibuprofen or acetaminophen.

Range: ng/ml
Standard curve r-squared: > 0.999
Standard curve precision: 1.9 - 8.0%
Standard curve accuracy: 92.1 - 108.5%
Recovery: Approximately 100%
Quality control sample performance:
Target concentration: 10.0 ng/ml
Mean measured concentration: 11.0 ng/ml
Mean accuracy: 110%
Intra-assay precision: 6.6%
Inter-assay precision: 6.1%
Target concentration: 100 ng/ml
Mean measured concentration: 100 ng/ml
Mean accuracy: 100%
Intra-assay precision: 6.4%
Inter-assay precision: 12.8%
Target concentration: 400 ng/ml
Mean measured concentration: 423 ng/ml
Mean accuracy: 106%
Intra-assay precision: 1.7%
Inter-assay precision: 8.7%

Stability of ZD1033 samples:
* Stable at room temperature for 3 hours
* Stable in methyl t-butyl ether after extraction for 2 hours
* Stable in injection solvent for 24 hours
* Stable up to 4 freeze-thaw cycles
* Stable for 1 month if frozen at approximately -10°C

CONCLUSION: This method is precise and accurate and validation results are found to be acceptable.

APR 19 1995

NDA 20-541 Submission Date: March 28, 1995

Drug Name, Dose and Formulation: Arimidex® (Anastrozole) Tablets, Anastrozole 1 mg

Sponsor: Zeneca Pharmaceuticals, Wilmington, Delaware 19897

Reviewer: Venkata Ramana K. Sista, Ph.D.

Type of Submission: New Drug Application, NME, 1S

ISSUE: 21-day Filing Meeting

I. BACKGROUND

Arimidex® Tablet contains anastrozole which is a nonsteroidal aromatase inhibitor. This drug is a triazole derivative, is achiral and exists as a single polymorph. The aromatase enzyme complex catalyses the synthesis of estrogens from androgens. Since estrogens promote growth of certain breast tumors, inhibition of oestrogen synthesis by aromatase enzyme inhibition is an effective treatment for hormone-dependent breast cancer. The sponsor has proposed to market the Arimidex tablets at a dose strength of 1 mg. The proposed indication for Arimidex is for the treatment of advanced breast cancer in postmenopausal women who have progressed following tamoxifen therapy. The proposed dose is 1 mg tablet to be taken once a day.

The sponsor met with the agency on 08/11/1994 (pre-NDA meeting) where various issues and aspects to be included in the NDA were identified.

II. OBJECTIVES

This NDA is submitted requesting approval of the Arimidex® Tablets containing 1 mg of anastrozole per tablet.

III. PHARMACOKINETIC / BIOAVAILABILITY STUDIES

The pharmacokinetics of anastrozole have been studied following both single and multiple dose administration. The sponsor has submitted studies related to analytical methodology, dissolution testing, single and multiple dose pharmacokinetics (both in healthy subjects and patients), dose proportionality, systemic bioavailability, metabolism and disposition of anastrozole and food effect study as part of human pharmacokinetics and biopharmaceutics. Drug interaction studies with antipyrine and cimetidine have been provided. Studies in patients with compromised

hepatic and renal function have also been submitted. No formal study in elderly subjects is provided, however data from clinical trials have been analyzed to determine effect of age. Information on gender effect on anastrozole pharmacokinetics have been provided based on across study comparisons. Effect of race on anastrozole pharmacokinetics has not been studied. Bioequivalence studies between the clinical formulation and to-be marketed tablet formulations have also been provided. Pharmacodynamic information is provided in this NDA, however no PK-PD analyses have been carried out. In vitro protein binding studies and in vitro cytochrome P450 enzyme inhibition studies have been carried out.

IV. COMMENTS

Studies to investigate the pharmacokinetics of anastrozole, as well as bioequivalence studies comparing the clinical formulations versus the to-be-marketed formulations have been carried out.

ITEMS to be noted:

1. No formal PK-PD analyses have been carried out.
2. Analyses of adverse events in clinical trials to analyze possible drug interactions as suggested by the agency previously have not been provided.
3. Even though PK data is available in phase III clinical trial, no population type of analyses is provided.
4. Dissolution data in 3 media is not provided and dissolution method development details not provided.
5. One of the metabolites (N-glucuronide) was found only in humans and not in animals. The activity and toxicity information of this metabolite is not available.
6. The enzymes responsible for anastrozole metabolism have not been identified.
7. Dixon plots in in vitro enzyme inhibition studies have not been submitted.
8. No absolute bioavailability data is provided.
9. Dosage form proportionality confounds dose proportionality in the dose proportionality study (study was done at different dose levels but utilized different tablet strengths instead of multiples of one tablet strength).

V. RECOMMENDATION

The Biopharmaceutics section of this NDA is organized, indexed, and paginated in a manner to initiate a substantial review. Hence, the submission is fileable from Biopharmaceutics point of view.

The sponsor should provide the following information to the agency:

1. Report of dissolution method development.
2. Dixon plots (and data) in the in vitro cytochrome P450 enzyme inhibition study.
3. Any information on enzymes involved in metabolism of anastrozole.

4. All the data from pharmacokinetic studies should be provided in ASCII format.

5. The pharmacokinetic data in all studies carried out in postmenopausal breast cancer patients should be provided in ASCII format. These files should include demographic information, smoking status and any other covariates available.

Please forward the above information request to the sponsor.

Venkata Ramana K. Sista, Ph.D.
Pharmacokinetics Evaluation Branch-I

FT Initialed by Lydia Kaus, Ph.D. 4/19/95
pp. Mehul Mehta.

CC list:
HFD-150: NDA 20-541;
HFD-150: Division file;
HFD-150: Dotti Pease; Leslie Vaccaro;
HFD-150: Linda Beitz;
HFD-150: Chemist;
HFD-150: Pharmacologist;
HFD-426: Mehul Mehta;
HFD-426: Nicholas Fleischer;
HFD-426: ChenM;
HFD-426: Chron;
HFD-426: Venkata Ramana K. Sista;
HFD-340: Viswanathan;
HFD-19 : FOI.

Chem

(F4)

NO BD #

N94
87

November 30, 1994

0180132 00

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

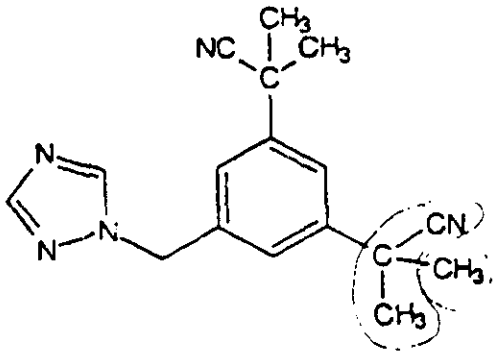
USAN (HH-1)	ANASTROZOLE
PRONUNCIATION	ăn ăs´ trō zōl
THERAPEUTIC CLAIM	aromatase inhibitor used in the treatment of advanced breast cancer

CHEMICAL NAMES

1) α,α,α′,α′-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-benzenediacetonitrile

2) α,α,α′,α′-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-*m*-benzenediacetonitrile

STRUCTURAL FORMULA



MOLECULAR FORMULA	$C_{17}H_{19}N_5$
MOLECULAR WEIGHT	293.4
TRADEMARK	Arimidex
MANUFACTURER	Zeneca Limited
CODE DESIGNATIONS	ICI D1033; ZD1033
CAS REGISTRY NUMBER	120511-73-1
WHO NUMBER	7274

SVF/gat

RHW 5-18-95

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-600) MPN II

FROM: Division of Oncology and Pulmonary Drug Products HFD-150
Attention: Sung K. Kim, Ph.D., Review Chemist, Phone: 594-5704

DATE: May 18, 1995

Subject: Request for Assignment of a Trademark for a Proposed Drug Product

Proposed Trademark: ARIMIDEX NDA # 20-541

Established name, including dosage form:
Anastrozole 1mg Tablets (Immediate release)

Other trademarks by the same firm for companion products:
NOLVADEX Tablets

Indications for Use:
Treatment of advanced breast cancer in post menopausal women who have progressed following tamoxifen (NOLVADEX Tablets) therapy.

Initial comments from the submitter: (concerns, observations, etc.)

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: HFD - to DR 5-18
to Mulle 5-18

Consult #448 (HFD-150)

ARIMIDEX — Anastrozole Tablets 1 mg

A review revealed no names which sound like or look like the proposed name.

The Committee notes that anastrozole is not in the 1995 USP Dictionary of USAN and International Drug Names, and urges Division reviewers to assure the name is submitted to USAN for selection. If the USAN is something other than anastrozole, the Division reviewers may want to resubmit the proposed proprietary name for reevaluation by the Committee in order to avoid any potential USAN conflict.

Other than the comments expressed above, the Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Elaine Keith Mille, Chair 7/9/9

COMPLETED

DEC 2 1 1995

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-541 CHEMISTRY REVIEW #: 4 REVIEW DATE: December 21, 1995

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	28-MAR-95	29-MAR-95	07-APR-95
Amendment (BC)	14-DEC-95	14-DEC-95	14-DEC-95

NAME & ADDRESS OF APPLICANT:

Zeneca Pharmaceuticals Limited
Macclesfield, Cheshire SK10 2NA
United Kingdom

Zeneca Pharmaceuticals (US Agent)
1800 Concord Pike- P.O.Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME:

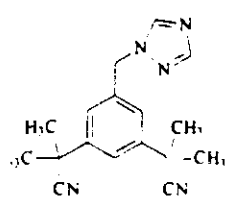
Proprietary:	Arimidex tablet
Nonproprietary/USAN:	Anastrozole
Code Name/Number:	ZD1033
Chem. Type/Ther. Class:	1 S

PHARMACOL. CATEGORY/INDICATION: Aromatase inhibitor for treatment of breast cancer in post menopausal women

DOSAGE FORM: Tablet
STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: Oral, QD
DISPENSED: _X_ Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: 1,3-Benzenediacetonitrile, α,α,α',α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)
IUPAC Name: 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]-bis-(2-methylpropiononitrile)
M.F.: $C_{17}H_{19}N_5$
M.W.: 293.4



Anastrozole

SUPPORTING DOCUMENTS:
INDs: IND

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

It is noted that the Biopharm. reviewer proposed a dissolution specification of Q % at minutes in the review notes of 9/28/95 and the proposed dissolution specification was accepted by the applicant

This amendment provides for the applicant's response to the chemistry deficiencies which were raised in the chemistry review #3 and faxed on 12/12/95. The response is adequate. Approval of NDA 20-541 is recommended from the standpoint of chemistry.

Sung K. Kim, Ph.D.
Review Chemist, HFD-150

cc:
Orig. NDA 20-541
HFD-150/Division File
HFD-150/SKim
HFD-150-/LVaccari
HFD-150/RWood
R/D Init. by: RHWood 12-21-95
filename: N20541.ad3

DEC 1 1

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-541 CHEMISTRY REVIEW #: 3 REVIEW DATE: December 11, 1995

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	28-MAR-95	29-MAR-95	07-APR-95
Amendment (BC)	03-NOV-95	03-NOV-95	03-NOV-95

NAME & ADDRESS OF APPLICANT:

Zeneca Pharmaceuticals Limited
Macclesfield, Cheshire SK10 2NA
United Kingdom

Zeneca Pharmaceuticals (US Agent)
1800 Concord Pike- P.O.Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME:

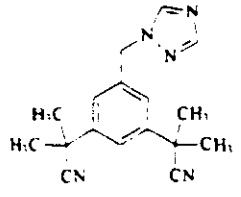
Proprietary:	Arimidex tablet
Nonproprietary/USAN:	Anastrozole
Code Name/Number:	ZD1033
Chem. Type/Ther. Class:	1 S

PHARMACOL. CATEGORY/INDICATION: Aromatase inhibitor for treatment of breast cancer in post menopausal women

DOSAGE FORM: Tablet
STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: Oral, QD
DISPENSED: _x_ Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: 1,3-Benzenediacetonitrile, α,α,α',α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)
IUPAC Name: 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]-bis-(2-methylpropiononitrile)
M.F.: $C_{17}H_{19}N_5$
M.W.: 293.4



Anastrozole

SUPPORTING DOCUMENTS:
INDs: IND

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Final update for EER was submitted on 11/15/95 and found to be acceptable on 11/27/95.

Stability data was consulted on 9/25/95 and the reviewer in the Biometrics Division concluded that the statistic. support an expiry life of 30 months in 30 count HDPE bottles and an expiry life of 28 months in 100 count HDPE bottles (attached statistical review completed on 12/4/95). It is noted that only 30 count package size will be marketed in the US. One hundred count package size is for UK market (communication with CSO, Lvaccari on 12/11/95).

It is noted that the CMC portions in labeling have been revised according to the comments in the chemistry review #2 ((communication with CSO, Lvaccari on 12/11/95).

EA consult was submitted originally on 4/18/95 followed by the second consult of 11/8/95. The EA was acceptable and the FONSI was issued on 12/8/95.

This amendment provides for the applicant's response to the chemistry deficiencies faxed on 10/6/95. The response is adequate pending resolution of the comments in the draft letter. NDA 20-541 is approvable from the standpoint of chemistry pending resolution of the comments made in this chemistry review #3.

Sung K. Kim, Ph.D.
Review Chemist, HFD-150

cc:
Orig. NDA 20-541
HFD-150/Division File
HFD-150/SKim
HFD-150-/LVaccari
HFD-150/RWood
R/D Init. by: RWood 12-1-95
filename: N20541.ad2

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-541 CHEMISTRY REVIEW #: 2 REVIEW DATE: November 1, 1995

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	28-MAR-95	29-MAR-95	07-APR-95
New Correspondence	09-AUG-95	15-AUG-95	22-AUG-95

NAME & ADDRESS OF APPLICANT:

Zeneca Pharmaceuticals Limited
Macclesfield, Cheshire SK10 2NA
United Kingdom

Zeneca Pharmaceuticals (US Agent)
1800 Concord Pike- P.O.Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME:

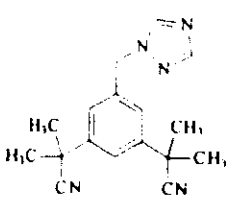
Proprietary: Arimidex tablet
Nonproprietary/USAN: Anastrozole (This name was adopted by the USAN Council, the publication of 11/30/94, see a copy attached)
Code Name/Number: ZD1033
Chem. Type/Ther. Class: 1 S

PHARMACOL. CATEGORY/INDICATION: Aromatase inhibitor for treatment of breast cancer in post menopausal women

DOSAGE FORM: Tablet
STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: Oral, QD
DISPENSED: _x_ Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: 1,3-Benzenediacetonitrile, α,α,α',α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)
IUPAC Name: 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]-bis-(2-methylpropiononitrile)
M.F.: $C_{17}H_{19}N_5$
M.W.: 293.4



Anastrozole

SUPPORTING DOCUMENTS:
INDs: IND

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:
CMC deficiencies were noted in the proposed package insert. The deficiencies indicated in the draft letter should be forwarded to the applicant.

Sung K. Kim, Ph.D.
Review Chemist, HFD-150

cc:
Orig. NDA 20-541
HFD-150/Division File
HFD-150/S.Kim
HFD-150-/L.Vaccari
HFD-150/R.Wood
R/D init. by: RHWood 11-6-95
filename: N20541.ad1

L. Vaccaro

OCT 4 1995

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-541 CHEMISTRY REVIEW #: 1 REVIEW DATE: September 29, 1995

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	28-MAR-95	29-MAR-95	07-APR-95
New Correspondence	02-JUN-95	07-JUN-95	07-JUN-95
New Correspondence	09-AUG-95	15-AUG-95	22-AUG-95
New Correspondence	21-AUG-95	25-AUG-95	25-AUG-95
New Correspondence	22-SEP-95	22-SEP-95	22 SEP-95

NAME & ADDRESS OF APPLICANT:

Zeneca Pharmaceuticals Limited
Macclesfield, Cheshire SK10 2NA
United Kingdom

Zeneca Pharmaceuticals (US Agent)
1800 Concord Pike- P.O.Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME:

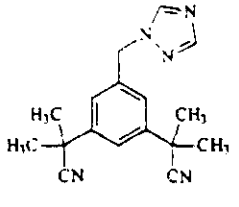
Proprietary: Arimidex tablet
Nonproprietary/USAN: Anastrozole (This name was adopted by the USAN Council, tne publication of 11/30/94, see a copy attached)
Code Name/Number: ZD1033
Chem. Type/Ther. Class: 1 S

PHARMACOL. CATEGORY/INDICATION: Aromatase inhibitor for treatment of breast cancer in post menopausal women

DOSAGE FORM: Tablet
STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: Oral, QD
DISPENSED: _x_ Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: 1,3-Benzenediacetonitrile, α,α,α',α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)
IUPAC Name: 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]-bis-(2-methylpropiononitrile)
M.F.: $C_{17}H_{19}N_5$
M.W.: 293.4



Anastrozole

SUPPORTING DOCUMENTS:

INDs: IND

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in this review
			Satisfactory	5/27/93	Reviewed by HFD-155
			Satisfactory	8.25.94	Reviewed by HFD-623
				N/A	
		Facility for Baltimore, MD		N/A	

* It is not clear whether information on the child-resistant closure system can be found in one of the above referenced DMFs (see deficiency letter).

RELATED DOCUMENTS (if applicable): NA

CONSULTS:

Environmental assessment submitted on 4/18/95, Pending.
EER for Zeneca UK and USA sites initiated on 5/18/95. Withhold recommendation for USA site on 8/8/95 (attached). Recently, the US and UK sites were acceptable on 8/25/95 (attached EER)
Trademark consultation on 5/18/95. Acceptable on 7/9/95 (attached).
Stability data was consulted to the Biometrics Division on 9/25/95. Pending
Method validation will be initiated after satisfactory response to deficiencies regarding method validation.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

CMC deficiencies were noted in this application. The deficiencies indicated in the draft letter should be forwarded to the applicant.

cc:
Orig. NDA 20-541
HFD-150/Division File
HFD-150/S.Kim
HFD-150-/L.Vaccari
HFD-150/P.Andrews
HFD-150/J.Beitz
HFD-150/R.Sista
HFD-150/R.Wood

Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

R/D Init. by: RHW 10-4-95

filename: N20541.org

E.A.
+
Fonsi

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Arimidex®

(anastrozole)

Oral Tablet (1 mg)

NDA 20-541

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Oncology Drug Products (HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

Arimidex®

(anastrozole)

Oral Tablet (1 mg)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Arimidex®, Zeneca Pharmaceuticals has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Anastrozole is a chemically synthesized drug which is administered as a 1 mg oral tablet in the treatment of advanced breast cancer. The drug substance is manufactured by Zeneca Limited, Macclesfield, Cheshire, England. The drug product will be formulated and final packing will take place at the Zeneca facility at Newark, Delaware. The finished drug product will be used in hospitals and private homes throughout the United States.

Drug substance that is introduced into the patient is substantially metabolized *in vivo*, and will be distributed into wastewater treatment systems throughout the United States. Chemical and physical test results indicate that anastrozole will most likely be restricted to the aquatic environment and may absorb to soil under acidic conditions. The principle method of depletion of anastrozole in the environment is by hydrolysis although a slow process. The effect of anastrozole to several environmental organisms was characterized. The Lowest Observed Effect Concentration (LOEC) to *Daphnia magna* was 5.6 mg/L. The maximum expected environmental concentration is several orders of magnitude lower than this toxicity value and therefore no adverse environmental impacts are expected.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Rejected or returned

drug product will be disposed of at licensed high temperature incinerators. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

12/07/95
DATE

Approved
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

12/08/95
DATE

Concurred
Nancy Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

HFD-150/CSO copy to NDA 20-541
HFD-357/FONSI File
HFD-357/Docket File
HFD-019/FOI COPY

CONTENTS

ARIMIDEX ENVIRONMENTAL ASSESSMENT

SECTION 1.

DATE: February 1995

SECTION 2.

APPLICANT:

ZENECA Limited,
Macclesfield, Cheshire, England

ZENECA Pharmaceuticals Group a business unit of ZENECA Inc is the authorised US agent for ZENECA Limited for the subject NDA

SECTION 3.

ADDRESSES:

Administrative Headquarters.

ZENECA Limited
Alderley Park
Macclesfield Cheshire
SK10 4TF England

Site for Manufacture of Active Material

ZENECA Limited
Macclesfield Cheshire
SK10 4TF England

Site for Formulation of Drug Product & US Distribution Centre

ZENECA Pharmaceuticals Group
587 Old Baltimore Pike
Newark, Delaware 19711

SECTION 4.

DESCRIPTION OF THE PROPOSED ACTION

4.1 Describe the requested action

ZENECA Limited is filing a new drug application for approval to manufacture and formulate Arimidex. The active agent of Arimidex, which is also known ZD 1033, is an aromatase inhibitor.

4.2 Describe the need for the proposed action

Arimidex is a drug for the treatment of advanced post-menopausal breast cancer.

3 Locations where the products are to be :-

(1) Produced

The active material will be produced at the ZENECA manufacturing site at Macclesfield.

The address of the facility is:-

ZENECA Limited
Charter Way, Hurdsfield Industrial Estate
Macclesfield, Cheshire, SK10 4TF. England

(2) Formulation and Final Packing

The active drug substance will be formulated and final packing will take place at the ZENECA facility at Newark, Delaware in the USA.

The address of the Newark facility is:-

ZENECA Pharmaceuticals Group
587 Old Baltimore Pike
Newark, Delaware 19711

The latter facility will be the distribution point for the USA.

(4) Used

Arimidex is indicated for the treatment of advanced postmenopausal breast cancer. The product will be used in hospitals and in home care therapy.

(5) Disposed

The product is used in hospitals and homes for treating patients with advanced post-menopausal breast cancer. It is administered in tablet form. The packaging would be disposed of by the normal methods used for disposing of the packaging of medicinal products. Any rejected, returned or time expired product will be disposed of by high temperature incineration in facilities approved by the relevant local authorities in that country. Details of the contractors currently used by Zeneca at Newark and Macclesfield are included in Section 6.

4.4 Types of location in which the manufacturing sites detailed in 4.3 (1) above are located.

4.4.1 Manufacture of Active Material

The ZENECA Pharmaceuticals site at Macclesfield is located in an area designated as an industrial zone. It is adjacent to other industrial properties and is bounded on one side by a residential area and on the other by farmland.

The site stands to the west of a range of hills on the edge of open country. The prevailing wind direction is from the south west.

The site itself is 82 acres of land which slopes from east to west. The site is located near the eastern edge of the Cheshire Basin. The Cheshire Basin contains Triassic sediments (approximately 225-190 million years old) which were deposited by very large north flowing braided rivers systems which flowed within fault controlled basins such as the Cheshire Graben during the Triassic Period. The Cheshire Basin was a subsiding structure which allowed the accumulation of several 1,000 metres of Triassic sediments. The gradual erosion and burial of the upland 'sediment source' areas during Triassic times led to a progressive change in the type of sedimentation. Early piedmont delta deposits gave way to water-lain sands and eventually to marls deposited in standing water. Thus, in general, deposits of progressively finer grain were laid down as the Triassic period continued.

Approximately 1 km to the east of the ZENECA site is located the north-south trending Red Rock Fault, which represented the former edge of the Triassic depositional basin. To the east of this fault lie the high grounds of the Peak District which comprise Carboniferous strata, notably the Millstone Grit Series in the vicinity of Macclesfield.

The Cheshire Basin Triassic Sandstone lithologic sequence comprise the Bunter and Keuper Formations. The Bunter Formation attains a thickness of nearly 1,000m and characteristically comprises soft red and mottled sandstone. The three sub-divisions of the Bunter are:

- Upper Mottled Sandstone;
- Bunter Pebble Beds;
- Lower Mottled Sandstone.

All are heavily stained with ferric oxide giving them their brick red coloration. The Bunter pebble Beds which are characteristically more indurated and coarser grained than the Mottled Sandstones are particularly thick in the Cheshire Basin.

The Keuper Formation overlies the Bunter and in most areas the basal Keuper is sharply differentiated from the underlying formation, being a hard, coarse grained sandstone. The Keuper Formation is over 1,250m thick in the Cheshire Basin and is made up of a three-fold division:

- Keuper Marl;
- Waterstone;
- Keuper Sandstone (bottom)

All three groups merge into one another becoming progressively finer in grain until the clay of the Keuper Marl, with its evaporitic beds, overspread the other Triassic rocks. In the Alderley Edge area, the Keuper Sandstone basal beds are noted as being coarse grained and conglomeratic. The Waterstones are an alternating series of thin bedded marly brown sandstones and soft sandy marls and variegated shales. They represent a transitional depositional phase between the underlying Keuper Sandstone and the overlying Keuper Marl. In the Cheshire Basin the Keuper Marl attains its fullest development in Britain. The Keuper Marl comprises a relatively homogeneous sequence silty red clay (Marl) with thin intercalations of dolomitic substance.

In the vicinity of the ZENECA Macclesfield site the Triassic Sandstone lithologies comprise Upper Mottled Sandstone and Bunter Pebble Beds of the Bunter Formation, and no impermeable Keuper lithologies are present.

Overlying the Triassic Sandstone Formations are a sedimentary succession of Pleistocene and recent deposits, which are 50-60m in thickness in the vicinity of the ZENECA Macclesfield facility. These drift deposits are generally differentiated as boulder clay or sands and gravels. This is somewhat misleading as they are characteristically intricately intercalated with both vertical and lateral gradation and discontinuity.

The site has been developed over the last 20 years to provide a comprehensive facility for the development, manufacture, formulation and distribution of pharmaceuticals together with associated laboratories and administration areas. The buildings are of modern design and construction.

4.4.2 Formulation, Final packing and Distribution

Geographically the ZENECA Pharmaceuticals Group facility is on the Delaware Peninsula where the weather is moderated by both the Chesapeake Bay to the west and the Delaware River and Bay and Atlantic Ocean to the east. The area of the plant site is a plain just south of hills which extend from northern Delaware into Pennsylvania.

The environment of the site itself is 87 acres of relatively flat second growth woodlands. The soils are a thin layer of organic soils over heavy clay and occasional sand or glacial till. The sedimentary rock beneath the soils is deeply buried at the plant site and nearby area. Development of the site is about 405,000 square feet of buildings which supports the pharmaceuticals business, substantial grass lawn areas and decorative plantings, paved walkways, paved and unpaved access roads, and paved parking lots. The buildings are of modern construction, designs and materials and have been built specifically for pharmaceuticals production since 1971. Site drainage improvements have been made by installing a pond to slow rainwater run-off from buildings and paved areas

The environment adjacent to the site is to the north, US interstate 95; to the west a casement for an interchange to US interstate 95, to the south, Old Baltimore Pike and a residential area; and to the east, Salem Church Road and a residential area.

The potable water is supplied by Wilmington Suburban Company and the wastewater from the site is treated in the New Castle County Municipal Sewer System at the Wilmington Treatment Facility.

ECTION 5.

IDENTIFICATION OF CHEMICALS SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

5.1 Drug Substance

The active drug substance is also known as ZD 1033

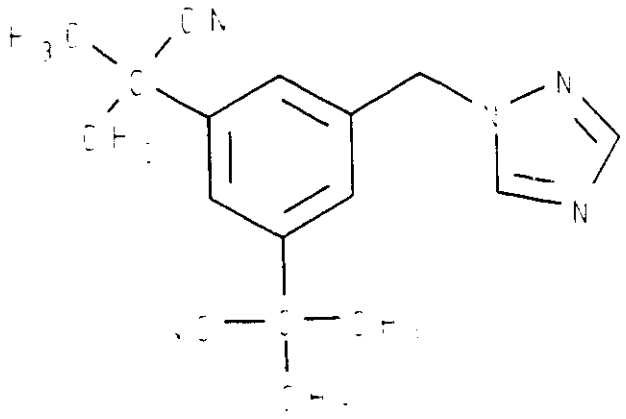
5.1.1 Complete Nomenclature

2,2' -[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]di(2-methylpropiononitrile)

5.1.2 CAS Registration Number

CAS 120511-73-1

5.1.3 Molecular Structure



5.1.4 Molecular Weight

293

5.1.5 Physical Description

Arimidex is a white crystalline powder.

5.2 Additives

The drug substance does not contain additives.

5.3 Impurities

A list of impurities is contained in Section 15.4

These impurities are controlled to a level less than 0.5% in total.

These materials are of similar chemical structure to ZD1033 so that the assessment of the properties of ZD1033 will provide an adequate assessment of any potential effect on the environment.

5.4 Materials used in Synthesis

A list of materials used in the synthesis is included in Section 14

SECTION 6.

INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 From Production of Drug Substance at Macclesfield

All production of active pharmaceuticals on the Macclesfield Site is authorised by Her Majesty's Inspectorate of Pollution (HMIP) under the terms and conditions of the Environmental Protection Act and Integrated Pollution Control (IPC). This requires that the site, as well as meeting all current operating consents and conditions, to employ the Best Available Techniques Not Entailing Excessive Costs (BATNEEC) to minimise all discharges to the environment. It is also required to utilise the Best Practical Environmental Option (BPEO) in minimising and disposing of wastes.

The Authorisation is numbered AK 4079 and the site's performance is continuously monitored by HMIP. Permission for the site to be allowed to continue to operate is dependant on continuing compliance with all the terms of the Authorisation.

A copy of the Authorisation is included in Section 14

A list of the substances used in the manufacture of ZD1033 is included in Section 15.

Wastes from the manufacture of ZD1033 are treated by common systems on the site. Individual streams are combined into a number of component streams for disposal as follows:

Aqueous Wastes for discharge
Non aqueous solvent wastes for recovery
Solvent wastes for incineration
Solid wastes for incineration

Process wastes are complex mixtures which have not been fully characterised. The composition of these streams will vary depending upon the current pattern of production on the site.

6.1.1 Aqueous Arisings from Manufacture of ZD 1033

Aqueous Layers from the production of drug substance are combined in the sites effluent collection/treatment system. The total effluent from the site is settled to remove solids and the pH adjusted to between 6.0 - 9.5 before being discharged to a sewage treatment facility owned and operated by the North West Water PLC.

All discharges to this facility are made under an agreement between ZENECA and the North West Water Authority, who were the predecessors to North West Water PLC, dated 24th September 1975. The Agreement is not numbered but the site's performance is continuously monitored by North West Water PLC. Permission for the site to be allowed to continue to discharge aqueous effluent is dependant on continuing compliance with all the terms of the agreement. A copy of the agreement is included in Section 14.

6.1.2 Major Requirements of the Agreement

Flow	1.2 million gallons/day up to a maximum of 7 million gallons /week.
COD	88,200 lbs / week
Total Solids	500mg/litre
pH	6.0 - 9.5

6.1.3 Non-aqueous Liquid Wastes

Non-aqueous liquid wastes are segregated where possible into separate components. These components are transported to specialised operators for recovery for non-pharmaceutical use. Where segregation and recovery is not feasible the streams are collected together in a common site system for high temperature incineration in a licensed facility off-site.

In this facility a destruction efficiency of >99.99% is assumed for all organic species. The flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal. The facility meets all relevant operating and discharge permits.

The facility currently used by Zeneca is

Cleanaway Ltd
Bridges Road
Ellesmere Port
Cheshire
L65 4EQ

Cleanaway Ltd is authorised by Her Majesty's Inspectorate of Pollution. The authorisation number is AG 8233.

All contractors are regularly audited by ZENECA.

1.4 Air Emissions

All air emissions from the manufacturing facilities are in compliance with local and national legislation.

6.1.5 Control of Air Emissions

Emissions from ZD 1033 production are discharged in such a manner as to comply with local legislation. Where appropriate emissions are discharged through scrubbers or are controlled by installing cooled condensers on reactors.

Monitoring to ensure compliance is carried out where specified in the site's Authorisation for operation or where deemed appropriate by the site's management.

6.1.6 Treatment of Solid Waste Arisings from Production of ZD 1033

All solid wastes are collected as part of a site-wide system and stored temporally, in appropriate containers, in a specially designated area. The storage and treatment of the wastes are controlled by a licence from the local Waste Disposal Authority. The licence is numbered 60909 and has been renewed in 1992. The site is regularly inspected for compliance by the Waste Disposal Authority and permission for continuing operation is dependant on full compliance with the terms of the licence. A copy of the licence is included in Section 14.

All organic wastes are transported, by licensed carriers, to an off-site facility for high temperature incineration.

In this facility a destruction efficiency of >99.99% is assumed for all organic species. The flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal. The facility meets all relevant operating and discharge permits.

The facility currently used by Zeneca is

Cleanaway Ltd
Bridges Road
Ellesmere Port
Cheshire
L65 4EQ

Cleanaway Ltd is authorised by Her Majesty's Inspectorate of Pollution. The authorisation number is AG 8233.

All contractors are regularly audited by ZENECA.

6.1.7 Emissions due to the manufacture of ZD 1033

It is estimated that less than 0.5 Kg/year of ZD 1033 will be emitted to waste water systems as a result of production of the active material. Emissions of other materials will be controlled so as to ensure that discharges remain within existing permitted levels and have no effect on the either the treatment processes or the wider environment.

6.1.8 Effect of Approval on Compliance with Current Limits at the Production Site

The production of ZD 1033 will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations The relevant authorities have been informed of the proposals to manufacture ZD 1033 and have raised no objection. The production of Arimidex will have no impact on compliance with current environmental legislation and permits.

6.2 Formulation of Drug Product - Newark, Delaware

The site is fully permitted in accordance with Local and Federal Regulations. All emissions from the processing facilities are treated in accordance with local legislation and are within permitted levels.

Manufacture of Arimidex will be carried out in existing areas used for the manufacture of pharmaceuticals It will not involve any new construction or major building modifications.

6.2.1 Aqueous waste

Entry of the product or raw material into the wastewater is only incidental to the cleaning of the production equipment and room surfaces. All aqueous wastes from the formulation of Arimidex are transferred to the sites effluent system. The total effluent from the site is discharged to the New Castle County Municiple Sewer System and treated at the Wilmington Delaware Plant. All discharges to the treatment plant are made under an agreement between Zeneca and the local Waste Authority.

It is estimated that less than 0.1kg/year of Arimidex is discharged to the sewage system.

6.2.2 Air Emissions

All discharges from the plant are filtered through high efficiency filters in accordance with local legislation and monitored as appropriate. The emission controls employed during the manufacturing process will result in insignificant particulate matter emissions.

6.2.3 Solid Wastes

All solid wastes are collected as part of a site wide system and stored temporarily,in appropriate containers, in a specially designated area.

All wastes that have come in contact with or potentially have come in contact with the active ingredient are transported by licensed contractors to an approved incineration facility. This facility operates under a licence from the local authority and meets all relevant operating and discharge consents.

The Contractor Currently used by Zeneca is
Lancaster County Solid Waste
Management Authority Resource
Recovery Facility
Route 441 South
Bainbridge PA 17502

All contractors are audited by Zeneca.

6.2.4 Permits

Waste Water Permit

Departmental of Public Works of New Castle County Number #WDP-76-025.

Hazardous waste generator permit

United States Environmental Protection Agency. Number DED0547431909

Air permits

Departmental of Natural Resources and Environmental Resources of the State of Delaware and are as follows:

Permit #	Name
80-0863	Steam Boiler #1
80-0864	Steam Boiler #2
80-0872	Sorbitrate Dust Collector
81-0049	Pilot Plant Granulator
81-1017	Sorbitrate Granulator
82-0961	Nolvadex Dust Collector
82-0962	Nolvadex Granulator
82-0963	Nolvadex Vacuum System
82-0964	Tenormin Vacuum System
82-0965	Tenormin Granulator
82-0966	Tenormin Dust Collector
88-0010	Steam Boiler #3
89-0110	Pilot Plant Dying Oven Exhaust
89-0123	Pilot Plant Coating Pan Exhaust
89-0155	Liquid Manufacturing Dust Collector
90-0015	Packaging Dust Collector
91-0596	Pilot Plant Dust Collector

6.2.5 Effect of Approval on Compliance with Current Limits at the Production Site

The formulation of the Arimidex drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations. The production of Arimidex will have no impact on compliance with current environmental legislation and permits.

6.3 The Statement of Compliance

See attached.

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ZENECA

ZENECA Pharmaceuticals
Alderley House
Alderley Park
Macclesfield
Cheshire SK10 4TF
England

Telephone 0625 582828
Telex 669095/669388 ZENPHA G
Fax- Main 0625 585022/582572
Fax- Department 0625

Direct Fax: 0625 585618

TO WHOM IT MAY CONCERN

ENVIRONMENTAL IMPACT STATEMENT

This is to certify that we ZENECA Limited of Macclesfield, Cheshire, England, being the manufacturer of 'Arimidex' in the United Kingdom comply or will comply with all applicable United Kingdom regulations and bye-laws governing the emissions resulting from the manufacturing process for 'Arimidex'.

Yours faithfully
For and on behalf of
ZENECA Limited

Approved as to legal form by

L Biggins
Authorised Signatory
Zeneca Pharmaceuticals

ref: JRM233/mh

SECTION 7.

.ATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Metabolites

Arimidex is substantially metabolised in vivo. The pattern of metabolites has been determined as part of the clinical development programme using radio labelled materials. In studies using doses of either [^{14}C]-tyriazole ZD1033 or [^{14}C]-cyano ZD1033, the majority of radioactivity was excreted in the urine. Faecal elimination was minor.

The materials would be expected to be more polar than ZD1033 and on the basis of their structures to have similar properties.

It is therefore appropriate to consider that the emission patterns and properties of Arimidex alone will provide an adequate basis for assessment of any potential risks to the environment. The test data therefore refers to the drug active agent.

.2 Summary of Results of Physical Testing

7.2.1 Water Solubility

Mean solubility of Arimidex in water at 25^{0}C is 0.53 mg/ml

A graph plotted of concentration (mg/ml) against time (days) shows that equilibrium was reached after 7 days.

7.2.2 Hydrolysis

After 5 days at 50°C, less than 10% hydrolysis occurred at pH 5, 7 and 9. ZD1033 is, therefore, considered not to be hydrolysed and stable with a half-life equal to or greater than one year at 25°C.

7.2.3 Dissociation Factor

The mean dissociation factor is 1.4

7.2.4 n-Octanol/Water Partition Coefficient (log P)

The log P value of Arimidex is 1.59 at Arimidex concentrations of 0.2 mg/l and 0.02 mg/l in Octanol.

7.2.5 Vapour Pressure

ZD1033 melts at 83 - 86°C. The structure of the material is such that it would not be expected to sublime. Therefore Zeneca believes that the vapour pressure will be very low and not relevant to the environmental assessment

7.1.6 UV Spectrum

See Section 15.11

7.3 SUMMARY OF BIOLOGICAL TESTING

7.3.1 Biodegradability

Biological Oxygen Demand (28 days)	=	0
Carbon Loss	=	<5%
Test Substance Loss	=	0%

7.3.2 Anaerobic Biodegradability

Anaerobic Biodegradation	=	0
Test Substance Loss (in presence of sludge)	=	3%

7.3.3 Chronic Toxicity to Daphnia Magna

LC 50 after 21 days = >18

No observed effect concentration (NOEC) for reproduction and length = 3.2 mg/l

Lowest observed effect concentration (LOEC) for reproduction and length = 5.6 mg/l

7.3.4 Toxicity to Blue Green Algae *Microcystis aeruginosa*

a) Based on largest specific growth rates during the study:

No observed effect (P=0.05) concentration (NOEC) = 3.0 mg/l

Lowest observed concentration (P=0.05) = 6.0 mg/l

b) Based on maximum standing cell densities achieved:

No observed effect (P=0.05) concentration (NOEC) = 1.5 mg/l

Lowest observed concentration (P=0.05) = 3.0 mg/l

7.3.5 **Toxicity to Green Algae *Selnastrum capricornutum***

a) Based on largest specific growth rates during the study:

No observed effect (P=0.05) concentration (NOEC) = 27 mg/l

Lowest significant effect (P=0.05) concentration = 81 mg/l

b) Based on maximum standing cell densities achieved:

No observed effect (P=0.05) concentration (NOEC) = 27 mg/l

Lowest significant effect (P=0.05) concentration = 81 mg/l

7.3.6 **Soil Sorbtion and Desorbtion**

Results based upon mean measured concentrations as mg. Arimidex per litre

SOIL	pH	Koc
Nebo	5	>1100
East Jubilee	5.8	>180
Kenny Hill	7.7	>63

7.3.7 **Acute Toxicity to Bluegill Sunfish**

96 hour no observed effect concentration (NOEC) 10mg/l

7.3.8 **Acute Toxicity to Rainbow Trout**

96 hour no observed effect concentration (NOEC) 32 mg/l

SECTION 8.

ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Maximum Expected Environmental Concentration (MEEC) of Drug Substance

8.1.1 Assumptions in Calculation of MEEC

Fraction of US Population using Waste Water Treatment Plants $F_{(sewered)}$ 0.74

Annual US Sewage Flow (SF_{annual}) $3.7*10^{13}$ L/yr

Annual Yield of Dry Sludge from W/WTP (DS_{annual})

$5.9*10^{9}$kg/yr

Dilution Rate of Application of Sludge to Agricultural Land (DR_{annual}) 0.025

Estimated Annual Volume of Drug Substance (MV_{total}) 50 kg

Fraction of Drug Substance not excreted. 0

Kp Arimidex 39 (Mean value ex Section 15)

The MEEC of Arimidex into the environment from use of the drug product is calculated as follows, assuming 100% excretion of the drug and its metabolites.

8.2 Calculation of MEEC for Drug Substance

Quantity emitted into WWTPs = $MV_{(total)}*F_{(sewered)}$

= 50*0.74

= 37 kg/yr

Based on the distribution between sludge and water

$$Kp = \frac{\text{Concentration in sludge } (C_2)}{\text{Concentration in water } (C_1)}$$

$$39 = \frac{C_2}{C_1}$$

$$C_2 = 39 * C_1 \quad \text{(equation 1)}$$

Since the total quantity emitted is distributed between the sludge and the effluent the material balance between the compartments is

$$C_1 * SF_{annual} + C_2 * DS_{annual} = 37 \text{ kg} \quad \text{(equation 2)}$$

Substitution for C_2 (equation 1) into equation 2 gives

$$(C_1 * 3.7*10^{13}) + (C_1 * 39 * 5.9*10^{9}) = 37$$
$$C_1 * 3.72*10^{13} = 37$$

$$C_1 = 1.0*10^{-12} \text{ kg/kg} \quad \text{or} \quad 1.0*10^{-6} \text{ mg/kg}$$

$$C_2 = 39 * C_1$$

$$C_2 = 39 * 1.0*10^{-6}$$

$$C_2 = 3.9*10^{-5} \text{ mg/kg}$$

Since the maximum dilution rate resulting from land application of sludge is 0.025 the maximum expected concentration of drug substance assuming 100% land application of all sludge is:

$$MEEC_{(terrestrial)} = DR_{annual} * C_2$$

$$= 0.025 * 3.9*10^{-5}$$

$$= 9.75*10^{-7} \text{ mg/kg}$$

$$MEEC_{(aquatic)} = C_1$$

$$= 1.0*10^{-6} \text{ mg/l}$$

8.3 Effect of Drug Substance on the Environment

The material is strongly absorbed to acidic soils but less stongly absorbed to soils at a higher pH. Some material will therefore enter the aquatic environment. However as the MEEC for aquatic systems is $1.0*10^{-6}$ mg/l the drug substance is not expected to have any adverse effect on aquatic species.

The material is not expected to have a tendency to bioaccumulate and although biodegradation of ZD1033 was not demonstrated under test conditions it cannot be excluded under environmental conditions.

Photolysis is not considered to provide a significant mechanism for depletion as only negligible amounts of ZD1033 will be exposed to low wavelength sunlight.

The principle method of depletion in the environment is to be by hydrolysis. The total amount of material expected to be introduced into the United States of America is below 50kg/year at peak production. Therefore although the hydrolysis rate is low, it is anticipated that since there is a substantial margin between the predicted MEEC and the lowest "no effect" levels of the drug substance on aquatic organisms, that this will provide an adequate margin of safety to the environment.

Although biodegredation of Arimidex was not demonstrated in simple test systems, it cannot be ruled out under environmental conditions.

8.4 Effect of Other Releases on the Environment

All emissions released during the production of Arimidex are made in accordance with the levels set in local permits. Compliance with these levels ensures that any effect on the environment is minimised.

8.5 Effect of Releases on the Workforce

8.5.1 Standards of Control

All emissions of materials into the workplace are controlled with limits set by the relevant authorities. Where no official limits exist Zeneca establishes internal control values.

Workplace exposures are kept below these levels.

SECTION 9

.SE OF RESOURCES AND ENERGY

9.1 Energy

The incremental increase of the use in energy as a result of .he manufacture of Arimidex is estimated to be less than 2% of the current energy used by the manufacturing facilities. Therefore this increase is not deemed to be significant.

9.2 Effect on Threatened Species and Property of Historic Interest

Each of the manufacturing sites have conducted surveys to identify any threatened or endangered species on or adjacent to their property. None have been identified.

There are no properties of historic interest in the immediate area of the sites.

Given the controls on the manufacturing process and disposal of waste materials there will be no effect on threatened species or property of historic interest.

SECTION 10

MITIGATION MEASURES

The measures for controlling emissions from the manufacturing processes are described in Section 6.

ZENECA Pharmaceuticals has a policy of minimising the environmental effects of the manufacture of its products by assessing the environmental impact of new and proposed processes at an early stage in their development. The impact of each process step is evaluated and efforts are made to minimise both waste and energy use. Each new process is subject to a series of hazard studies which evaluate the potential risks to both people and the environment and put in place suitable controls to ensure the risks are minimised.

10.1 Emergency and Spillage Procedures

There is an emergency plan covering all aspects of the sites' activities. Plans are in place to contain and remove any spillages or other loss of containment. The manufacture of Arimidex will be covered by these arrangements.

10.2 Control of Workplace Exposure

10.2.1 Control Procedures

Primary control is by containment within the manufacturing plants. This is supplemented, where appropriate, by local exhaust ventilation. Where necessary personal protective equipment is used to prevent workplace exposure.

10.2.2 Monitoring

Monitoring programmes are in place to ensure that the controls remain effective. These programmes include monitoring both the performance of equipment and sampling the atmosphere in the workplace.

0.2.3 Information and Training

Safety Data Sheets are available for all materials used in the manufacture of Arimidex.

All operators are fully trained to understand the hazards of the materials and the procedures in place to prevent emissions to the environment.

10.3 Waste Minimisation

ZENECA Pharmaceuticals has a policy of minimising waste and developing routes of manufacture which have the minimum impact to the environment. The Company's management have programmes in place to ensure these policies are progressed

SECTION 11

ALTERNATIVES TO PROPOSED ACTION

There are no alternatives to the proposed action. Failure to approve the proposed action will result in denying patients with advanced breast cancer the potential benefits of a novel therapy.

No adverse environmental effects resulting from use of the product have been identified. The actions taken in controlling emissions and disposing of waste materials arising from manufacture will ensure that there are no adverse effects on the environment arising from these activities.

SECTION 12.

PREPARERS

This assessment was prepared by Martin Rackham, Occupational Hygiene and Environmental Affairs Manager for ZENECA PHARMACEUTICALS. He has a Bachelors Degree in Chemistry and Physiology and a Masters Degree in Occupational Hygiene.

SECTION 13.

CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for the preparation of the environmental assessment.

Martin Rackham MSc BSc MIoH
Occupational Hygiene and Environmental Affairs Manager
International Safety, Health and Environment Department
ZENECA Pharmaceuticals

SECTION 14.

REFERENCES

14.1 **Methodology for Physical Testing**

Test Protocols US Food and Drug Administration Technical Assistance Handbook.

14.2 **Methodology for Biological Testing**

14.1 **Estimate of Maximum Yearly Market Volume**

The maximum amount of Arimidex expected to be introduced into the United States of America is expected to be in the order of 50 Kg/year

4.2 **Methodology for Biological Testing**

Aerobic Biodegradability (BOD_{28})

Test Protocol — Organisation for Economic Co-operation and Development Guideline 301C (UK Version)

Anaerobic Degradation

Test Protocol — ISO Committee Draft CD11734

Chronic Toxicity to Daphnia magna

Test Protocol — US Food and Drug Administration Technical Assistance Document 4.09

Algal Tests

Test Protocol — US Food and Drug Administration Technical Assistance Document 4.01

Fish Tests

Test Protocols — US Food and Drug Administration Technical Assistance Document 4.11

SECTION 15

APPENDICES

References to specific tests and test protocols are included with the test results in 15.2 & 15.3.

15.1 Summary Data tables for ZD 1033

Water Solubility (25C)	0.53 mg/ml
log p Octanol/Water	1.59
Vapour pressure	Not relevant
Hydrolysis Rate Constant	Hydrolytically stable under conditions of test with a half life greater than one year at 25°C
BOD (28 day)	0%
Anaerobic Degradation	0%
NOEC Daphnea	3.2 mg/l
NOEC Blue Green Algae	
(growth rate)	3.0 mg/l
(cell densities)	1.5mg/l
NOEC Green Algae	
(growth rate)	27mg/l
(cell densities)	27 mg/l
Soil sorption	
Koc	
pH 5	>1100
pH 5.8	>180
pH 7.7	>63
NOEC Bluegill Sunfish	
(96 hour)	10mg/l
NOEC Rainbow Trout	
(96 hour)	32 mg/l

15.2 **Estimate of Maximum Yearly Market Volume**

confidential

15.3 **Materials used in the Synthesis of ZD1033**

confidential

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15.4 IMPURITIES

confidential

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15.5 MATERIAL SAFETY DATA SHEET FOR ZD 1033

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ZENECA Pharmaceuticals

SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION

Name: ZENECA ZD1033 PURE

Alternative Names
Arimidex
ZD1033

2. COMPOSITION/INFORMATION ON INGREDIENTS

CAS No. : 120511-73-1
EEC No. : None assigned
Use : aromatase inhibitor

HAZARDOUS INGREDIENT(S)	CAS No.	Symbol	R Phrases
ZD1033			

3. HAZARDS IDENTIFICATION

May cause reproductive effects in males and females.

Health Hazard Category : A

4. FIRST-AID MEASURES

Inhalation : Remove patient from exposure, keep warm and at rest. Obtain medical attention.
Skin Contact : Remove contaminated clothing. Wash skin with water. If symptoms (irritation or blistering) occur obtain medical attention.
Eye Contact : Irrigate with eyewash solution or clean water, holding the eyelids apart, for at least 10 minutes: Obtain medical attention.
Ingestion : Wash out mouth with water. Obtain immediate medical attention.

Further Medical Treatment
Symptomatic treatment and supportive therapy as indicated.

5. FIRE-FIGHTING MEASURES

Burns with flames.
Group A dust. The material can form flammable dust clouds in air.
Thermal decomposition will evolve flammable vapours.

Extinguishing Media : water spray, foam, dry powder or CO2.

6. ACCIDENTAL RELEASE MEASURES

Ensure suitable personal protection (including respiratory protection) during removal of spillages.
Clear up spillages. Wash the spillage area with water. Transfer to a container for disposal.

7. HANDLING AND STORAGE

7.1 HANDLING

Do not breathe dust. Avoid contact with skin and eyes. Atmospheric levels should be controlled in compliance with the occupational exposure limit.
Use extraction and ventilation arrangements.

7.2 STORAGE

Keep container tightly closed.
Storage Life : at least 2 year(s) at 25 Deg C

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Wear suitable respiratory protective equipment if exposure to levels above the occupational exposure limit is likely. Wear suitable protective clothing, gloves and eye/face protection.

Occupational Exposure Limits

HAZARDOUS INGREDIENT(S)	LTEL 8hr TWA ppm	LTEL 8hr TWA mg/m3	STEL ppm	STEL mg/m3	Time mins	
ZD1033	-	0.01	-	-	-	COM (Provisional)

SAFETY DATA SHEET

Name: ZENECA ZD1033 PURE

9. PHYSICAL AND CHEMICAL PROPERTIES

Form	: powder
Colour	: off-white
Melting Point (Deg C)	: 83-86
Solubility (Water)	: slightly soluble
Solubility (Other)	: soluble in: alcohols acetone acetonitrile
Partition Coefficient	: 1.56
Flammable Powder Class	: A
Minimum Ignition Temperature (Deg C)	: 500-550
Minimum Ignition Energy (mJ)	: 2.5-10

Dissociation constant: 2.4 (estimated) (protonated form)

10. STABILITY AND REACTIVITY

Stable at (Deg C) 25 at least 2 year(s)

Hazardous Reactions : None known.

Hazardous Decomposition Product(s) : None known.

11. TOXICOLOGICAL INFORMATION

Inhalation : Atmospheric concentrations in excess of the occupational exposure limit may lead to adverse effects as described under long term.

Skin Contact : Non-irritant following single and repeated applications to rabbit skin. Unlikely to cause skin irritation in man.
It is not a skin sensitiser in animal tests.

Eye Contact : Non-irritant to rabbit eyes. Unlikely to cause eye irritation in man.

Ingestion : May cause adverse effects as described under long term.

Long Term Exposure : Studies in animals have shown that repeated doses produce adverse reproductive effects.
None of these effects are likely to occur in humans, provided exposure is maintained at or below the occupational exposure limit.

Short term tests and a consideration of the structure have shown that it is unlikely to be a carcinogenic hazard to man.

12. ECOLOGICAL INFORMATION

Environmental Fate and Distribution
The substance is soluble in water.
The substance has low potential for bioaccumulation.

Toxicity
No information available.

13. DISPOSAL CONSIDERATIONS

Disposal should be in accordance with local, state or national legislation.

14. TRANSPORT INFORMATION

Not Classified as Dangerous for Transport.

15. REGULATORY INFORMATION

Not Classified as Dangerous for Supply/Use.

Users should ensure that they comply with any relevant local, state or national legislation.

16. OTHER INFORMATION

This data sheet was prepared in accordance with Directive 91/155/EEC.

The following sections contain revisions or new statements:
1,8

SAFETY DATA SHEET

Name: ZENECA ZD1033 PURE

GLOSSARY

OES : Occupational Exposure Standard (UK HSE EH40)
MEL : Maximum Exposure Limit (UK HSE EH40)
COM : The company aims to control exposure in its workplace to this limit
TLV : The company aims to control exposure in its workplace to the ACGIH limit
TLV-C: The company aims to control exposure in its workplace to the ACGIH Ceiling limit
MAK : The company aims to control exposure in its workplace to the German limit
Sk : Can be absorbed through skin
Sen : Capable of causing respiratory sensitisation

15.6 OTHER MATERIAL SAFETY DATA SHEETS

confidential

15.7 SITE PERMITS, AUTHORISATIONS AND AGREEMENTS

confidential

15.8 Results of Physical Testing

confidential

15.9 Results of Biological Testing

confidential

END

S.D.

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

NDA 20-541

Missing Pages 17, 21, 35-55

MOR

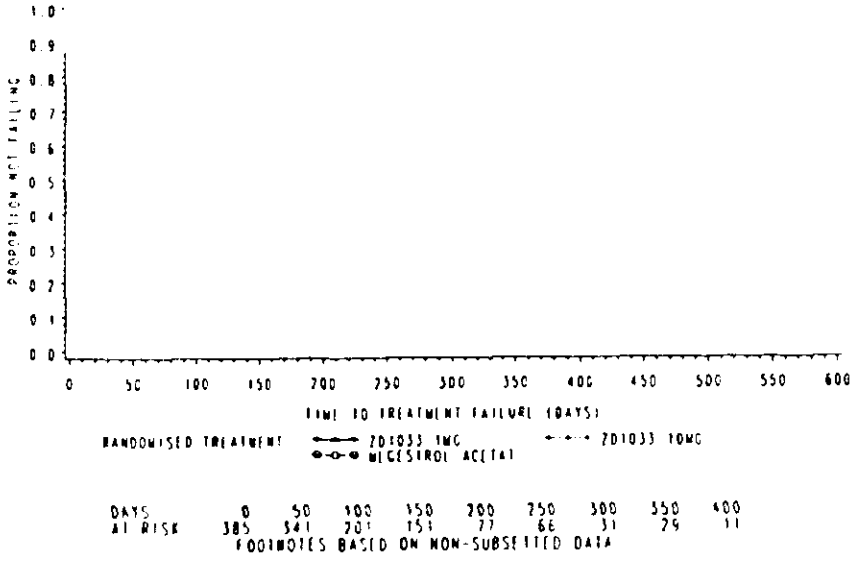
- **Time to Treatment Failure**

A total of 74 (58%) patients treated with 1 mg anastrozole, 82 (63%) patients treated with 10 mg anastrozole, and 85 (66%) patients treated with megestrol acetate failed treatment. For the majority of patients, the reason for treatment failure was disease progression. Median times to treatment failure (with 97.5% confidence intervals) were: 168 days (97-196 days) for patients treated with 1 mg anastrozole, 133 days (92-170 days) for patients treated with 10 mg anastrozole, and 125 days (91-184 days) for patients treated with megestrol acetate.

Comparison of 1 mg anastrozole with megestrol acetate revealed a hazard ratio of 0.85 (CI: 0.59-1.23, p= 0.33). The hazard ratio for the comparison of 10 mg anastrozole with megestrol acetate was 0.99 (CI: 0.70-1.41, p= 0.97). There was no statistical difference between either dose of anastrozole and megestrol acetate.

STUDY NUMBER 1033IL/0004 FIGURE 6

KAPLAN MEIER PROBABILITY OF TIME TO TREATMENT FAILURE
Subsetting on variables TRTSEQ



DAYS	0	50	100	150	200	250	300	350	400
AT RISK	385	341	201	151	77	66	31	19	11

FOOTNOTES BASED ON NON-SUBSETTED DATA

Reviewer's Assessment of Time to Treatment Failure:
1) The time to treatment failure was confirmed for all randomized patients. Dates of treatment failure were available for the 241 patients failing treatment after randomization (Table G4.4). The remaining 145 (38%) patients were censored for analysis of this endpoint.

2) Treatment was continued for several of the patients following documentation of treatment failure (see scatter plot of date of treatment failure vs. date treatment stopped in the Appendix).

- **Pharmacokinetic Assessments**

After daily dosing of 1 mg anastrozole, steady-state concentrations ranged from ng/ml. As expected, steady state concentrations with the 10 mg dose were higher, ranging from ng/ml. C_{min} values ranged from ng/ml for the 1 mg dose, and from ng/ml for the 10 mg dose, with no major age-related trends.

Patients with hepatic or renal impairment had slightly higher plasma anastrozole concentrations compared with those who were not impaired. These results are considered to be within the range of intrasubject and intersubject variability seen in earlier clinical pharmacology trials. Note that hepatic impairment was defined as one or more of the following: total bilirubin $\geq$ 2 x ULN; alkaline phosphatase, AST, and ALT $\geq$ 3 x ULN; albumin below the lower limit of normal. Renal impairment was defined as a serum creatinine above the ULN.

- **Sponsor's Conclusions on Efficacy Results**

There was no statistical difference between anastrozole 1 or 10 mg daily and megestrol acetate 40 mg four times daily in time to disease progression, objective response rate, or time to treatment failure.

The response rates in this trial were lower than those reported in the literature for megestrol acetate, due in part to the nature of the patients enrolled (all with prior hormonal therapy, many with prior chemotherapy, and only one-third with soft tissue only disease) and the strict interpretation of objective responses.

All treatment groups had a high percentage of patients with a best response of stable disease of 24 or more weeks (ranging from 24-30%). Published data (Howell et al., Eur J Clin Oncol, 1988) suggest that time to progression and survival of advanced breast cancer patients with stable disease for 5 or more months on endocrine therapy would not differ significantly from those for patients with a PR as best response.

- **Duration of Response**

The duration of response among complete and partial responders ranged from 105- >458 days (median of 261 days) for the 1 mg anastrozole group, from 128- >427 days for the 10 mg anastrozole group, and from 116- >427 days (median 257 days) for the megestrol acetate group.

Reviewer's Assessment of Response Duration:
1) Response durations were confirmed for each of the responders.

2) Six patients were in CR as of the "last alive date". Of these, two were on the 1 mg anastrozole arm (in CR at 253 and 458 days), two were on the 10 mg anastrozole arm (276 and 427 days), and two were on the megestrol acetate arm (186 and 265 days).

3) Twenty patients were in PR as of the "last alive date". Of these, seven were on the 1 mg anastrozole arm (in PR at 105, 119, 168, 175, 210, 256, and 455 days), nine were on the 10 mg anastrozole arm (153, 168, 183, 203, 254, 254, 258, 266, and 295 days), and four were on the megestrol acetate arm (166, 169, 270, and 427 days).

4) Calculation of response duration from the date of randomization rather than the date of first documentation of response inflates these response times.

- **Time to Treatment Failure**

A total of 95 (70%) patients treated with 1 mg anastrozole, 78 (66%) patients treated with 10 mg anastrozole, and 89 (71%) patients treated with megestrol acetate failed treatment. For the majority of patients, the reason for treatment failure was disease progression. Median times to treatment failure were: 121 days for patients treated with 1 mg anastrozole, 128 days for patients treated with 10 mg anastrozole, and 115 days for patients treated with megestrol acetate.

Comparison of 1 mg anastrozole with megestrol acetate revealed a hazard ratio of 1.01 (CI: 0.72-1.40, p= 0.96). The hazard ratio for the comparison of 10 mg anastrozole with megestrol acetate was 0.87 (CI: 0.61-1.23, p= 0.36) There was no statistical difference between either dose of anastrozole and megestrol acetate See Kaplan-Meier plot below.

reporting declined.

The incidence of asthenia and pain did not appear to be related to dose; these events could be attributed to the underlying disease. Reporting of asthenia also occurred most frequently in the first 12 weeks of treatment. The incidence of asthenia increased with age > 50 years.

- **Megestrol Acetate (Controlled Trials)**

The majority of patients (60%) were exposed to 2-3 mg/kg/day of megestrol acetate (range). The most common drug-related events in patients treated with megestrol acetate were weight gain, dyspnea, edema, hot flushes, asthenia, non-specific pain, nausea, increased appetite, and vaginal hemorrhage. Weight gain, dyspnea, and edema are expected effects of the glucocorticoid and mineralocorticoid properties of megestrol acetate.

The incidence of weight gain increased with increasing drug exposure: 9% in patients receiving < 2 mg/kg/day, 11% in patients receiving 2-3 mg/kg/day, and 16% in those who received more than 3 mg/kg/day. The incidence of weight gain remained constant throughout the trials, with the highest incidence recorded between 12 and 24 weeks.

While peripheral edema was often recorded during the first 24 weeks of treatment, dyspnea occurred up to 48 weeks on study.

The incidence of hot flushes increased somewhat with increasing drug exposure: 7% in patients receiving < 2 mg/kg/day, 8% in patients receiving 2-3 mg/kg/day, and 11% in those who received more than 3 mg/kg/day. Hot flushes were reported early in the trials.

The incidence of asthenia increased with increasing drug exposure: 11% in patients receiving < 2 mg/kg/day, 18% in patients receiving 2-3 mg/kg/day, and 32% in those who received more than 3 mg/kg/day. The onset of asthenia was often early in the trials. The incidence of asthenia also increased with age, particularly in women > 80 years.

The incidence of non-specific pain also increased with increasing drug exposure: 7% in patients receiving < 2 mg/kg/day, and 23% in those who received more than 3 mg/kg/day.