SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ARIMIDEX™ 1 mg tablet

ACTIVE INGREDIENT: Anastrozole

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

Clinical phase: IIIb

First patient recruited: 08 June 1998
Last patient completed: 03 March 1999
AstraZeneca approval date: 22 January 2002

Principal investigator and location (centre number): (Centre 0118), (Centre 0001)

Publications: Dowsett M on behalf of the ATAC Trialists' Group. Pharmacokinetics of 'Arimidex' and tamoxifen alone and in combination in the ATAC adjuvant breast cancer trial. Breast Cancer Research and Treatment 2000;64(1):64 (Abstract 236).
The ATAC Trialists' Group. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex™ and Tamoxifen Alone or in Combination' (ATAC) trial. Br J Cancer 2001;85:317-24.

OBJECTIVES

The primary objectives of this sub-protocol were to assess the effect of anastrozole on the pharmacokinetics of tamoxifen and to assess the effect of tamoxifen on the pharmacokinetics of anastrozole.

There were no secondary objectives to this sub-protocol.

METHODS

Design: This was a randomised, double-blind, multicentre trial designed together with the Cancer Research Campaign, United Kingdom, and subsequently conducted in conjunction with various collaborative groups as well as with individual investigators. A subset of patients who were already participating in the ATAC main trial (protocol number 1033IL/0029) was recruited. Patients were randomised on a 1:1:1 basis into 1 of 3 treatment arms, ie, anastrozole (ARIMIDEX) alone, tamoxifen (NOLVADEX) alone, or a combination of anastrozole and tamoxifen. Participation in this trial involved having one blood sample taken (in addition to any samples taken in the main trial) after the patient had been taking trial treatment for at least 3 months.

Treatment for the ATAC main trial will be for 5 years or until the first confirmed recurrence or death, and follow-up (within the main trial) will be for up to 10 years after starting randomised treatment or until death.

Following the initial pharmacokinetic assessments, an additional evaluation was undertaken to assess the effects of anastrozole, with or without tamoxifen, on oestradiol suppression. This information was obtained from a separate ATAC sub-protocol (protocol number 1033ID/0029) and required blood samples to be taken from patients at baseline and after 3 months of treatment, allowing baseline and steady-state oestradiol concentrations to be determined. These data are reported in this trial report to enable a full assessment of the clinical significance of the results.

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

Dosage: Patients were given once-daily oral doses of anastrozole (1 mg) (batch numbers: F011292, 11292) and tamoxifen placebo (F011003, 12062), tamoxifen (20 mg) (F006293, 12061) and anastrozole placebo (F011314, 11314), or anastrozole (1 mg) plus tamoxifen (20 mg). Trial treatment continued until disease recurrence, or until the patient withdrew from treatment for any other reason, or until the end of the trial.

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

Adverse events occurring during this trial were recorded and the incidence will be assimilated into the adverse event summary data for the ATAC main trial.

RESULTS

Demography: A total of 357 patients from 26 centres received treatment; demographic details are presented in Table A.

Table A Age, weight, and race of patients at entry: all randomised patients

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

SD Standard deviation.

Age distribution was similar across the 3 groups. Breast cancer history and baseline characteristics of breast cancer status were also similar for the 3 groups.

Ten patients (of whom, 7 [5.1%] were randomised to receive anastrozole 1 mg, 2 [1.8%] to tamoxifen 20 mg, and 1 [0.9%] to the combination of anastrozole 1 mg plus tamoxifen 20 mg) were excluded from the pharmacokinetic analyses because the results of laboratory tests did not correspond with those that would be anticipated from their recorded treatment allocation.

Two patients (1 patient [0.7%] receiving anastrozole 1 mg and 1 patient [0.9%] taking anastrozole 1 mg plus tamoxifen 20 mg) withdrew from this sub-protocol.

Pharmacokinetics and pharmacodynamics: Table B summarises the steady-state trough plasma concentrations of anastrozole, tamoxifen, and N-desmethyltamoxifen and the results of the statistical analyses.

Table B Steady-state trough plasma concentrations (C_{min} [ng/mL]) of anastrozole, tamoxifen, and N-desmethyltamoxifen: main analysis population

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

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

Co-administration of anastrozole 1 mg with tamoxifen 20 mg did not affect the steady-state plasma trough concentrations of tamoxifen or N-desmethyltamoxifen. Co-administration of anastrozole 1 mg with tamoxifen 20 mg resulted in an estimated 27% decrease in anastrozole levels. Results from the secondary per-protocol analysis were comparable.
Baseline serum oestradiol concentrations were not determined in this sub-protocol; however, this information was available from a similar ATAC sub-protocol, evaluating bone mineral density (1033ID/0029). Geometric mean serum oestradiol levels were 21.5 and 18.5 pmol/L prior to treatment and 4.44 and 3.63 pmol/L after 3 months of treatment for the anastrozole 1-mg and the anastrozole 1-mg plus tamoxifen 20-mg treatment groups, respectively. Excluding 3 patients with extreme values (oestradiol concentrations of 585, 321, and 291 pmol/L at 3 months), geometric mean oestradiol concentrations were 21.1 pmol/L prior to treatment and 3.75 pmol/L following 3 months of treatment with anastrozole 1 mg. Table C presents the results of the statistical analysis for the comparison of oestradiol concentrations between these two groups.

Table C Statistical analysis of the comparison of oestradiol concentrations [a]

Treatment comparison	Ratio of glsmeans [b]	2-sided 90% CI
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg	0.86	0.71 to 1.04
Anastrozole 1 mg plus tamoxifen 20 mg versus anastrozole 1 mg (excluding data from 3 outliers)	1.00	0.91 to 1.09

[a] Oestradiol concentrations were determined in a subgroup of patients from protocol number 1033ID/0029.
[b] Ratio of the geometric mean concentration at 3 months to the baseline value.
CI Confidence interval; glsmean Geometric least squares mean.

The observed interaction following the co-administration of anastrozole 1 mg with tamoxifen 20 mg did not appear to reduce the levels of anastrozole sufficiently to impact upon its oestradiol suppressive effects and is therefore not expected to be of clinical significance when anastrozole and tamoxifen are administered in combination.

Safety: All safety data were collected as part of the ATAC main trial and are presented in the clinical trial report for that study (1033IL/0029).