SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ARIMIDEX™ 1 mg tablet

ACTIVE INGREDIENT: Anastrozole

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

Clinical phase:	IIIb	**First patient recruited:**	13 June 1997
		Last patient recruited:	03 September 1999
		Data cut-off date:	2-year visit
		AstraZeneca approval date:	13 February 2002

Principal investigator and location (centre number): (Centre 0009), (Centre 0001)

Publications: Jackson TL, Duffy SRG, on behalf of the ATAC Trialists Group (Endometrial Sub-Protocol). The ATAC (arimidex, tamoxifen, alone or in combination) adjuvant breast cancer trial in post-menopausal women: Baseline endometrial sub-protocol data. European Journal of Cancer 2000;36(Suppl):S69 (Abstract 140).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists Group (Endometrial Sub-Protocol). The ATAC ('Arimidex', tamoxifen, alone or in combination) trial: transvaginal ultrasound scan findings overestimate observed pathological findings in postmenopausal gynaecologically asymptomatic women before treatment. Breast Cancer Research and Treatment 2000;64(1):64 (Abstract 233).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists' Group (Endometrial Sub-Protocol). The ATAC (Arimidex, Tamoxifen, Alone or in Combination) Trial: transvaginal ultrasound scan findings overestimate observed pathological findings in postmenopausal gynaecologically asymptomatic women before treatment. The Breast 2001;10(Suppl 1):S30 (Abstract P55).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists Group (Endometrial Sub-Protocol). The ATAC ('Arimidex', tamoxifen, alone or in combination) trial: the effectiveness of transvaginal ultrasonography and diagnostic hysteroscopy in the prediction of endometrial abnormalities in asymptomatic postmenopausal women. Breast Cancer Research and Treatment 2000;64(1):63 (Abstract 232).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists' Group (Endometrial Sub-Protocol). The ATAC (Arimidex, Tamoxifen, Alone or in Combination) Trial: The effectiveness of transvaginal ultrasonography and hysteroscopy in the prediction of endometrial abnormalities in asymptomatic menopausal women. The Breast 2001;10(Suppl 1):S30-1 (Abstract P56).

OBJECTIVES

The primary objective of this sub-protocol was to compare the difference between the anastrozole (ARIMIDEX) group and the tamoxifen (NOLVADEX) group in the incidence of abnormal endometrial histological findings arising after treatment had commenced.
The secondary objectives of this sub-protocol were:

- to assess non-inferiority of this incidence between the tamoxifen 20-mg group and the anastrozole 1-mg plus tamoxifen 20-mg combination (if non-inferiority is concluded, to assess the difference between these 2 groups)
- to characterise the nature of any abnormal uterine and ovarian findings and to compare the different incidences of these across all 3 treatment groups

- to evaluate transvaginal ultrasound scanning (TVUS) as a screening tool for endometrial changes in postmenopausal women with early breast cancer for which they were receiving hormonal therapy
- to assess the 'background' incidence of endometrial pathology in the asymptomatic postmenopausal early breast cancer population, before they received hormonal therapy
- to assess the nature and extent of medical intervention required for endometrial abnormalities, including the hysterectomy rate, for the 3 treatment groups, and compare this between the anastrozole 1-mg and tamoxifen 20-mg groups
- to assess the correlation between vaginal bleeding and endometrial pathology

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METHODS

Design: This was a randomised, double-blind, multicentre, collaborative trial designed in conjunction with the Cancer Research Campaign, United Kingdom. It was conducted as a sub-protocol to the main Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial (protocol number 1033IL/0029). Trial treatment was planned for a period of 5 years; this report evaluates data up to and including the 2-year visit.

The trial was led by a Steering Committee (consisting of the principal investigator from the ATAC main trial, other trial investigators and scientists, an independent statistician, and representatives from the various collaborative groups plus clinical and statistical personnel from AstraZeneca) supported by an Independent Data Monitoring Committee (IDMC).

Population: Postmenopausal women (with no endometrial abnormalities at baseline except fibroids or an atypical polyp that was removed) who were candidates to receive adjuvant hormonal treatment for early primary breast cancer. Approximately 500 patients were to be recruited for this sub-protocol from a number of selected oncology clinics participating in the main ATAC trial (protocol number 1033IL/0029), where the expertise existed for the additional endometrial assessments. Recruitment into this sub-protocol was closed once the main trial had recruited the necessary patient numbers. Thus, the intended number of patients was not recruited into this sub-protocol.

Dosage: Patients were given once-daily oral doses of anastrozole (1 mg) (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). Patients continued to take trial treatment until disease recurrence was confirmed, continued treatment was refused, or until trial treatment completion (5 years), whichever was earlier. Patients continued to be followed up for recurrence and survival.

Endometrial assessments: TVUS, hysteroscopy, and Pipelle sampling were performed before randomised treatment for baseline measurements and 12, 24, 60, and 72 months after the start of treatment; this report will present data up to and including the 2-year visit. The primary endpoint was the incidence of any histologically-confirmed endometrial abnormality occurring after the start of trial treatment. Time to first endometrial abnormality was used as a secondary analysis of the incidence of endometrial abnormalities. The secondary endpoints were the incidence of serious and non-serious abnormalities, evaluation of TVUS as a screening tool for endometrial changes, the 'background' abnormality rate, incidence of specific abnormalities,

medical intervention required for endometrial abnormalities, and vaginal bleeding in combination with endometrial pathology.
Safety was further assessed by recording adverse events; these results are summarised in the ATAC main trial report.

RESULTS

Demography: A total of 285 patients (from 31 centres in Europe, Australia, and South Africa) were recruited into this sub-protocol, 6 of whom did not receive trial therapy. The patient population and disposition for the remaining 279 patients are presented in Table A. For logistical reasons, recruitment into the ATAC main trial (protocol number 1033IL/0029) commenced prior to entry to this sub-protocol. As a result of the significant scientific interest in the main trial, recruitment was extremely rapid. This resulted in the required patient numbers being attained before recruitment into this sub-protocol was completed; therefore, recruitment into this sub-protocol was closed once the main trial had recruited the necessary patient numbers. Thus, the endometrial sub-protocol did not recruit the intended 500 patients in order to have sufficient power based on the previous literature results.

Table A Patient population and disposition

	Anastrozole 1 mg (N = 99)	Tamoxifen 20 mg (N = 92)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 88)
Population			
Mean age (range) (years)[a]	60.2 (45.0 to 78.7)	60.7 (47.0 to 75.1)	59.7 (46.5 to 80.0)
Body weight (range) (kg)[a]	67.0 (45.0 to 101.0)	69.7 (50.0 to 116.0)	69.6 (39.0 to 104.5)
Caucasian (n [%])[b]	95 (97.9)	88 (98.9)	84 (98.8)
Disposition			
Withdrawal (n[%])			
At baseline due to endometrial abnormalities[c]	2 (2.0)	3 (3.3)	3 (3.3)
From sub-protocol[b,d]	25 (25.8)	27 (30.3)	23 (27.1)
Primary analysis population (n[%])	97 (98.0)	89 (96.7)	85 (96.6)
PP population (n[%})	87 (87.9)	81 (88.0)	73 (83.0)

[a] Summaries are for the primary analysis population (for patients with available data).
[b] Percentages calculated with the primary analysis population as the denominator.
[c] The denominator was based upon the 285 patients randomised to treatment.
[d] Number of patients withdrawn (by treatment first received).
N Number of patients receiving treatment.
n Number of patients.
P P Per protocol.

The treatment groups were generally comparable for the demographic characteristics. However, an imbalance was noted in the numbers of patients who had received previous hormone-replacement therapy (48 [49.5%] patients who had received anastrozole 1 mg; 28 [31.5%] patients who had received tamoxifen 20 mg; and 32 [37.6%] patients who had received the combination of anastrozole 1 mg plus tamoxifen 20 mg) or oral contraceptives (47 [48.5%] patients who had received anastrozole 1 mg; 31 [34.8%] patients who had received tamoxifen 20 mg; and 40 [47.1%]) patients who had received the combination of anastrozole 1 mg plus tamoxifen 20 mg). As both hormone-replacement therapy and oral contraceptives contain oestrogen, this would increase the likelihood of oestrogenic endometrial stimulation within the anastrozole group, and could possibly have affected the results in favour of tamoxifen.

Primary endpoint:

Table B summarises the hysteroscopy/histopathology results for all patients in the primary analysis population up to and including the 2-year visit, by treatment first received.

Table B Hysteroscopy/histopathology results: primary analysis population

Hysteroscopy/histopathology in first 2 years	Treatment first received		
	Anastrozole 1 mg (N = 97)	Tamoxifen 20 mg (N = 89)	Anastrozole 1 mg plus tamoxifen 20 mg (N = 85)
Patients with complete information	69	54	58
Abnormal[a]	6 (8.7)	9 (16.7)	16 (27.6)
Normal	63	45	42

[a] Percentages calculated with the primary analysis population with complete information as the denominator.
Note that if a patient experienced a post-baseline endometrial abnormality prior to their 2-year visit, this patient was considered to have complete information irrespective of their follow-up.
N Number of patients in the primary analysis population.
Data derived from Tables T5.1.1.

Endometrial abnormalities occurring after the start of trial treatment were confirmed histologically in 31 patients. The proportion of patients with abnormalities was lowest for the anastrozole 1 mg group, compared to the other 2 treatment groups.
Table C summarises the results of the primary statistical analysis for the incidence of any histologically-confirmed endometrial abnormality.

Table C Primary analysis of incidence of any histologically-confirmed endometrial abnormality: primary analysis population[a]

Treatment comparison	Odds ratio[b]	Upper 1-sided 95% CL	2-sided 95% CI	p-value
Anastrozole 1 mg versus tamoxifen 20 mg	0.487	NA	0.159 to 1.489	0.2070
Anastrozole 1 mg plus tamoxifen 20 mg versus tamoxifen 20 mg	1.833	3.980	0.728 to 4.617	0.1983

[a] Covariate adjusted analysis.
[b] An odds ratio of <1.00 indicates that treatment with tamoxifen 20 mg is associated with a greater odds of experiencing an endometrial abnormality than the other group in the treatment comparison.
CI Confidence interval; CL Confidence limit; NA Not applicable.
Data derived from Tables T5.2 and H2.1 to H2.3.

The odds of experiencing an endometrial abnormality were numerically lower for patients who received anastrozole 1 mg compared with tamoxifen 20 mg. This difference was not statistically significant.
The odds of experiencing an endometrial abnormality were numerically higher for patients who received anastrozole 1 mg plus tamoxifen 20 mg in combination compared with tamoxifen 20 mg monotherapy. Non-inferiority was not concluded.
Due to the low number of endometrial abnormalities (31 in total for the 3 treatment groups), the results for the time to first endometrial abnormality analysis are inconclusive. However anastrozole 1 mg was associated with a numerically longer time to first endometrial abnormality than tamoxifen 20 mg (hazard ratio 0.55, 95% CI 0.19 to 1.60). The anastrozole 1 mg plus

tamoxifen 20 mg in combination group was associated with numerically shorter time to first endometrial abnormality than tamoxifen 20 mg monotherapy (hazard ratio 1.90, 95% CI 0.80 to 4.51).

Secondary endpoints:

- Two patients had serious endometrial abnormalities (1 in the tamoxifen 20 mg group and 1 in the anastrozole 1 mg plus tamoxifen 20 mg in combination group). Due to this small number of serious abnormalities, the statistical analysis for this secondary endpoint was not performed.
- The most frequently reported endometrial abnormalities were the occurrence of polyps with no atypia (5 [7.2%] patients who received anastrozole 1 mg; 8 [14.8%] patients who received tamoxifen 20 mg; and 9 [15.5%] patients who received the combination of anastrozole 1 mg plus tamoxifen 20 mg) and secretory endometrium (1 [1.4%] patient who received anastrozole 1 mg; 0 patients who received tamoxifen 20 mg; and 3 [5.2%] patients who received the combination of anastrozole 1 mg plus tamoxifen 20 mg). No statistical differences were seen between the anastrozole 1 mg and tamoxifen 20 mg treatment groups, or the anastrozole 1 mg plus tamoxifen 20 mg in combination and the tamoxifen 20 mg treatment groups. It should be noted that the number of patients with these abnormalities was very small.
- Median endometrial thickness was less than 5 mm at baseline in all 3 treatment groups (anastrozole 1 mg: 3.0 mm; tamoxifen 20 mg: 3.9 mm; anastrozole 1 mg plus tamoxifen 20 mg in combination: 3.0 mm). The median thickness was <5 mm at both Year 1 and Year 2 for the anastrozole 1 mg group, but >5 mm for the other 2 treatment groups (anastrozole 1 mg: 4.0 mm at Year 1 and 3.0 mm at Year 2; tamoxifen 20 mg: 6.0 mm at Year 1 and 7.0 mm at Year 2; anastrozole 1 mg plus tamoxifen 20 mg in combination: 7.0 mm at Year 1 and 7.0 mm at Year 2).
- When the TVUS was ‘abnormal’ (endometrial thickness >5 mm), the consistency between TVUS and hysteroscopy/histopathology was much worse than when the TVUS was ‘normal’ (≤5 mm).
- The background abnormality rate for patients recruited into this sub-protocol was 9.1%.
- Fewer patients in the anastrozole 1 mg group required medical intervention for endometrial abnormalities, compared with the other 2 treatment groups (1 [1.4%] patients who received anastrozole 1 mg; 6 [11.1%] patients who received tamoxifen 20 mg; and 8 [13.8%]) patients who received the combination of anastrozole 1 mg plus tamoxifen 20 mg).
- There were no patients who received either anastrozole 1 mg or tamoxifen 20 mg who had both endometrial abnormalities and vaginal bleeding. Six (10.3%) patients who received anastrozole 1 mg plus tamoxifen 20 mg in combination had both endometrial abnormalities and vaginal bleeding.