Drug product:	Anastrozole	**SYNOPSIS**	
Drug substance(s):	Arimidex		
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Study code:	1033IL/0039		
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A randomised, double-blind, study comparing ARIMIDEX™ with NOLVADEX™ as neo-adjuvant and adjuvant treatment in post-menopausal women with large operable (T2 [≥3 cm], T3, N0-2, M0) or potentially-operable, locally advanced (T4b, N0-2, M0), ER+ and/or PR+ breast cancer

REPORT AT UNBLINDING OF STUDY[1]

Study centres

This study was conducted in Japan (25 centres), in the USA (12 centres), and in Europe/Rest of World (RoW) (44 centres).

[1] The study is ongoing in Japan to meet regulatory commitments but has been closed in the rest of the world.

Publications

Cataliotti L, Buzdar A, Noguchi S, Bines J. Efficacy of PReOperative Arimidex (anastrozole) Compared with Tamoxifen (PROACT) as neoadjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer. European Breast Cancer Conference (EBCC) 16-20th March 2004, Abstract.

Cataliotti L, Buzdar A, Noguchi S, Bines J, Takatsuka Y, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer – the pre-operative "Arimidex" compared to Tamoxifen (PROACT) trial. Cancer 2006;106:2095-103.

Study dates		**Phase of development**
First patient enrolled	8 August 2000	Therapeutic confirmatory (III)
Data cut-off for neo-adjuvant analysis	20 January 2003	
Last patient unblinded[a] ("data cut-off")	27 February 2006	

[a] The study is ongoing in Japan on an open-label basis to meet regulatory commitments but has been closed in the rest of the world. No data were collected from patients in the rest of the world after unblinding and study closure. Data collected after unblinding in Japanese patients are not included in this report. All patients were unblinded by the date shown.

Objectives

The primary objectives of the study were addressed in the neo-adjuvant Clinical Study Report (CSR) dated 17 May 2004. The objectives relating to the follow-up adjuvant treatment period were:

- Compare the treatment arms with respect to recurrence-free survival
- Compare the 2 treatment arms with respect to survival

As the study was stopped prematurely, there were insufficient data to allow a statistical analysis of the recurrence-free survival and overall survival endpoints and these objectives have therefore not been formally addressed.

This report provides a summary of the incidence of recurrence-free survival, overall survival and also of safety in the whole study period and adjuvant study period. The summaries are spilt by ethnicity (Japanese vs RoW).

Study design

This was a randomised, double-blind, double-dummy, multicentre international study comparing Arimidex (anastrozole) with Nolvadex (tamoxifen) as neo-adjuvant and adjuvant treatment in post-menopausal women with large, operable or potentially operable, locally advanced breast cancer.

In the neo-adjuvant phase, patients received study medication for 3 months following which an assessment of tumour response was made (primary endpoint). The efficacy and safety data referring to the neo-adjuvant part of the study have already been analysed and reported (CSR dated 17 May 2004).

Following surgery, patients entered the adjuvant phase and were to continue to receive study medication for 5 years or until recurrence, intolerable toxicity or patient refusal. Assessments of survival, recurrence and safety were to be made every 6 months in this phase of the study. Following the 5-year completion analysis of the ATAC study (ARIMIDEX, Tamoxifen, Alone and in Combination), which confirmed the superior efficacy and tolerability profile of Arimidex compared with Nolvadex in the primary adjuvant setting (Howell et al, 2005), and the combined analysis of the Austrian Breast and Colorectal Cancer Study Group study 8 (ABCSG8) with the German Adjuvant Breast Group Study ARNO (ARIMIDEX/NOLVADEX) 95 (Jakesz et al 2004), the principal investigators for PROACT recommended that the study be unblinded and closed. The study was therefore closed in all countries except Japan where it would provide important data on the adjuvant use of Arimidex in Japanese patients with hormone positive early breast cancer. The data cut-off (defined as the date the last patient was unblinded) was 27 February 2006.

At unblinding, patients in Japan had the option to re-consent and continue treatment on an open-label basis. (Data collected after the unblinding of Japanese patients who are continuing in the study have not been included in this report.) In all other countries ongoing patients were withdrawn from the study citing "Investigator's discretion" and provided with continuing medication outside of the study.

Target patient population and sample size

Approximately 440 post-menopausal women were to be enrolled with large operable (T2 [≥3 cm], T3, N0-2, M0; assessed by either ultrasound [U/S] or calliper) or potentially operable, locally advanced (T4b, N0-2, M0), oestrogen receptor (ER) positive and/or progesterone receptor (PgR) positive breast cancer.

Investigational product and comparator: dosage, mode of administration and batch numbers

The investigational products were:

- Arimidex 1 mg orally once daily (od) + Nolvadex placebo, or
- Nolvadex 20 mg orally od + Arimidex placebo

Active and placebo Arimidex were supplied as white film-coated tablets, and active and placebo Nolvadex as white, round, biconvex tablets, all for od use. Arimidex formulation numbers were F11292 (active) and F11314 (placebo). Nolvadex formulation numbers were F6293 (active), F12061 (active), F11003 (placebo), F12062 (placebo). The batch numbers for the study drugs are provided in Appendix 12.1.6. The study drugs (active/placebo Arimidex and active/placebo Nolvadex) were packaged in high-density polyethylene (HDPE) bottles as

a 26-week supply of 224 tablets. Patients were instructed to take 1 tablet orally from each bottle od.

Duration of treatment

Patients were to receive study drugs (with or without chemotherapy; with or without radiotherapy) for 12 weeks before primary surgery and were to continue to receive study medication for 5 years or until recurrence, intolerable toxicity or patient refusal.

Criteria for evaluation

Primary endpoint:

- The primary endpoint (objective tumour response at 3 months) has already been addressed and reported in the neo-adjuvant CSR (17 May 2004).

Secondary endpoints:

The secondary endpoints presented in this adjuvant report are:

- Safety
  - Safety profiles:
    The primary safety endpoint was frequency of adverse events (AEs). All patients were monitored for AEs during the study period and up to 30 days following administration of the last study drug. Any Serious Adverse Events (SAEs) commencing within 30 days of cessation of therapy were to be followed to resolution.
- Efficacy
  - Recurrence-free survival:
    Recurrence-free survival was measured from the date of randomisation to the date of recurrence or death, whichever occurred first. The site of recurrence of breast cancer (local or metastatic) was recorded. A new breast primary tumour, whether contra-lateral or ipsilateral, was also recorded as a recurrence event.
  - Survival:
    Survival was measured from the date of randomisation to the date of death.

Statistical methods

The efficacy variables are summarised on an intention-to-treat basis. The male patient (0080/5645) who was incorrectly randomised into the study is excluded from all summaries although his details are included in the individual patient listings.

The safety data are summarised on the basis of the actual first received treatment.

No formal statistical analyses have been performed for this report.

The data presented in this report were all collected between the point of randomisation and the data cut-off for the whole population. Data collected after unblinding from Japanese patients who are continuing in the study have not been included in this report.

Safety data (AEs, SAEs, drug-related AEs, chemotherapy AEs, and discontinuations from treatment) are summarised according to treatment received as follows:

- All patients who began study therapy
- All events in all patients who underwent surgery and entered the adjuvant part of the study.

In order to investigate country of origin differences, demography, recurrence-free survival, overall survival and safety data have been presented for Japanese patients (living in Japan) and those from the rest of the world (RoW).

Patient population

Approximately 440 patients (220 per treatment arm) were to be enrolled into the study. To explore the effect of ethnicity (Japanese patients [patients living in Japan] versus others) with treatment, approximately 40 Japanese patients (patients living in Japan) per treatment arm were to be enrolled.

RESULTS

Patient population and disposition are shown in Table S1.

Table S1 Patient population and disposition

	Arimidex		Nolvadex	
Population				
N randomised (N planned)[a]	228	(220)	223	(220)
Demographic characteristics				
Sex [n (%) of patients]				
Female	228	(100.0)	223	(100.0)
Age (years)				
Mean (sd)	67.3	(9.6)	66.7	(9.8)
Range	48.7 to 91.5		44.1 to 95.9	
Race [n (%) of patients]				
Caucasian	156	(68.4)	153	(68.6)
Japanese[b]	48	(21.1)	49	(22.0)

Table S1 Patient population and disposition

	Arimidex		Nolvadex	
Hispanic	8	(3.5)	7	(3.1)
Afro-Caribbean	4	(1.8)	10	(4.5)
Other	12	(5.3)	4	(1.8)
Baseline characteristics				
Height (cm)	N=226		N=219	
Mean (sd)	157.2	(6.8)	156.4	(7.1)
Range	140.0 to 178.0		137.0 to 173.0	
Weight (kg)	N=225		N=217	
Mean (sd)	67.3	(15.0)	67.3	(13.8)
Range	35.0 to 144.0		38.0 to 118.0	
Body mass index (kg/m^2)	N=224		N=217	
Mean (sd)	27.3	(5.7)	27.5	(5.1)
Range	15.2 to 60.7		16.3 to 48.6	
Disposition				
N (%) of patients who:				
Completed neo-adjuvant phase[c]	192	(84.2)	195	(87.4)
Discontinued neo-adjuvant phase	36	(15.8)	26	(11.7)
Completed adjuvant phase	4	(1.8)	3	(1.3)
Discontinued adjuvant phase	155[d]	(68.0)	166[d]	(74.4)
Were ongoing	33	(14.5)	26	(11.7)
were included in whole safety population[e]	228		221	
were included in adjuvant safety population[c]	192		195	
were included in ITT population (efficacy)	228		223	
N (%) of Japanese patients[b] who:				
Completed neo-adjuvant phase[c]	43	(89.6)	43	(87.8)
Discontinued neo-adjuvant phase	5	(10.4)	5	(10.2)
Completed adjuvant phase	0	(0)	0	(0)
Discontinued adjuvant phase	10	(20.8)	17	(34.7)
Were ongoing	33	(68.8)	26	(53.1)
were included in whole safety population[e] (Japanese only)	48		48	

Table S1 Patient population and disposition

	Arimidex	Nolvadex
were included in adjuvant safety population[c] (Japanese only)	43	43
were included in ITT population (efficacy) (Japanese only)	48	49

Source data: Tables T1.1, T1.2, T1.4, T2, T4.1 and J2 and J4.1, Section 11.

[a] A male patient (0080/5645) was incorrectly randomised to the study. This patient was excluded from all analyses and summaries, but is included in the listings.

[b] Patients living in Japan (Japanese is taken from the case report form [CRF] 'Japanese [living in Japan]').

[c] Patients were considered to be in the adjuvant phase from the point of surgery onwards.

[d] Includes the withdrawal of patients due to stopping and unblinding the study.

[e] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.

ITT Intention to treat; NC Not calculated; sd Standard deviation.

The 2 treatment arms were generally similar in terms of demographic and baseline characteristics. Patients in the ITT population had a mean age of 67 years (range: 44.1 to 95.9 years). The majority (approximately 70%) of patients were Caucasian, and approximately one-fifth were Japanese (living in Japan).

Efficacy results

The results of the primary efficacy analysis (objective tumour response at 3 months) and the secondary efficacy analyses (percentage tumour shrinkage, extent of breast surgery, pathological response at 3 months, comparison between ultrasound [U/S] response and calliper response, axillary down staging at 3 months, Quality of Life [QoL] outcomes, health economics [HE] outcomes and effect of ethnicity) are presented in the CSR dated 17 May 2004.

Recurrence-free survival: Fewer patients in the Arimidex arm (28.9%: 66/228) experienced a recurrence event (defined as the first occurrence of disease progression, recurrence, new breast primary or death) compared with patients in the Nolvadex arm (34.5%: 77/223). Similarly, a decrease was also seen for two of the recurrence-free survival categories: disease progression (3.9% for Arimidex vs 5.8% for Nolvadex) and recurrence/new breast primary (15.8% for Arimidex vs 19.7% for Nolvadex). The numbers of deaths occurring as first events were balanced between the two treatment groups (9.2 % for Arimidex vs 9.0% for Nolvadex).

Overall survival: There was little difference between the treatment groups in terms of overall survival (deaths from any cause, following or in the absence of progression): 17.5% (40/228) in the Arimidex group vs 18.8% (42/223) in the Nolvadex group.

Recurrence-free survival in Japanese patients (living in Japan): Fewer Japanese patients in the Arimidex arm (8.3%: 4/48) experienced a first recurrence event compared with patients

in the Nolvadex arm (40.8%: 20/49). Similarly a difference was also seen for two of the recurrence-free survival categories: disease progression (2.1% for Arimidex vs 12.2% for Nolvadex) and recurrence/new breast primary (6.3% for Arimidex vs 26.5% for Nolvadex). There was only one death reported as a first recurrence event and this was in the Nolvadex group. The number of first-recurrence events in the RoW patients was balanced (34.4% in the Arimidex group and 32.8% in the Nolvadex group).

Overall survival in Japanese patients (living in Japan): Consideration of overall survival (deaths from any cause, following or in the absence of progression) found a reduction in the Arimidex group: 2.1% (1/48) in the Arimidex group vs 14.3% (7/49) in the Nolvadex group.

Safety results

The safety data for the neo-adjuvant + 30-day phase are provided in the CSR dated 17 May 2004.

Safety in all patients: Table S2 gives an overview of AEs, discontinuations and deaths according to treatment received for the whole study period.

Table S2 Overview of adverse events: Whole study period (Safety population)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]			
	Arimidex (N=228)		Nolvadex (N=221)	
Any adverse event[b]	201	(88.2)	200	(90.5)
Treatment-related adverse events[c]	91	(39.9)	92	(41.6)
Chemotherapy-related adverse events[c]	83	(36.4)	86	(38.9)
Serious adverse events	74	(32.5)	70	(31.7)
Total deaths[d]	40	(17.5)	42	(19.0)
Due to an adverse event	18	(7.9)	11	(5.0)
Following recurrence/progression	19	(8.3)	22	(10.0)
Discontinuations[e]	191	(83.8)	191	(86.4)
Due to adverse events	30	(13.2)	20	(9.0)

Source data: Table T6.2.1, Section 11.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Events occurring on study or up to 30 days after stopping treatment.

[c] As determined by the investigator

[d] Includes deaths occurring in the absence of recurrence up to 30 days after cessation of study therapy.

[e] 17 patients had an AE that led to discontinuation reported on their AE form, but did not record this on their withdrawal forms. 15 recorded death, 1 recorded withdrawal of consent and one recorded progression. Therefore these patients are included in the total discontinuations and the discontinuations due to an AE categories.

Both Arimidex and Nolvadex were well tolerated as treatment of post-menopausal patients with hormone receptor-positive, large operable (>3 cm) or potentially operable, locally advanced breast tumours. The safety profiles of Arimidex and Nolvadex were broadly consistent with those observed in other studies in the clinical programme and with the existing safety profiles for the 2 study drugs in this patient population.

SAEs occurred in 32.5% of patients in the Arimidex arm and 31.7% of patients in the Nolvadex arm. Of the patients in the Arimidex arm 13.2% discontinued due to an AE compared with 9.0% in the Nolvadex arm. These discontinuations were not attributable to a single event or group of events. There were 40 deaths (17.5%) in the Arimidex group and 42 (19.0%) in the Nolvadex group. Eighteen of those in the Arimidex group were due to AEs compared with 11 in the Nolvadex group.

The 3 most commonly reported AEs were nausea (31.6% vs 29.9% for Arimidex and Nolvadex, respectively), alopecia (21.9% vs 28.1%, respectively) and vomiting (16.7% vs 15.4%, respectively). Although these AEs have all been previously associated with Arimidex and Nolvadex, in this study they were, along with leukopenia, neutropenia and stomatitis, considered by the investigators to be related to concomitant chemotherapy in the majority of patients.

Of the remaining commonly occurring AEs (ie incidence ≥5% of patients), most were reported at a similar frequency in both treatment groups (ie, <2% difference between groups in incidence). The exceptions were:

- reports more frequent in the Arimidex group: hot flushes (15.8% vs 13.1%), post-procedural pain (11.8% vs 8.6%), oedema peripheral (10.5% vs 8.1%), osteoarthritis (7.9% vs 5.4%), dyspepsia (7.0% vs 5.0%), radiation injury (7.0% vs 4.5%), osteoporosis (6.1% vs 1.4%) and gastritis (6.1% vs 0.9%)

- reports more frequent in the Nolvadex group: fatigue (12.7% vs 9.6%), lymphoedema (11.3% vs 7.9%), anorexia (10.4% vs 8.3%), cough (10.9% vs 7.9%), pyrexia (11.8% vs 4.8%), urinary tract infection (8.6% vs 4.8%), dizziness (8.6% vs 4.4%), bone pain (7.7% vs 4.8%), vertigo (6.3% vs 3.5%), back pain (6.3% vs 2.2%), and cellulitis (5.4% vs 3.1%).

Hot flush and osteoporosis are recognised side-effects of Arimidex. Fatigue is a known side-effect of Nolvadex.

For most of the common AEs where there was a difference between treatment groups, this resulted from events reported in the adjuvant phase of the study. All patients in this phase of the study had received surgery and many would also have received concomitant medications for post-operative management of pain and complications. Many patients would also have received adjuvant chemotherapy, radiotherapy or both. In many cases the observed

differences between treatment groups will be due to random variation but may also have been caused or influenced by the concomitant procedures and treatments.

Safety in Japanese patients: Table S3 gives an overview of AEs, discontinuations and deaths according to treatment received for the whole study period in Japanese patients (living in Japan) and patients from RoW.

Table S3 Overview of AEs: Japanese and RoW - whole safety population

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]							
	Japanese patients[b] (N=96)				Rest of world (N=353)			
	Arimidex (N=48)		Nolvadex (N=48)		Arimidex (N=180)		Nolvadex (N=173)	
Any adverse event[c]	43	(89.6)	48	(100.0)	158	(87.8)	152	(87.9)
Treatment-related adverse events[d]	29	(60.4)	33	(68.8)	62	(34.4)	59	(34.1)
Chemotherapy-related adverse events[d]	10	(20.8)	22	(45.8)	73	(40.6)	64	(37.0)
Serious adverse events	8	(16.7)	8	(16.7)	66	(36.7)	62	(35.8)
Total deaths[e]	1	(2.1)	7	(14.6)	39	(21.7)	35	(20.2)
Due to an adverse event	0		0		18	(10.0)	11	(6.4)
Following recurrence/progression	1	(2.1)	6	(12.5)	18	(10.0)	16	(9.2)
Discontinuations	15	(31.3)	22	(45.8)	176	(97.8)	169	(97.7)
Due to adverse events	6	(12.5)	3	(6.3)	24	(13.3)	17	(9.8)

Source data: Table J6.2.1, Section 11.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Ethnicity - Japanese is taken from the case report form [CRF] 'Japanese (living in Japan)'.

[c] Events occurring on study and up to 30 days after stopping treatment.

[d] As determined by the investigator

[e] Includes deaths occurring in the absence of recurrence up to 30 days after cessation of study therapy.

RoW, rest of the world.

Both Arimidex and Nolvadex were well tolerated as treatment of post-menopausal Japanese patients with hormone receptor-positive, large operable (>3 cm) or potentially operable, locally advanced breast tumours. The safety profiles of Arimidex and Nolvadex were broadly consistent with those observed in other studies in the clinical programme and with the existing safety profiles for the 2 study drugs in this patient population. The incidences of SAEs, AEs leading to discontinuation and deaths were all low in Japanese patients. This may be due to a reduced use of adjuvant chemotherapy and adjuvant radiotherapy in Japanese patients compared with the RoW. Discontinuation from the study because of AEs was rare; only

9 Japanese patients had AEs leading to discontinuation in the whole study. There were 8 deaths in Japanese patients during the study: 1 in the Arimidex group and 7 in the Nolvadex group. None of these were due to an AE.

Categories where there was a notable increase in the reporting of AEs by Japanese patients who received Nolvadex relative to Arimidex, with no notable difference between groups in patients from the RoW were: fatigue, pyrexia, cystitis, anorexia, back pain, cough, and pruritus.

Categories where there was a notable increase in the reporting of AEs by Japanese patients who received Arimidex relative to Nolvadex, with no notable difference between groups in patients from the RoW were: constipation, gastritis and osteoarthritis.

There was no notable difference in the incidence of dizziness for Japanese patients. The incidence of dizziness was increased in patients from the RoW who received Nolvadex (9.2%) compared with those who received Arimidex (3.9%).

Insomnia was increased in Japanese patients who received Nolvadex (31.3%) compared with those who received Arimidex (16.7%). The opposite trend was seen in patients from the RoW (13.3% for Arimidex vs 7.5% for Nolvadex).

Hot flushes was the most common treatment-related AE in both Japanese patients and patients from the RoW. There were no deaths following an AE in Japanese patients. Of all the SAE categories, only cataracts (1 patient each for Arimidex and Nolvadex) and endometrial hyperplasia (2 patients for Nolvadex) were reported by more than 1 Japanese patient. The incidence of serious myocardial infarction, fractures and thrombotic events was low in Japanese patients.