AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Anastrozole (ZD1033)
Study Code	D539BC00001
Edition Number	1
Date	12 May 2010

Multi-centre, randomised, double-blind, parallel-group study to compare efficacy and safety between anastrozole (ZD1033) and tamoxifen in pre- and post-operative administration under goserelin acetate treatment for premenopausal breast cancer patients

Study dates:
First patient randomised: 2 October 2007
Last patient last visit*: 30 November 2009
* Last breast surgery day of randomised patients

Phase of development:
Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was conducted at 27 centres in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective of this study was to compare tumour response (best overall tumour response rate: BORR) between anastrozole group and tamoxifen group during 24 weeks in pre-operative administration under goserelin acetate treatment for premenopausal breast cancer patients. The objectives of this study including secondary and exploratory objectives were shown in Table S 1. This clinical study report (CSR) describes the results of main analysis (based on the data in all patients who completed 24 weeks pre-operative treatment period and received breast cancer surgery or withdrew before breast cancer surgery) provided in the clinical study protocol (CSP), therefore the results of a part of outcome variables are not included in this CSR. The details are presented in Table S 1. In addition, the change of aromatase for exploratory variables is not included in this CSR for main analysis because any evaluation methods for aromatase have not been established when the CSR was prepared.

Table S 1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Title and description**
Primary	Efficacy	To compare tumour response (BORR) between anastrozole group and tamoxifen group during 24 weeks in pre-operative administration under goserelin acetate treatment for premenopausal breast cancer patients.	BORR during 24 weeks in pre-operative administration
Secondary	Safety	To evaluate the safety in the anastrozole and tamoxifen groups by adverse events (AEs), clinical laboratory test value, blood pressure, pulse rate, and World Health Organisation (WHO) performance status in pre- and post [a)]-operative administration under goserelin acetate treatment.	AEs, clinical laboratory test value, blood pressure, pulse rate, WHO performance status
		To evaluate changes in bone mineral density (BMD) and bone turnover markers in the anastrozole and tamoxifen groups in pre- and post [a)]-operative administration under goserelin acetate treatment.	BMD, bone turnover markers
	Efficacy	To evaluate changes in serum oestron (E1) and oestradiol (E2) concentrations in the anastrozole and tamoxifen groups in pre- and post [a)]-operative administration under goserelin acetate treatment.	Changes of serum E1 and E2 concentrations
		To evaluate changes in oestrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) in the anastrozole and tamoxifen groups before initiation and after 24 weeks in pre-operative administration under goserelin acetate treatment.	Changes of ER, PgR and HER2

Table S 1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Title and description**
		To evaluate histopathological response (histopathological response rate: HRR) in the anastrozole and tamoxifen groups after 24 weeks in pre-operative administration under goserelin acetate treatment.	HRR after 24weeks in pre-operative administration
		To evaluate overall survival in the anastrozole and tamoxifen groups under goserelin acetate treatment [a)].	Overall survival
		To evaluate progression-free survival (period until time of recurrence) in the anastrozole and tamoxifen groups under goserelin acetate treatment [a)].	Progression-free survival (period until time of recurrence)
	PRO	To evaluate Quality of Life (QoL) using Functional Assessment of Cancer Therapy-Breast (FACT-B) and Endocrine Subscale (ES) instruments in the anastrozole and tamoxifen groups in pre- and post [a)]-operative administration under goserelin acetate treatment.	QoL (FACT-B and ES) score
	PK	To evaluate plasma anastrozole concentrations of the anastrozole group in pre-operative administration under goserelin acetate treatment.	Anastrozole plasma concentration (C_{min})
Exploratory	Efficacy	To evaluate changes in aromatase [b)] and Ki67 in the anastrozole and tamoxifen groups before initiation and after 24 weeks in pre-operative administration under goserelin acetate treatment.	Changes of Aromatase and Ki67
		To evaluate E1 and E2 concentrations in the breast cancer tissues in the anastrozole and tamoxifen groups before initiation and after 24 weeks in pre-operative administration under goserelin acetate treatment.	E1 and E2 concentrations in breast cancer tissue

CSP Clinical study protocol; PRO Patient reported outcomes.
a) Not applicable for this CSR.
b) The evaluation methods and results for the change of aromatase will be reported separately from this CSR.

Study design

This study was a multicentre, randomised, double-blind, controlled with active drug by double-dummy, parallel group comparative study to compare efficacy and safety between anastrozole 1 mg and tamoxifen 20 mg in pre- and post-operative administration under goserelin acetate treatment for Japanese premenopausal female patients with oestrogen receptor (ER) positive breast cancer.

Target subject population and sample size

Japanese premenopausal female patients aged 20 years and over with ER positive breast cancer who have operable and measurable lesion (T (2 cm – 5 cm), N0, M0).

A total of at least 194 patients were to be recruited in this study.

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

In this study the following test products were used:

- Investigational products (active and placebo)
  - Anastrozole 1 mg Tablet (Investigational product); F11292
  - Anastrozole placebo Tablet; F11314
- Comparators (active and placebo)
  - Tamoxifen 20 mg Tablet(Comparator); F6293
  - Tamoxifen placebo Tablet; F11003

Anastrozole group

Both anastrozole (investigational product) 1 mg tablet and tamoxifen placebo tablet were given once a day orally.

Tamoxifen group

Both tamoxifen (comparator) 20 mg tablet and anastrozole placebo tablet were given once a day orally.

For all patients, goserelin (Zoladex 3.6 mg depot), subcutaneous injection as a concomitant drug was administered. Commercially available goserelin were used as concomitant drug in this study.

Duration of treatment

24 weeks (neo-adjuvant period) before operation.

Statistical methods

For the tumour response (BORR) during 24 weeks in pre-operative administration by each measurement method (calliper, ultra sound [US], magnetic resonance imaging [MRI] [or computed tomography; CT]), the difference between anastrozole group and tamoxifen group (anastrozole group - tamoxifen group) and its 2-sided 95% confidence interval were estimated. If the lower 2-sided 95% confidence interval was greater than -10%, then the non-inferiority of anastrozole group with respect to tamoxifen group in the best overall response was concluded. In case the non-inferiority of anastrozole group with respect to tamoxifen group in the BORR was concluded, then it was checked whether the lower 2-sided 95% confidence interval of the difference between anastrozole group and tamoxifen group (anastrozole group - tamoxifen group) in the BORR was greater than 0 or not. If the lower 2-sided 95% confidence interval was greater than 0, then the superiority of anastrozole group with respect

to tamoxifen group in the best overall response was concluded. In addition, analysis for the data with Calliper was set as the main analysis. The serum E1 and E2 concentrations and the E1 and E2 concentration in breast cancer tissue at each time point were summarised using the descriptive statistics. Similar analysis to tumour response was done based on histopathological effect. For changes of ER, PgR, and HER2 evaluated at each study site at each time point, shift tables were made. The QoLs were analysed using the data up to surgery based on an ANCOVA model with treatment fitted as a factor and the relevant score at baseline as covariates. For safety variables, quantitative data were summarised using descriptive statistics and qualitative data were summarised using a frequency table.

Subject population

The correct patient population has been recruited and adherence to the CSP was high.

In total 197 premenopausal breast cancer patients were randomised in this study and 185 of 197 patients completed the 24 weeks pre-operative treatment and received breast surgery. The remaining 12 patients discontinued study treatment due to disease progression (6 patients), voluntary patient discontinuation (5 patients), and AE (1 patient).

There were no clinically important differences between two treatment groups in the demographic and baseline disease characteristics.

The demographic characteristics of the study population in the ITT population are described in Table S 2.

Table S 2 Patient disposition and study population (ITT)

	Number (%) of patients					
	anastrozole		tamoxifen		Total	
Patients randomised	98		99		197	
Patients who received treatment	98	(100.0)	98	(99.0)	196	(99.5)
Patients who prematurely discontinued study	3	(3.1)	9	(9.1)	12	(6.1)
Adverse event	0		1	(1.0)	1	(0.5)
Condition under investigation worsened	1	(1.0)	5	(5.1)	6	(3.0)
Voluntary discontinuation by Subject	2	(2.0)	3	(3.0)	5	(2.5)
Age group						
20 - 29 years	2	(2.0)	0		2	(1.0)
30 - 39 years	21	(21.4)	20	(20.2)	41	(20.8)
40 - 49 years	65	(66.3)	68	(68.7)	133	(67.5)
50 - 59 years	10	(10.2)	11	(11.1)	21	(10.7)
Tumour grade						
Grade 1 (Well Differentiated)	42	(42.9)	48	(48.5)	90	(45.7)
Grade 2 (Moderately Differentiated)	36	(36.7)	26	(26.3)	62	(31.5)

Table S 2 Patient disposition and study population (ITT)

	Number (%) of patients		
	anastrozole	tamoxifen	Total
Grade 3 (Poorly Differentiated)	4 (4.1)	14 (14.1)	18 (9.1)
Grade X (Unassessable)	1 (1.0)	0	1 (0.5)
Not Done	15 (15.3)	11 (11.1)	26 (13.2)
Oestrogen Receptor Status			
Positive	98 (100.0)	99 (100.0)	197 (100.0)
Progesterone Receptor Status			
Negative	5 (5.1)	12 (12.1)	17 (8.6)
Positive	93 (94.9)	87 (87.9)	180 (91.4)

Summary of efficacy results

BORR during 24 weeks in the anastrozole group was statistically significantly higher than that of tamoxifen group by calliper measurement (estimate difference: 19.9%, 95% CI of estimate difference: 6.5 to 33.3, p=0.004) as well as other measurements.

The HRR in the anastrozole group was statistically significantly higher than that of tamoxifen group at Week 24.

Serum E1 and E2 suppression in the anastrozole group was greater than those in the tamoxifen group from Week 4 through Week 24.

Changes of ER and HER2 status were observed in a few patients in two treatment groups, respectively. The number of changes from positive to negative of PgR status in the anastrozole group was larger than that in the tamoxifen group.

The changes of ER were similar between the study site evaluation and CPRC evaluation in both treatment groups. The change of PgR in the anastrozole group was similar between the study site evaluation and CPRC. In the tamoxifen group, the number of changes from positive to negative in the study site evaluation was larger than that in CPRC evaluation.

QoL slightly worsened in both treatment groups. No statistically significant differences were shown in all QoL variables between the two treatment groups.

Summary of efficacy results of this study is shown in Table S 3 and Table S 4.

Table S 3 Summary of best overall tumour response during 24 weeks (population: ITT)

Measurement method	Response	Number (%) of patients	
		anastrozole (n=98)	tamoxifen (n=99)
Calliper	CR+PR	69 (70.4)	50 (50.5)
US	CR+PR	57 (58.2)	42 (42.4)
MRI [or CT]	CR+PR	63 (64.3)	37 (37.4)

Table S 4 Comparison of best overall tumour response rate during 24 weeks

	Measurement method	Estimate of difference between treatment groups	95% Confidence interval		Chi square test
			Lower	Upper	p -value
anastrozole - tamoxifen	Calliper	19.9	6.5	33.3	0.004
	US	15.7	1.9	29.5	0.027
	MRI (or CT)	26.9	13.5	40.4	<0.001

Summary of pharmacokinetic results

Trough plasma concentrations (C_{min}) of anastrozole were determined in 29 premenopausal patients in anastrozole group who were concomitantly treated with goserelin acetate. The values of C_{min} were generally consistent during Week 4 to 12, suggesting that steady state was reached within the first 4 weeks of once daily treatment with anastrozole. In comparison with the postmenopausal patients administered anastrozole alone in the previous study, the steady state C_{min} values were approximately 25% lower, and this would result in no safety concerns related to drug interaction between anastrozole and goserelin acetate or related to difference of pre-/post-menopausal population.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

In the safety population, a total of 369 AEs were reported by 87 (88.8%) of 98 patients in the anastorozole group, and a total of 316 AEs were reported by 84 (85.7%) of 98 patients in the tamoxifen group.

One patient (1.0%) reported a SAE (CTCAE grade 3) not to leading to death in the anastrozole group. One patient (1.0%) was discontinued treatment due to an AE (CTCAE grade 1) in the tamoxifen group. Four patients (4.1%) in the anastrozole group and one patient (1.0%) in the tamoxifen group reported a worst CTCAE grade 3 or higher AE. No patient died due to an AE and there were no OAEs in both treatment groups.

The most commonly reported AE in each treatment group was hot flush (52.0% [51/98] in the anastrozole group and 53.1% [52/98] in the tamoxifen group), most of which were mild or moderate events (CTCAE grade 1 or 2).

There were no clinically important findings or abnormalities in the clinical laboratory test and vital signs.

Both bone-alkaline phosphates (BAP) and crosslinked N-telopeptide of type 1 collagen (NTX) were gradually increased in anastrozole + goserelin treatment. These changes were consistent with the known safety profile of anastrozole.

Both anastrozole + goserelin and tamoxifen + goserelin combined pre-operative treatments were well tolerated in premenopausal women with ER positive breast cancer and the results were consistent with the known safety profile of anastrozole, tamoxifen and goserelin. Anastrozole and tamoxifen combined with goserelin resulted in an increased incidence of hot flush.

Summaries of safety results are presented in Table S 5 and Table S 6.

Table S 5 Summary of adverse event (population: Safety analysis set)

Number (%) of patients [a)]	**Anastrozole (n=98)**	**Tamoxifen (n=98)**
Any AE	87 (88.8)	84 (85.7)
Any SAE including events with outcome=death	1 (1.0)	0
Any SAE with outcome other than death	1 (1.0)	0
Any AE leading to discontinuation of IP	0	1 (1.0)
Any AE with worst CTCAE grade ≥ 3	4 (4.1)	1 (1.0)
Number of adverse events [b)]		
Any AE	369	316
Any SAE including events with outcome=death	1	0
Any SAE with outcome other than death	1	0

Table S 5 Summary of adverse event (population: Safety analysis set)

Number (%) of patients [a)]	Anastrozole (n=98)	Tamoxifen (n=98)
Any AE leading to discontinuation of IP	0	1
Any AE with worst CTCAE grade ≥ 3	4	1

a) Patients with multiple events in the same category are counted once in that category. Patient with events in more than one category is counted once in each of those categories.
b) Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple times in each of those categories.

Table S 6 Number (%) of patients who had any adverse events by SOC and PT (population: Safety analysis set)

System Organ Class / Preferred Term	Number (%) of patients [a)]	
	anastrozole (n=98)	tamoxifen (n=98)
VASCULAR DISORDERS	52 (53.1)	54 (55.1)
Hot Flush	51 (52.0)	52 (53.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	52 (53.1)	31 (31.6)
Arthralgia	35 (35.7)	20 (20.4)
Musculoskeletal Stiffness	21 (21.4)	10 (10.2)
INFECTIONS AND INFESTATIONS	35 (35.7)	35 (35.7)
Nasopharyngitis	28 (28.6)	24 (24.5)
GASTROINTESTINAL DISORDERS	25 (25.5)	28 (28.6)
Constipation	4 (4.1)	13 (13.3)
NERVOUS SYSTEM DISORDERS	29 (29.6)	21 (21.4)
Headache	20 (20.4)	16 (16.3)

A cut off 10% has been used.