Clinical Study Report Synopsis

Drug Substance	ZD9393
Study Code	D8664C00008
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An Open Label, Randomised, Parallel Group, Multicentre Study to Compare ZOLADEX™ 10.8 mg Given Every 12 Weeks with ZOLADEX 3.6 mg Given Every 4 Weeks in Pre-menopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer

Study dates: First patient enrolled: 25 April 2006
Last patient completed: 18 November 2009

Phase of development: Therapeutic confirmatory (III)

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

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Study Centers

This study was conducted in 39 active centres in 7 countries. The countries included in this study were: Czech Republic, Italy, Japan, Poland, Romania, Russia and Ukraine .

Publications

None at the time of writing this report.

Study dates

		Phase of development
First patient enrolled	25 April 2006	Therapeutic exploratory (III)
Last patient completed	18 November 2009	

Objectives

The primary objective of this study was to evaluate whether ZOLADEX 10.8 mg was non-inferior to ZOLADEX 3.6 mg in pre-menopausal women with oestrogen receptor (ER) positive advanced breast cancer (ABC), by assessment of progression-free survival (PFS) at Week 24.

Secondary objectives were

1. To provide supportive data confirming that ZOLADEX 10.8 mg every 12 weeks was non-inferior to ZOLADEX 3.6 mg every 4 weeks by assessment of:

   - Objective response rate (ORR) at Week 24, with response defined as complete or partial response as determined by Response Evaluation Criteria In Solid Tumours (RECIST 1.0) criteria

   - Oestradiol (E2) serum concentrations at Week 24

2. To compare the safety and tolerability profile of ZOLADEX 10.8 mg and ZOLADEX 3.6 mg by assessment of adverse events (AEs)

3. To assess the pharmacokinetics (PK) of goserelin in Japanese and Caucasian patients who have received ZOLADEX 10.8 mg by assessment of goserelin plasma-concentration time profiles

Study design

This was a multicentre, open label, randomised, parallel group study to compare ZOLADEX 10.8 mg given every 12 weeks with ZOLADEX 3.6 mg given every 4 weeks in pre-menopausal women with ER positive ABC.

On 24 December 2007, recruitment into this study was terminated prematurely in Europe as a result of changes in treatment philosophies and practices. At the time of premature termination, 98 of the planned 260 patients had been randomised.

Target population and sample size

The target population was pre-menopausal women with locally advanced/metastatic breast cancer without surgery, or relapsed disease after prior therapy for early breast cancer (EBC). Eligibility was dependent on patients having at least 1 measurable lesion (not located in a previously irradiated area) according to RECIST 1.0. Exceptions were patients with bone metastases only, or patients documented to be in complete remission after prior taxane- or anthracycline-based first line chemotherapy for ABC (stage IIIb/IV). Patients without measurable disease at baseline (ie, patients with bone metastases only or with complete remission after prior taxane- or anthracycline-based first line chemotherapy for ABC) were not evaluated for objective tumour response, and were assessed for disease progression only.

The study planned to randomise approximately 260 patients in order to obtain 216 evaluable patients (108 per treatment group) to achieve an 80% power to assess non-inferiority of the primary endpoint.

Overall 98 patients were randomised, 49 to ZOLADEX 3.6 mg and 49 to ZOLADEX 10.8 mg.

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

Investigational product: ZOLADEX (goserelin acetate) 10.8 mg depot for injection (equivalent to 10.8 mg goserelin) homogeneously dispersed in co-polymer. Excipients: 95/5 lactide/glycolide biodegradable copolymer. Formulation number: F006054. Administered as a subcutaneous (s.c.) depot injection into the anterior abdominal wall. Batch numbers: CG747, CT490, CV802, FA447.

Comparator: ZOLADEX (goserelin acetate) 3.6 mg depot for injection (equivalent to 3.6 mg goserelin) homogeneously dispersed in co-polymer. Excipients: 50/50 lactide/glycolide biodegradable copolymer. Formulation number: F005589. Administered as a s.c. depot injection into the anterior abdominal wall. Batch numbers: CK958, CR216, CT663, CV788, CV789, EW420

Patients also received tamoxifen: 20 mg oral tablet (containing 30.4 mg tamoxifen citrate equivalent to 20 mg of tamoxifen). Excipients: carboxymethylcellulose calcium, magnesium stearate, mannitol, starch. Formulation number: F006293

Duration of treatment

ZOLADEX 10.8 mg: 1 injection every 12 weeks (±7 calendar days) from Day 1 until disease progression, or completion of 2 years of therapy (Week 84), whichever occurred sooner.

ZOLADEX 3.6 mg: 1 injection every 4 weeks (±7 calendar days) from Day 1 until disease progression or completion of 2 years of therapy (Week 92), whichever occurred sooner.

In addition, all patients took 1 oral tamoxifen 20 mg tablet daily from Day 1 until disease progression or completion of 2 years therapy, whichever occurred sooner.

Criteria for evaluation – efficacy, pharmacodynamics (PD) and pharmacokinetics (PK) (main variables)

Primary outcome variable (efficacy)

- PFS at Week 24, defined as a patient for whom neither objective disease progression nor death (due to any cause) was observed

Secondary outcome variables (efficacy/PD)

- ORR at Week 24, defined as either a complete or partial response based on the RECIST 1.0 criteria
- E2 serum concentrations at Week 24

Secondary outcome variables (subgroup analyses)

- Goserelin plasma concentration–time profile and related PK parameters
- E2 serum concentration–time profile

Criteria for evaluation - safety (main variables)

Secondary outcome variables (safety)

- AE profile

Statistical methods

The primary analysis for this study was intended to be undertaken once all patients had been followed up for 24 weeks of treatment and presented in the main clinical study report (CSR), with the follow-up analysis to be completed once all patients had been followed up for 96 weeks post-randomisation, and to be presented in an addendum to the main CSR. However, both analyses are presented in this CSR, produced after all patients had completed 96 weeks post-randomisation.

The primary analysis set for evaluation of the primary and secondary efficacy and PD outcome variables was the full analysis set (FAS). Evaluations of safety outcome variables was performed using the safety set. For analyses in the subgroups, PK and E2 analyses were performed using the PK subgroup set and E2 subgroup set, respectively.

For PFS, the proportion of patients who were progression-free at Week 24 was calculated for each treatment group. Non-inferiority of ZOLADEX 10.8 mg (every 12 weeks) to ZOLADEX 3.6 mg (every 4 weeks) was concluded if the lower limit of the 95% confidence interval (CI) for the difference between the treatments (10.8 mg minus 3.6 mg) was above -17.5%.

The ORR at Week 24 was determined for each treatment group and the data was presented as for PFS. Patients without measurable disease at baseline were not included in the analysis of ORR.

Mean E2 serum concentrations at Week 24 were compared using analysis of covariance (ANCOVA), with treatment group and baseline E2 serum concentrations as covariates. Least square means and the 95% CI for the difference between treatment groups were presented, as well as non-parametric methods as the data did not fulfil the assumptions of a normal distribution.

The goserelin plasma concentration-time profiles for each subject in the PK subgroup set were assessed using descriptive statistics and derived PK parameters calculated. The E2 concentration-time profiles were also investigated in the PK subgroup using the E2 subgroup set, and descriptive statistics were presented at each scheduled timepoint.

Safety was evaluated using descriptive statistics by means of frequency counts and summaries of AEs. Haematology, clinical chemistry, body weight and body mass index values were evaluated using descriptive statistics.

Patient population

An equal number of patients were randomised to each treatment group (49 per treatment group). Thirty-nine patients were randomised in Japan, and 59 patients were randomised in non-Japanese centres. A total of 70 patients attended Week 24, 35 patients in the ZOLADEX 10.8 mg group and 38 patients in the ZOLADEX 3.6 mg group. Twelve patients (24.5%) in the ZOLADEX 10.8 mg group and 16 patients (32.7%) in the ZOLADX 3.6 mg group completed Week 96. The main reason for discontinuation of study treatment was disease progression.

All 98 randomised patients were included in the FAS, with 49 in each treatment group. Patient E3002009 was randomised to ZOLADEX 3.6 mg but received ZOLADEX 10.8 mg. This patient was included in the FAS for the ZOLADEX 3.6 mg group, and the safety set for the ZOLADEX 10.8 mg group. This patient was not included in the PK or E2 subgroups.

Generally, the demographic and baseline disease characteristics were similar between the treatment groups, overall and when stratified by region (Japanese versus non-Japanese). The small differences observed between the treatment groups may have been partly due to the smaller than planned sample size. These included race and prior EBC treatment. Consistent with expectations, Japanese patients had not received prior chemotherapy for locally advanced

or metastatic breast cancer. Non-Japanese patients had received chemotherapy prior to study entry. Other baseline characteristics were well balanced.

A higher percentage of patients in the ZOLADEX 10.8 mg group were fully compliant compared to the ZOLADEX 3.6 mg group. This would be expected as ZOLADEX 10.8 mg had fewer depots to comply with compared to the ZOLADEX 3.6 mg regimen.

Summary of efficacy and pharmacokinetic results

ZOLADEX 10.8 mg showed similar efficacy to ZOLADEX 3.6 mg in terms of PFS at Week 24 (34 patients [69.4%] in the ZOLADEX 10.8 mg group and 36 patients [73.5%] in the ZOLADEX 3.6 mg group were progression free; 95% CI for the difference: -4.1 [-21.4, 13.6]), ORR at Week 24 (13 patients [28.9%] in the ZOLADEX 10.8 mg group and 11 patients [25.6%] in the ZOLADEX 3.6 mg group had an unconfirmed best objective response) and mean serum E2 at Week 24 (7.24 pmol/L in the ZOLADEX 10.8 mg group and 10.36 pmol/L in the ZOLADEX 3.6 mg group).

The criteria for non-inferiority were not met for the primary efficacy endpoint (PFS at Week 24). However, since recruitment was terminated prematurely, the study was no longer adequately powered to detect non-inferiority.

The plasma concentration of goserelin increased rapidly after administration of the ZOLADEX 10.8 mg depot. The plasma concentration decreased rapidly up to 48 hours before decreasing more slowly, approaching the lower limit of quantification at Weeks 12 to 24. Although the trough plasma concentration of goserelin (at Week 12 and Week 24) was below the lower limit of quantification for approximately half of the Japanese patients, a continued effect was demonstrated by suppression of E2. E2 suppression was successfully achieved and maintained in both Japanese and non-Japanese patients, suggesting that the lower goserelin plasma concentration (especially Cmax) observed in Japanese patients has no clinical significance.

There were no clinically important difference between Japanese and non-Japanese patients in terms of the efficacy and PK parameters.

Summary of safety results

There were no clinically important differences in the profile and tolerability of AEs or drug-related AEs between ZOLADEX 3.6 mg and ZOLADEX 10.8 mg in this study. Furthermore, there were no new safety concerns or unknown clinically important findings from AE results in this study.

A similar number of patients reported AEs within each treatment group (78.0% in the ZOLADEX 10.8 mg group, and 77.1% in the ZOLADEX 3.6 mg group). The most frequently reported SOC was vascular disorders (38.0% in the ZOLADEX 10.8 mg group and 39.6% in the ZOLADEX 3.6 mg group), and the most frequently reported AE was hot flush (38.0% of patients in the ZOLADEX 10.8 mg group and 37.5% of patients in the ZOLADEX 3.6 mg group).

There were a higher number of event episodes in the ZOLADEX 3.6 mg group (194 events) compared to the ZOLADEX 10.8 mg group (139 events). However, this can be largely attributed to the 3 patients who reported 18 events of asthenia, and 4 patients who reported 10 events of nausea, all in the ZOLADEX 3.6 mg group. No administration site condition AEs were observed for either treatment group. ZOLADEX-related AEs were experienced by 30 patients (60.0%) in the ZOLADEX 10.8 mg group, and 27 patients (56.3%) in the ZOLADEX 3.6 mg group. Forty-six patients (46.9%) experienced AEs that were possibly related to tamoxifen. There were a higher number of AEs possibly related to ZOLADEX in the ZOLADEX 3.6 mg group (90 events), than the ZOLADEX 10.8 mg group (65 events). However, this can be largely attributed to the 2 patients who reported 17 ZOLADEX-related events of asthenia in the ZOLADEX 3.6 mg group. No patients experienced AEs of CTC grade 4, and 20 patients (20.4%) experienced AEs of CTC grade 3. The incidence of SAEs was low: 2 patients (4.0%) in the ZOLADEX 10.8 mg group, and 3 patients (6.3%) in the ZOLADEX 3.6 mg group, and there were no SAEs leading to death. One patient in the ZOLADEX 3.6 mg group had a AE which lead to withdrawal from the study.

There were no clinically important differences between the ZOLADEX 10.8 mg group and the ZOLADEX 3.6 mg group in terms of clinical laboratory results or physical findings. Any small differences were likely due to the complexity of the underlying disease.

There were no clinically important differences between the safety data for Japanese and non-Japanese centres.

Date of the report

08 June 2010