
Clinical Study Report Synopsis
Addendum Report including the data after data cut-off

Drug substance:	ZD9393
Edition No.:	1
Study code:	D8664C00004
Date:	22 June 2009

An Open-label, Randomised, Parallel Group, Multicentre Study to compare Oestradiol Suppression between ZOLADEX 10.8 mg depot given 3 monthly and ZOLADEX 3.6 mg depot given monthly in Pre-menopausal Patients with ER positive Early Breast Cancer

Addendum Report including the data after data cut-off of 31 August 2007

Study dates:	First subject enrolled: 4 January 2006 Last subject completed: 11 February 2009
Phase of development:	Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice.

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Co-ordinating investigator

Not applicable

Study centre(s)

This study was conducted in Japan (29 centres).

Publications

None at the time of the writing of this report

Study dates

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Last subject completed 11 February 2009

Phase of development

Therapeutic exploratory (II)

Objectives

The primary objective for this study was to examine that ZOLADEX 10.8 mg depot was non-inferior to ZOLADEX 3.6 mg depot in terms of oestradiol (E₂) suppression in pre-menopausal patients with estrogen receptor positive (ER+) early breast cancer by assessment of area under the curve (AUC) of E₂ serum concentration during the first 24 weeks of treatment.

Secondary objectives were:

- To examine that ZOLADEX 10.8 mg depot had similar safety and tolerability profiles to ZOLADEX 3.6 mg depot in women with ER+ early breast cancer by assessment of the following variables:

- Adverse events, clinical laboratory test values, blood pressure and pulse rate
- To examine goserelin pharmacokinetics (PK) in Japanese patients after injection of ZOLADEX 10.8 mg depot by assessment of goserelin plasma concentration-time profiles and related PK parameters
- To examine that the efficacy of ZOLADEX 10.8 mg depot was similar to that of ZOLADEX 3.6 mg depot by assessment of disease-free survival (DFS)
- To assess the influence on menstuous condition after injection of ZOLADEX 10.8 mg depot or ZOLADEX 3.6 mg depot
- To assess the hormonal condition after injection of ZOLADEX 10.8 mg depot comparing with ZOLADEX 3.6 mg depot by assessment of following variables:
 - E₂ serum concentration(s)
 - Follicle stimulating hormone (FSH) serum concentration(s)
 - Percentage of patients who had mean E₂ concentration below 30 pg/mL

Study design

This study was a multicentre, open-label, randomised, parallel group study.

Target subject population and sample size

A total of 168 pre-menopausal women with ER positive early breast cancer who had received radical operation were to be recruited from approximately 30 centres in Japan in order to obtain 152 evaluable patients required for the analysis.

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

The investigational products administered were as follows:

- ZOLADEX 10.8 mg depot, subcutaneous depot injection once every 12 weeks
- ZOLADEX 3.6 mg depot, subcutaneous depot injection once every 4 weeks.

All patients were also administrated tamoxifen 20 mg tablet daily as concomitant medication.

ZOLADEX 10.8 mg depot formulation number was F06054. ZOLADEX 3.6 mg depot formulation number was F05589. Tamoxifen formulation number was F6293. The batch numbers for the investigational products and concomitant medication are provided in Appendix 12.1.6 in the clinical study report published in August 2008. ZOLADEX 10.8 mg depot and 3.6 mg depot were supplied sterile in a disposable syringe applicator, which were sealed in a moisture-proof aluminium pouch. Study centres were supplied with sufficient

medication for a total of 96 weeks for individual patient. Tamoxifen was supplied by AstraZeneca KK and also was distributed to each Japanese centre. Patients were prescribed packs of tamoxifen containing sufficient tablets for 24 weeks supply at Day 0 and at each 24-week visit.

Duration of treatment

Patients were to receive the investigational product and tamoxifen until any of criteria for discontinuation was met or completion of 96 weeks of therapy (the last injection was at Week 84 and Week 92 in the 10.8 mg group and 3.6 mg group, respectively), whichever was sooner.

Criteria for evaluation (main variables)

Primary variable

- Pharmacodynamic (PD):
 - AUC of E₂ serum concentration during the first 24 weeks of treatment.

Secondary variables

- Pharmacodynamic (PD):
 - E₂ serum concentration(s)
 - Percentage of patients who had mean E₂ serum concentration below 30 pg/mL
 - Menstruation
 - FSH serum concentration(s)
- Pharmacokinetic (PK):
 - Goserelin plasma concentration-time profiles
 - PK parameters
- Efficacy variable:
 - Disease-free Survival (DFS)
- Safety:
 - Adverse events
 - Clinical laboratory test values

- Vital signs (blood pressure and pulse rate)

Statistical methods

The data of E₂ were analysed using analysis of covariance (ANCOVA) with baseline values and treatment received fitted in the model. The AUC values of E₂ were log-transformed prior to analysis and the results were exponentiated. The 95% confidence intervals were constructed around the ratio of the AUCs, with ZOLADEX 3.6 mg being the reference treatment. Non-inferiority was to be concluded if the upper limit of the 95% confidence interval of the ratio of the area under the E₂ concentration-time curves is less than or equal to 1.25. A patient whose AUC was reported as Not Calculated (NC) was to be excluded from the analysis above.

The data for DFS were to be updated after all patients have completed the 2-year study treatment.

Study results including the data after data cut-off on 31 August 2007

The last patient completed the 2-year study treatment on 11 February 2009.

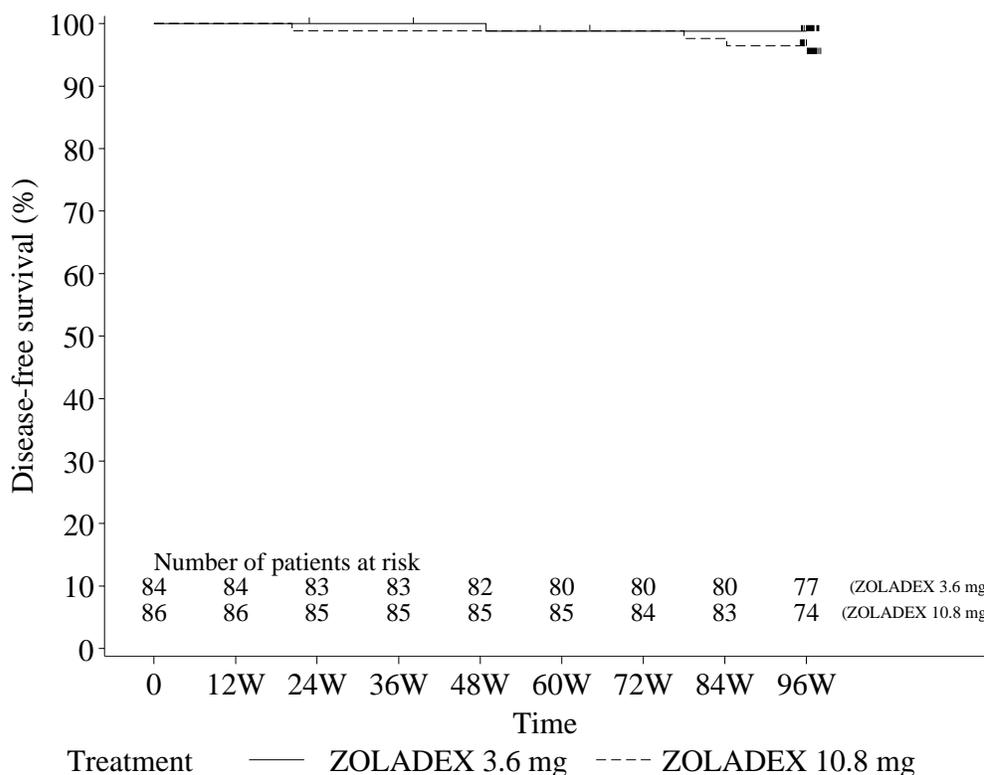
The bioassay of a part of PK plasma samples was carried out outside the period assuring the stability of the goserelin in plasma. However, it was carried out within the period assuring the stability of the compound in serum. It was considered acceptable to adopt the data due to no difference of two matrix with exception of clotting factor.

All the study results showed that no changes needed to be given to the study conclusions and key messages in the CSR published in August 2008. Therefore, description of the addendum report was just focused on the updated DFS. All tables/figures and listings including the data after data cut-off on 31 August 2007 are shown in Sections 11 and 12.

Disease Free Survival (DFS)

Follow-up durations for DFS were 657.6±84.7 (mean ± SD) days and 664.3±64.2 days in the 3.6 mg group and 10.8 mg group, respectively (see Table 1). Kaplan-Meier plot of DFS in the FAS is illustrated in Figure 1. A total of 5 events were observed during the study (1 and 4 in the 3.6 mg group and 10.8 mg group, respectively). The DFS in the 3.6 mg group and 10.8 mg group were comparable and clinically meaningful, thus at least not worse than those in the ZIPP trial (Zoladex In Premenopausal Patients trial) and the ABCSG-5 trial (Austrian Breast and Colorectal Study Group Trial).

Figure 1 **Kaplan-Meier plot of Disease-free survival (FAS)**



Data derived from Figure 11.2.8.1, Section 11.2.

Table 1 **Summary of duration of follow-up for Disease-free survival (FAS)**

Treatment	n	Mean	SD	Min	Median	Max
ZOLADEX 3.6 mg	84	657.6	84.7	160	675.5	685
ZOLADEX 10.8 mg	86	664.3	64.2	142	675.0	687

Data derived from Table 11.2.8.2, Section 11.2.