AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Anastrozole
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A Prospective, Randomized, Multicentre, Comparative and Open-label Study on Hepatotoxicity of ARIMIDEX Compared with Tamoxifen in Adjuvant Therapy in Postmenopausal Women with Hormone Receptor+ Early Breast Cancer

Study dates:	First subject enrolled: 18 Sept 2007 Last subject last visit: 28 Dec 2011
Phase of development:	Phase IV
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Patients were enrolled in 28 centres in the People's Republic of China.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To compare ARIMIDEX (anastrozole) 1 mg once daily with Tamoxifen 20 mg once daily as adjuvant treatment in terms of: incidence of fatty liver diseases	Incidence of fatty liver disease
secondary	Safety	To compare ARIMIDEX (anastrozole) 1 mg once daily with Tamoxifen 20 mg once daily as adjuvant treatment in terms of: incidences of abnormal liver function test	Incidence of abnormal liver function
secondary	Safety	To compare ARIMIDEX (anastrozole) 1 mg once daily with Tamoxifen 20 mg once daily as adjuvant treatment in terms of: incidences of time to treatment failure.	Time to Treatment Failure (TTF)

Study design

This was a prospective, multicentre, comparative, open-label study conducted in postmenopausal women with histologically proven operable hormone receptor positive early-stage breast cancer. Eligible patients were randomised 1:1 to Arimidex group and Tamoxifen group. Patients were followed for fatty liver disease, treatment failure or abnormal liver function test until 3 years after randomisation.

Target subject population and sample size

Postmenopausal HR+ early breast cancer patients who had completed the primary treatment were enrolled to this study. With a 0.05 two-sided significance level and 80% power to detect the difference, 150 patients in each group were needed. Considering 10% non-evaluable rate, total sample size was 334 patients, with 167 in each treatment arm.

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

Tamoxifen was given as 20 mg p.o once a day and ARIMIDEX as 1 mg p.o once daily

Duration of treatment

The follow up period was of 3 years, unless there was evidence of fatty liver diseases detected by hepatic CT scan, breast cancer recurrence, or withdrawal for any reason

Statistical methods

Fisher's exact test was performed to assess statistical difference in frequency such as incidence of fatty liver disease, and incidences of abnormal liver function test. Chi square test was used for testing difference in proportion of steatosis levels and of liver biochemistry grading. Kaplan-Meier method was used to assess time to treatment failure and a log-rank test to provide a comparison of treatment groups.

Subject population

A total of 384 patients were screened (informed consent signed and CRF started) and 353 patients were randomized with 175 patients in the Tamoxifen group and 178 in the Arimidex group in 28 centres. The last patient completed the last visit on 28 Dec 2011(data cut off). 263 (74.5%) patients completed the study. Demographic and baseline characteristics were balanced in treatment groups.

Summary of efficacy results

Primary result:

Patients in Arimidex group developed less fatty liver disease in 48, 96 and 144 weeks time points during the follow up period. The cumulative incidence of fatty liver disease within 3 years in Arimidex group was much lower than Tamoxifen group (14.6% vs. 41.1%, $p<0.0001$) in ITT population. The relative risk for Arimidex to Tamoxifen from the primary analysis was 0.30 (RR=0.30, 95% CI: 0.21, 0.45), indicating that Arimidex would reduce 70% risk of developing fatty liver disease compared with Tamoxifen.

Secondary results:

In the ITT population, the cumulative incidence of abnormal liver function after 3 years' treatment showed no significant difference between Tamoxifen group and Arimidex group (24.6% vs. 24.7%, $p=0.6186$). No statistically significant difference was observed in other visits (3, 6, 12, 18, 24, 30 months) between the two groups either.

Tamoxifen group had higher treatment failure rate than Arimidex group in 48, 96 or 144 weeks. The median time to treatment failure for Tamoxifen group was 15.1months (454 days)

while 37.1 months (1112 days) for Arimidex group. Group comparison on time to treatment failure from log-rank test had p-value <0.0001.

Summary of safety results

During the study period 268 Treatment-emergent adverse events (TEAEs) were reported by 108 (31.6%) of the 342 patients in the safety analysis set. The number (%) of patients reporting at least one TEAE was similar for each treatment group with 49 (29.9%) in Tamoxifen group vs. 59 (33.1%) in Arimidex group. In total, 12 SAEs were reported by 10 (2.9%) of the 342 patients. The number (%) of patients with at least one SAE was 4 (2.4%) and 6 (3.4%) in Tamoxifen group and Arimidex group respectively and 2 patients had at least 1 SAE which led to death in Arimidex group. Overall, 25(7.3%) patients discontinued study treatment due to AEs with 16 (9.8%) in Tamoxifen group and 9 (5.1%) in Arimidex group. The most commonly reported AEs belonged to 'Reproductive system and breast disorders' in Tamoxifen group (17.1%) and 'Musculoskeletal and connective tissue disorders' in Arimidex group (14.6%).

Conclusion(s)

The results from this study indicate that Arimidex demonstrate better liver safety than Tamoxifen for postmenopausal women with hormone receptor positive early breast cancer in adjuvant setting.

Primary efficacy variable:

Arimidex associated with less fatty liver disease than Tamoxifen.

Secondary efficacy variables:

Incidence of abnormal liver function –there was no statistical difference of abnormal liver function between Arimidex and Tamoxifen.

Time to treatment failure –TTF of Arimidex was significantly longer than Tamoxifen.

Safety:

Tamoxifen and Arimidex had distinct safety profiles, but TEAEs did not present much difference in general. Both drugs were well tolerated.