AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ANASTROZOLE (Arimidex®)
Study Code	ARI-IPEP-0104
Edition Number	1
Date	16 Sep 2008

An Electronic Pharmacovigilance Study in Early Stage Breast Cancer Patients Who are Using Anastrozole (Arimidex®)

Study dates: First patient enrolled: 1. Jan. 2004
Last patient completed: 22. May. 2008

Phase of development: Therapeutic confirmatory (IV)

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

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Study centre(s)

Study was conducted in 48 centers in TURKEY. First patient was enrolled on Jan 1, 2004.

Publications

Poster presentation at a local Breast cancer congress in Turkey in October 2008

Objectives

The primary objective of the trial was:

- To gather information about adverse events in patients with early stage breast cancer who were using Anastrozole (Arimidex®).

Secondary objective was:

- To determine the compliance of early stage breast cancer patients who were using Anastrozole (Arimidex®), with the treatment and to physician's suggestions

Study design

The present study was a national, open, multi-center, non comparative and non-interventional observational study. Electronic case report forms installed in laptops were used to increase the quality of data collected from the centers. Electronic case report forms helped the physicians to record the data and enhanced the safety of data, by decreasing the mistakes which might be made in case of manual data recording.

Study consisted of a one year period of patient enrolment and 2 years of follow up. Duration of patient enrolment was extended in case of failing to reach the targeted patient number. Additional visits after the end date of the study were performed if the physician decided that it was necessary.

The main aim of the study was to determine the information about adverse event profiles of patients with early stage breast cancer who were using Anastrozole in natural clinical settings, without any intervention and comparison. These points were taken into consideration in the design of the study.

By using this study design, determination of side effects of the drugs which were not recognized during daily practice, probable alterations of known side effects, approaches to improve the study safety, collection of additional information about drug usage optimization were obtained.

There was no intervention to the physician's approach about adverse events; patients' adaptation and satisfaction, only information about these parameters were collected.

Target healthy volunteer population and sample size

Totally, 874 patients who were diagnosed as early stage breast cancer in 2001 - 2006 were enrolled, in the present study. The mean age of the patients was 60.2±9.6. Sample size was calculated approximately as 1800 to determine 0.05 type 1, 0.20 type 2 error with the frequency of side effects as 2-35% and this side effect frequency would not to exceed 3% fallibility. Considering the drop-outs, 1850 patients were planned to be enrolled into the study.

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

Name of the evaluated product was ANASTROZOLE (ARIMIDEX®). ANASTROZOLE was administered in tablet form as a once daily dose of 1 mg tablet.

Duration of treatment

Study consisted of a one year patient enrolment period and 2 years of follow-up. An additional visit was added if the physicians decided that it was necessary. Patients, who had any relapse or intolerable adverse event, were excluded at any time during the study.

Criteria for evaluation - efficacy (main variables)

NA.

Criteria for evaluation - safety (main variables)

The main variable of safety was the determination and frequencies of adverse events in patients who were using Anastrozole (Arimidex®). Relation of these adverse events with the study drug, clinical intervention and outcome, were also investigated.

Statistical methods

Primary evaluation criteria;

- Adverse events and the frequencies of adverse events in patients who were using Anastrozole (Arimidex®)
- Relation of adverse events with the study drug, clinical intervention and outcome.

Secondary evaluation criteria

- Ratios of patients who were in compliance with the study drug and still using it at the end of the study.

Descriptive statistical analysis was performed for independent variables and the above mentioned criteria. Similarly, descriptive analysis was done for the sub groups.

Subject population

Totally, 1850 patients from 75 centres were planned to be enrolled into the study, but, only 874 postmenopausal women from 48 centres were included to the trial.

Summary of efficacy results

NA

Summary of safety results

During the follow up, 17 (1.9%) patients were excluded due to relapse, and 35 adverse events were observed in 18 patients. These adverse events were; joint and muscle pain (n=9, 1.0%), hot flashes (n=5, 0.6%), vaginal dryness (n=4, 0.5%), weight gain(n=3, 0.3%), sleep disorders (n=3, 0.3%), vaginal bleeding (n=2, 0.2%), nausea (n=2, 0.2%), eruption (n=2, 0.2%), asthenia (n=2, 0.2%), dyspnea and cough (n=1, 0.1%), cholelithiasis (n=1, 0.1%), and hair loss (n=1, 0.1%). Totally, 45% of the adverse events were mild, 9% of them were moderate and 46% of them were severe adverse events. Four patients got better when the study drug was stopped or the dose was reduced. In one patient who had muscle and joint pain, symptoms were observed again when he drug was restarted. 90% of the patients stated that, it was not difficult to take the study drug in the recommended fashion and 82-88% of the patients had stated that, they have taken the entire treatment, as recommended. Drug compliance was evaluated in 126 patients, it was very good in 50% (n=63), good in 32% (n=40), moderate in 9% (n=12) and poor in 9% (n=11) of the patients. Tolerability was evaluated in 125 patients; 49% (n=61) of the patients had very high tolerability, while 34% (n=43) had high, 10% (n=12) had moderate, and 7% (n=9) had poor tolerability. Bone, joint and muscle pains, hot flashes and diaphoresis symptoms were strongly related with the study drug, relation of cholelithiasis, vaginal dryness and vaginal bleeding with the study drug was stated as suspicious.

Table 1 Adverse Events

Center no	Patient no	Race	Definition of adverse event	Severity of adverse events	Results of adverse events	Did the patient get better when the drug was stopped or the dose was reduced?	Was the adverse event repeated when the drug was restarted?	Was there any causal relationship between adverse event and the study drug?	Time duration between the initiation of the study and detection of the adverse event (days)
4	P001		Hot flashes, asthenia, sleep disorders, knee pain, vaginal dryness, bleeding, diarrhea, hair loss, nausea						
7	P007	White	Severe, disseminated bone pain	Severe	Not recovered	Yes	Unknown	Yes	436
22	P006	White	Joint pain	Moderate	Recovering	Yes	Unknown	Yes	458
37	P0022		Vaginal dryness, hot flashes						
47	P0021		Severe arm and leg pain						
47	P0026		Vaginal dryness, hot flashes						
47	P0051		Severe arm and leg pain						
49	P0005	White	Cholelithiasis, post-menopausal complaints (hot flashes and vaginal dryness)	Mild	Recovering	Unknown	Unknown	Possible	
49	P0003	Asian	Dyspnea, cough, fatique	Mild	Recovered	Unknown	No	No	469
49	P0011	Asian	Sleep disorders,	Mild		Unknown	Unknown	No	743

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			weight gain						
52	P0015	White	Muscle and joint pain	Severe	Recovered	Yes	Yes	Yes	360
52	P0027		Nausea, weight gain						
53	P0019		Joint pain, induration, eruption						
55	P001	White	Vaginal bleeding	Mild	Unknown	Unknown	Unknown	Possible	311
59	P002	White	Arthralgia on both knees	Severe	Not recovered	Yes	Unknown	Yes	240
66	P001	White	Fever and diaphoresis at night	Mild	Not recovered	Unknown	Unknown	Yes	31
66	P005		Hot flashes, asthenia, sleep disorders						
67	P001		Hot flashes, knee pain						

Date of the report

16 Sep 2008