AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: ARIMIDEX
ACTIVE INGREDIENT: Anastrozole

Study No: D5392L00013
A MULTICENTRE, OPEN STUDY ASSESSING JOINT DISORDERS UNDER ARIMIDEX® (1 mg/day) AS ADJUVANT TREATMENT IN POST MENOPAUSAL WOMEN WITH EARLY BREAST CANCER

Developmental phase: IV
Study Completion Date: 26 January 2009
Date of Report: 02 December 2009

OBJECTIVES:

The primary objective was to describe the joint symptoms and structural joint changes in postmenopausal women under anastrozole by the evaluation of proportion and incidence of arthralgia onset and Visual Analogical Scale (VAS) score for hand pain and hand handicap from baseline to 6 and 12 months.

The secondary objectives were:

1. To study clinical characteristics in patients under anastrozole based on Functional Index of Cochin + Articular Index and Synovitis Index at baseline, at 6 and 12 months.
2. To study radiological characteristics in patients under anastrozole based on:

- for X-ray study: number of pathologic joint disorders, assessment and calculation of Kellgren and Lawrence score at baseline and 12 months and
- for sonographic study: measurements of synovial membrane thickness and cartilage thickness at baseline, at 6 and 12 months.

3. To identify determinants of joint disorders based on the description of personal and familial joint disorders and baseline characteristics of breast cancer.
4. To study biological characteristics in patients under anastrozole based on dosage of bone and cartilage biomarkers (serum collagen degradation type I - CTX-I and urinary collagen degradation type II - CTX-II and creatinine) from baseline to 6 and 12 months.
5. To evaluate the rate of therapeutic maintenance under anastrozole

METHODS:

The ADAT (Arthralgia During Anastrozole Therapy) study was an open, multicentre, one arm 12-month prospective phase IV study, assessing joint disorders under oral Arimidex® 1 mg once daily as adjuvant treatment in postmenopausal women with hormone receptor positive early-stage breast cancer.
Patients with WHO (World Health Organisation) performance status from 0 to 2 were included by an investigator-oncologist (Visit 1 or M0), who followed them up every 3 months over a period of one year (i.e., 5 visits).
An investigator rheumatologist carried out the rheumatological evaluations at inclusion and then every 6 months over a period of one year (i.e., 3 visits).
Overall, 100 women had to be enrolled by 10 oncologists.

RESULTS:

A total of 114 patients were included in the study by 8 French oncologists and 110 patients were followed by 5 French rheumatologists.
Ninety-four patients completed the study and 20 patients (17.5%) were prematurely withdrawn (12 adverse events, 2 consent withdrawals, 2 incorrect enrolments, and 4 other reasons).
Overall 110 patients received at least one dose of study treatment (safety population) and 106 patients performed at least one follow-up rheumatologist visit (efficacy population).
In the efficacy population (N=106), five patients presented 7 protocol deviations, i.e. 4 deviations concerning the exclusion criteria and 3 other deviations.
The study population was composed by postmenopausal women suffering from early-stage ER and/or PgR positive breast cancer treated with daily anastrozole 1 mg (mean compliance of 100.4 ± 14.9%), with a mean age of 62.9 years (34.9% of patients over 65 years old), and a mean BMI of 26.4 kg/m².
The mean time from menopause was 12.7 years.
All patients had a good performance status (82.1% with a WHO PS=0 and 17.9% with a WHO PS=1).
The majority of patients had T0 or T1 (22.6% and 52.8% respectively) N0 (81.1%), and M0 (91.5%) tumours according to the TNM classification
Surgery was conservative for 76.4% of patients and the majority of patients (87.7%) underwent axillary node dissection (curage); 89.6% of patients had prior radiotherapy and 33.0% received prior chemotherapy, mainly anthracycline-based chemotherapy.
Medical history mainly consisted of hypertension (30.2% of patients), hypercholesterolaemia (29.3%), depression (17.0%), arthralgia (16.0%) and hot flushes (15.1%). Prior osteoarthritis was observed for 38.7% of patients and 49.1% of the patients had personal history of arthralgia.
The most frequent concomitant treatments were treatments for nervous system, i.e. analgesics (48.1%), psycholeptics (34.0%), and psychoanaleptics (23.6%).

Efficacy evaluation results

Study objectives	Variables	Results
Primary analyses		
To study the proportion of arthralgia at baseline, 6 and 12 months, the incidence of arthralgia at 6 and 12 months, and the time to arthralgia onset.	Arthralgia at baseline, 6 and 12 months Time to arthralgia onset	Proportion of arthralgia increased during the study (40.6% of patients at baseline *vs* 59.1% at 6 months *vs* 60.6% at 12 months). Among the 63 women without arthralgia at baseline, 37 patients developed arthralgia during the study: 26 patients developed arthralgia between baseline and 6 months and 11 patients between 6 and 12 months, giving incidence rates of 41.3% [95% CI, 29.1; 53.4] and 17.5% [95% CI, 8.1; 26.8] at 6 and 12 months, respectively. The mean time to arthralgia onset under anastrozole 1 mg (N=37) was 4.6 ± 2.9 months (median 4.0 months). Overall, 21.7% of patients (23/106) did not present any arthralgia during the 12-month study period.
To describe the hands and wrists pain and handicap graduated on VAS, at baseline, 6 months and 12 months.	Hands and wrists pain score and intensity of the hands and wrists functional discomfort using VAS at baseline, 6 months and 12 months.	The mean VAS scores for overall appreciation of the hands and wrists pain increased between M0 (7.6 ± 16.5), M6 (18.0 ± 23.8) and M12 (19.8 ± 22.9) (medians: 0, 2 and 7, respectively). The mean VAS scores between M0 and M6 and between M0 and M12 significantly differed ($p<0.0001$). The mean VAS scores for overall appreciation of the intensity of the hands and wrists functional discomfort increased between M0 (7.15 ± 16.2), M6 (15.4 ± 22.1) and M12 (18.0 ± 24.3) (medians: 0, 2 and 1, respectively). The mean VAS scores between M0 and M6 and between M0 and M12 significantly differed ($p<0.001$ and $p<0.0001$, respectively). The absolute variation VAS scores between M0 and M12 for the hands and wrists pain was 11.70 ± 22.84 (median of 1), and for the hands and wrists functional discomfort 10.38 ± 25.25 (median of 0).

Secondary analyses		
To describe and characterise all the articular manifestations of the hands and wrists at each visit	Focus of the hand pains, focus of other articular pains, presence of pain in the pression of tendinomuscular area, times of the pains, night wakings, duration of morning 'loosening up', articular swellins, Heberden's and Bouchard's nodes and tenosynovitis of the flexors.	During the study, hand pains (wrists, MCP, PIP, DIP and TMC) and other articular pains (knee, elbow and hip) increased between M0 and M6 and to a lesser extent between M6 and M12. Pains mainly occurred during movements (25.5% to 31.3%) or at rest (12.3% to 31.4 %).
▪ To evaluate the functional incapacity of the hand, activities requiring strength and pronosupination movements, precision and dexterity and thumb opposition of the dominant hand ▪ To evaluate the intensity of the pain (recorded by pressure or by passive mobilisation) ▪ To evaluate the presence of synovitis at each articular site ▪ To evaluate the extent of the radiographic lesions of the arthritis	▪ Functional index of Cochin (questions on activities involving the hand) and its 3 sub scores ▪ Articular index (score at each articular site) ▪ Synovitis index (score at each articular site) ▪ Kellgren and Lawrence score (score at each articular site)	The global Cochin score increased during the study (+1.44 between M0 and M6, +1.69 between M6 and M12 and +2.55 between M0 and M12). The mean scores were significantly different, between M0 and M6 ($p=0.021$), M6 and M12 ($p=0.021$) and between M0 and M12 ($p<0.001$). For the 3 sub-scores, activities requiring strength and pronosupination movements, activities requiring precision and dexterity and dynamic activities using thumb opposition of the dominant hand, the scores increased by 1.42, 0.50 and 0.63, respectively between M0 and M12. The articular index increased from M0 to M6 (0.42 ± 1.09 vs 1.17 ± 3.00: +0.75) and M6 to M12 (1.17 ± 3.00 vs 1.56 ± 3.16: +0.61). Differences between each score were statistically significant (M0-M6: $p<0.001$; M0-M12: $p<0.001$; M6-M12: $p=0.003$). At baseline, no patient had synovitis (all scores equal to 0). Mean score at M6 and M12 were close to 0, and there was no statistically significant difference between scores. Kellgren and Lawrence score increased between M0 and M12 (no radiography performed at M6). Mean Kellgren and Lawrence score was 11.5 ± 13.8 at M0 and 12.7 ± 13.6 at M12. The mean difference between the two scores was 0.6, and the difference was not statistically significant.

To describe synovial membrane thickness, number of synovitis and tenosynovitis during the 12 months follow-up visit	Synovial membrane thickness, synovitis and tenosynovitis	At each visit, the mean synovial thickness was equal to 1.8 mm. Approximately half of patient had synovitis in the wrists/fingers whatever the visit with approximately one quarter of patients presenting inflammatory signal. Approximately 15% of patients had tenosynovitis in the tendon.
To identify the determinant factors of joint disorders at 12 months	Patient's characteristics at inclusion, arthralgia at 12 months	No factor was significantly associated to the presence of arthralgia at 12 months with the multivariate analysis. Based on the univariate analysis, only 2 factors were significantly associated with arthralgia at 12 months: previous osteoarthritis (OR=2.90, p=0.016) and personal history of arthralgia (OR=2.80, p=0.015).
To describe the dosage of bone and cartilage biomarkers (serum CTX-I and urinary CTX-II) from baseline, at 6 and 12 months	Laboratory values of serum CTX-I and urinary CTX-II	The mean CTX-I levels at baseline, 6 and 12 months were equal to 0.47 ± 0.30, 0.52 ± 0.26 and 0.50 ± 0.28 ng/mL, respectively. The difference was statistically significant between M6 and M0 (p=0.0002). The mean CTX-II levels at baseline, 6 and 12 months were equal to 2.1 ± 1.7, respectively 1.9 ± 1.6 and 2.4 ± 2.5 µg/L, respectively. No statistically significant difference was observed between the visits.
To describe efficacy biological data from baseline, at 6 and 12 months	Laboratory values of CRP, antinuclear antibody, rheumatoid factor, CK and ESR	Values of CRP, antinuclear antibody, rheumatoid factor and ESR remained constant at each visit. CK values significantly increased during the 12-month period with mean values of 79.5 ± 36.0, 91.3 ± 57.4 and 100.3 ± 75.2 mg/L at M0, M6 and M12, respectively (p <0.01).

Safety evaluation results

Adverse Events

A total of 110 patients were included in the safety analysis.

Among them, 106 patients (96.4%) presented at least one AE during the study with a total number of 586 AEs.

The most common AEs occurring during the study were arthralgia (59 patients; 53.6%), hot flushes (35 patients; 31.8%) and pain in extremity (31 patients; 28.2%). Arthralgias (N=59) mainly consisted of gonalgia (30.5%), pain ankle (27.1%), pain in joint involving hand (27.1%) and wrist pain (15.3%). The majority of AEs were mild or moderate in

intensity. The most common severe AEs involved musculoskeletal and connective tissue disorders (11 patients, 10.0%), mainly arthralgia (7 patients).

Overall, 88 patients (80.0%) experienced a total of 286 AEs (48.8%) considered as related to anastrozole by the investigators. The most common related AEs were arthralgia (53 patients; 48.2%), hot flushes (34 patients; 30.9%), pain in extremity (24 patients; 21.8%), and asthenia (14 patients; 12.7%).

Overall, 12 patients experienced 25 AEs leading to treatment discontinuation. The most common AE leading to treatment discontinuation was arthralgia (14 AEs in 8 patients).

Overall, 12 patients experienced 20 AEs leading to premature withdrawal from the study.

Serious Adverse Events

Six patients experienced eight SAEs during the study, including one fatal SAE (sudden death of unknown origin), which was considered as related to anastrozole.

The seven non fatal SAEs, considered as not related to anastrozole, were severe pain, severe lymphangitis, severe femur fracture, parathyroid benign tumour, moderate depression, severe bladder calculus and severe lung disorder.

Biological safety

Haematological parameters:

A significant increase in mean platelet values was observed during the study (at 6 and 12 months; $p < 0.01$). A significant increase in mean leukocyte ($p < 0.05$) and lymphocyte values ($p < 0.0001$) was also noted. A significant increase in mean neutrophils value was observed at 6 months ($p < 0.05$) and a significant decrease in monocyte value ($p < 0.01$) was observed at 12 months.

No statistically significant differences between visits were observed for erythrocyte, haemoglobin, haematocrit, eosinophils, basophils, ESR 1°h and ESR 2°h mean values.

Biochemical parameters:

A significant increase was observed at 6 months for mean CTX I values ($p=0.0002$) and TSH values ($p=0.018$). A significant increase was observed at 12 months for mean calcium values ($p=0.042$). A significant increase was observed at 6 and 12 months for mean CK values ($p=0.007$ and $p=0.005$, respectively).

No statistically significant differences between visits were observed for CRP, phosphorus, and ASAT.

No relevant differences were observed between the visits for antinuclear antibody and rheumatoid factor.

Urinalysis:

No significant differences between the visits were observed for urinary CTX II levels.