AstraZeneca

Non-Interventional Study Report Synopsis	
Drug Substance	Anastrozole
Study Code	NIS-ODE-ARI 2006/1 1033GR/0002
Edition Number	1.0
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EudraCT Number	NCT00555867

Patient's Anastrozole Compliance to Therapy Programme (PACT):

A randomised in practice evaluation of the influence of patient's understanding of her disease and therapy on persistence and compliance to adjuvant therapy for post-menopausal hormone sensitive early breast cancer

Study dates:

First subject enrolled: 10 Oct 2006

Last subject last visit: 15 Feb 2011

Date of early study termination: 15 Feb 2011

Reason for early study termination: High drop-out rate leads to the conclusion: not enough data will be available to perform proper analyses of data collected after follow-up month 24 visit

Phase of development: Non interventional study (NIS)

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

Study centre(s)

The study was performed in Germany by 109 specialized clinics (breast centers) which collaborated with 1361 office-based gynecologists or oncologists for recruitment of patients.

Publications

• Lück H-J, Hadji P, Harbeck N, Jackisch C, Blettner M, Glados M, Terhaag J, Hackenberg R, Göhler T, Zaun S, Rexrodt von Fircks A, Kreienberg R. 24 months follow-up from the Patient's Anastrozole Compliance to Therapy Programme (PACT) evaluating the influence of a standardized information service on compliance in postmenopausal women with early breast cancer. J Clin Oncol 2011, 29 (No 15S) 526 (D526)

• Hans-Joachim Lück, Peyman Hadji, Nadia Harbeck, Christian Jackisch, Maria Blettner, Silke Zaun, Christine Windemuth-Kieselbach, Thomas Beck, Uwe Köhler; Schmitt D; Rolf Kreienberg. 24 months follow-up results from PACT (Patient's Anastrozole Compliance to Therapy Programme), a non-interventional study evaluating the influence of a standardized information service on compliance in postmenopausal women with early breast cancer. Cancer Research 2011, Vol 71, Suppl, P5-17-05

• Runnebaum IB, Stickeler E, Baier B, Hadji P, Jackisch C, Harbeck N, Blettner M, Lück HJ, Zaun S, Martin RR, Schmitt D, Schulte H, Rexrodt von Fircks A, Haidinger R, Kreienberg R. First results from the PACT programme (patient´s anastrozole compliance to therapy programme) evaluating the compliance of postmenopausal women with early breast cancer to endocrine adjuvant therapy and the impact of a standardised information service. Onkologie 2010; 33 (suppl 2): Abs PO060

• Harbeck N, Hadji P, Jackisch C, Landthaler R, Heilmann, Baier, Blettner M, Lück HJ, Rexrodt von Fircks A, Kreienberg R. First results from the Patient's Anastrozole Compliance to Therapy Programme (PACT) evaluating the influence of a standardized information service on compliance in postmenopausal women with early breast cancer (EBC). J Clin Oncol 2010, 28 (No 15S), 523 (73s)

• Hadji P, Harbeck N, Heilmann V, Jackisch C, Landthaler R, Lück HJ, Blettner M, Martin RR, Klevesath M, Kreienberg R. Erste Ergebnisse aus dem Patient's Anastrozole Compliance to Therapy Programme (PACT) zur Auswirkung eines standardisierten Informationsservices auf die Compliance bei postmenopausalen Frauen mit Hormonrezeptor-positivem frühem Brustkrebs (HR+ EBC). Senologie 2010, 7, s125, Abs. 57

• Hadji P, Harbeck N, Jackisch C, Lück HJ, Söling U, Stickeler E, Zaun S, Blettner M, Schmitt DC, Kreienberg R. First results from the Patient's Anastrozole Compliance to Therapy Program (PACT) evaluating the influence of a standardized information service on compliance in postmenopausal women with early breast cancer (EBC). Arch Gynecol Obstet 2010; 282 (suppl 1): 63-270: PO-Onko 03.31

Hadji P, Harbeck N, Jackisch C, Blettner M, Lück H-J, Tesch H, Haidinger R, Windemuth-Kieselbach C, Zaun S, Kreienberg R. Influence of Demographic and Histopathological Characteristics on Compliance and Persistence in 4.923 Postmenopausal Women with Early Breast Cancer (EBC) –

Results of the Patient's Anastrozole Compliance to Therapy Programme (PACT). Cancer Research 2010, Vol 70, 24, Suppl, P5-11-05

- Jackisch C, Hadji P, Harbeck N, Blettner M, Lueck H-J, Kanis R, Kuemmel S, Zaun S, Schulte H, Kreienberg R. Quality of Life in the PACT-Programme (Patient's Anastrozole Compliance to Therapy Programme): Influence of a Standardized Information Service on Patient Satisfaction and Health Related Quality of Life in Postmenopausal Women with Early Breast Cancer (EBC). Cancer Research 2010, Vol 70, 24, Suppl, P5-11-12

- Jackisch C, Harbeck N, Blettner M, Hadji P, Lück HJ, Schmitt DC, Haidinger R, Köhler U, Zaun S, Kreienberg R. The patient's anastrozole compliance to therapy programme (PACT): Evaluating the influence of a standardized information service on compliance in postmenopausal women with early breast cancer. EJC Supplements (2009): Vol 7, 2; Abs. PD 5035

- Harbeck N, Jackisch C, Blettner M, Lück HJ, Hadji P, Landthaler R, Martin RR, Schmitt D, Schulte H, Rexrodt von Fircks A, Haidinger R, Jäger D, Zaun S, Kreienberg R; First results from the "patient´s anastrozole compliance to therapy programme" (PACT) evaluating the impact of a standardized information service on compliance in postmenopausal women with early breast cancer (EBC) receiving adjuvant endocrine therapy. Cancer Research 2009, Vol 69, 24, supplement. Abs 6079

- Hadji P, Blettner M, Haidinger R, Harbeck N, Jackisch C, Lück HJ, Martin RR, Rexroth von Fircks A, Schmidt DC, Kreienberg R. Patients' Anastrozole Compliance to Therapy Programme (PACT) Influence of the addition of a standardized information and reminder service on compliance in comparison to standard clinical care alone in women with early breast cancer. EJC Supplements Vol 6 (7) 2008; S127, #265

- Hadji P, Ziller V, Jackisch C, Blettner M, Lück HJ, Harbeck N, Torode J, Kreienberg R. Patients' Anastrozole Compliance to Therapy Programme (PACT) – Influence of the addition of a standardized information and reminder service on compliance in comparison to standard clinical care alone in women with early breast cancer. Senologie - Zeitschrift für Mammadiagnostik und -Therapie 2 (2007); S115, #40

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess and compare the difference in the persistence rates after 12 months of adjuvant hormone therapy between the Standard and Standard + educational material (EM) arm	The *persistence rate* was defined as the percentage number of patients with a '*persistent*' use of anastrozole. A patient was classified as a 'persistent' user of anastrozole, when the CRF documentation - independent from the evaluation of compliance - supported the intake of anastrozole during the full 12-months period.
Primary	Efficacy	To assess and to compare the difference in compliance rates after 12 months of adjuvant hormone therapy between the Standard and Standard + EM arm.	The *compliance rate* was defined as the percentage number of patients being 'compliant' with regard to the anastrozole therapy.
Secondary	Efficacy	Assessment and comparison of the persistence rates and compliance rates to adjuvant hormone therapy between the two arms after 24 months of adjuvant hormone therapy.	As described above
Secondary	Efficacy	Assessment of time to treatment discontinuation and reasons for treatment discontinuation and non-compliance.	Time to treatment discontinuation, defined as date of last intake of anastrozole minus date of start of therapy.
Secondary	Efficacy	Identification of factors influencing and correlating to the persistence and compliance rate; for example patient's characteristics (age, education), disease characteristics, quality of life, concomitant medication, daily intake of tablets and patient's drug-intake behaviour, patient's satisfaction, predefined AE etc.	Demographics and other baseline characteristics as well as information regarding concomitant medication, quality of life, etc. were used to identify factors with an influence on the compliance and persistence rate.
Secondary	Efficacy	Disease free survival after 12 and 24 months of adjuvant endocrine treatment and association of this clinical endpoint with compliance rates.	Time of disease free survival, defined as date of recurrence or progression of the tumor minus date of start of therapy. In case, the exact dates were not available they were estimated using other information from the CRF documentation.
Secondary	Safety	Assessment of treatment tolerability and toxicity	All variables related to adverse events and to some specific adverse events using a structured questionnaire, but also possible safety information related to withdrawal of anastrozole therapy and/or premature discontinuation of the NIS were used to evaluate the safety and tolerability.

Study design

This study was a prospective, randomized, open, parallel-group, multicentre Non-Intervention Study (NIS) according to the German Drug Law (AMG, §67[6]). It was performed in Germany by AstraZeneca GmbH as a NIS under daily routine conditions and without any intervention by the sponsor regarding the selection of patients, diagnostic procedures, therapeutic decisions (medicinal and non- medicinal therapy, dose, duration, etc.) and routine assessments. Patients were randomized on a 1:1 basis to receive standard therapy (adjuvant endocrine therapy [anastrozole 1 mg once daily]) or standard therapy plus educational material (EM). EM comprised nine letters and brochures sent to the patient by mail during the first year of therapy. The materials were designed with the aim of motivating participants to take their medication on a regular basis by dealing with issues likely to be of particular relevance at specific points in time during therapy. The materials were developed with the assistance of five patient advocates who had all been affected by breast cancer and were active in the sphere of patient advocacy.

During the study, patients were permitted to receive any further investigations and treatments deemed necessary by their investigators according to current standards of care. As this was an in-practice evaluation study, the decision to treat with anastrozole was required to be taken prior to offering participation in this program, in accordance with German guidelines.

Target subject population and sample size

Patients participating in this NIS had to have a histologically/cytologically confirmed primary diagnosis of early breast cancer with hormone sensitive tumour (ER+ve and/or PgR+ve). They had to be postmenopausal women aged 18 years or older.

Patients were eligible for inclusion in this NIS if the physician/tumour-board considered the patient suitable for endocrine therapy with an aromatase inhibitor.

Investigational product and comparator(s): dosage, mode of administration and batch numbers **Product under investigation:**

Anastrozole, 1 mg once daily. There was no comparator drug.

Duration of treatment

As this was a NIS, there was no treatment period defined by protocol.

Statistical methods

All statistical tests were performed two-sided at a 5% level of significance. However, the p-values of all statistical tests except the one related to the primary objective are interpreted only in a descriptive-exploratory way. Two-sided confidence intervals are displayed for important variables. Appropriate methods were used to derive confidence intervals, depending on data nature and distribution. All safety and tolerability data are presented in a purely descriptive manner. Data from patients who stopped

anastrozole treatment and continued adjuvant endocrine treatment with a different medication are presented in a descriptive way only.

Binary, categorical and ordinal parameters were summarized by means of absolute and percentage numbers within the various educational groups (including 'missing data' as valid category). Numerical data were summarized by means of standard statistics (i.e. number of available data, mean, standard deviation, minimum, median, maximum).

Subject population

Between October 2006 and November 2008, 4923 postmenopausal women starting adjuvant treatment with anastrozole were recruited. A total of 4844 women meeting inclusion-/exclusion criteria were then randomized 1:1 to standard therapy (n = 2402) or standard therapy plus EM (n = 2442). Of these, 4397 patients were evaluable for baseline characteristics as baseline documentation by physician, documentation of start of therapy and first patient questionnaire were available. The treatment groups were well balanced at baseline with regard to patient demographics, tumor characteristics, prior therapies and attitudes to therapy.

Summary of efficacy results

Analysis showed that at 12-months' follow-up, there was no difference in compliance and persistence rates between the standard treatment and EM arms. The overall compliance rate for anastrozole was 88.65% (62% of total patient population available for analysis). This is comparable to data reported in the 100-month analysis of the ATAC trial, which showed compliance rates of 88% for anastrozole and 87% for tamoxifen (49). Analysis of persistence in the PACT study provided rates of 41.79% overall, with no differences between the standard and EM arm.

Analysis at 24-months' follow-up showed again that there was no difference in compliance and persistence rates between the standard treatment and EM arms.

Attendance of rehabilitation actions significantly impacted on compliance ($P = .0452$). Patients attending rehabilitation actions showed the highest rate of compliance compared with patients for whom this parameter was not reported, who showed the lowest compliance. Employment status significantly impacted on compliance ($P < .0001$); women on certified sick leave, home-makers and women who had retired reported higher rates of compliance compared with women who were either employed or unemployed. Women who regularly attended follow-up appointments reported higher rates of compliance than patients who did not attend regular follow-up visits, or for whom there was no documentation of follow-up visits ($P < .0001$). In addition, patients who experienced AEs with AI therapy reported lower rates of compliance than those who did not experience AEs ($P = .0001$).

Summary of safety results

In total, 2901 adverse events were reported in 4680 patients available for the safety analysis. Adverse events were equally distributed between standard and EM arm (1447 and 1454 events). Most commonly reported adverse events according to the maximal NCI grade per patient were 'bone pain' (standard arm: 230 AE; EM arm: 201 AE) closely followed by 'arthralgia' (standard arm: 153 AE; EM arm: 173 AE) and by 'hot flush' (standard arm: 110 AE; EM arm: 129 AE). Additionally, 42 events of osteoporosis (standard arm: 22 events; EM arm: 20 events) and 18 events of bone fracture (standard arm: 12 events; EM arm: 6 events) were reported.

133 serious adverse events occurred in 94 patients during the observation period (59 events in the standard and 79 events in the educational arm). 35 deaths were reported (18 in the standard and 17 in the educational arm). The exact cause of death is known only for one patient (pulmonary embolism), however, in 14 cases, the event leading to death was reported (2 cases of cerebrovascular accident, one Creutzfeld-Jakob disease, one femoral neck fracture, one hypoglycemia, 3 cases of metastatic disease, 4 myocardial infarctions, one sepsis, one sudden cardiac death). In 20 cases, an event of death was reported as SAE without reporting the underlying morbidity leading to death.

Most frequently reported serious adverse events other than 'death' were arthralgia, bone pain and myocardial infarction (5 events each), followed by arthritis and cerebrovascular accident (4 events each). While 37% of SAE were judged as probably or possibly causally related (mostly musculoskeletal/joint effects and fractures, but also cerebral events and events related to hypersensitivity to the drug), 63% were judged by the investigators to be unlikely causally related or unrelated. Analysis of relatedness revealed no new, formerly unnoticed concerns. In 37,6% of cases, the serious adverse events lead to permanent discontinuation of anastrozole.