AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Anastrozole
Study Code	COMPACT NIS-ODE-ARI 2008/1
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NCT00857012

Arimidex: Compliance and arthralgias in clinical therapy (COMPACT): An in practice assessment of arthralgias and related costs as well as compliance in the first year of anastrozole therapy

Study dates: First subject enrolled: 23rd April 2009
Last subject last visit: 14th February 2012

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)

622 centres in Germany participated in this in practice evaluation program, including specialised clinics and office based gynaecologists or oncologists.

Publications

- Harbeck N et al., COMPliance and Arthralgia in Clinical Therapy: The COMPACT trial, assessing the incidence of arthralgia, therapy costs and compliance within the first year of adjuvant anastrozole therapy. SABCS/04.-08.12.2012, San Antonio

- König K et al., Das COMPACT Programm (Compliance and Arthralgias in Clinical Therapy): Aromatasehemmer-assoziierte Arthralgien in der adjuvanten endokrinen Therapie des Mammakarzinoms bei postmenopausalen Frauen. DGGG 09.- 12.10.2012 München/Germany

- Jackisch C et al., Aromatasehemmer-assoziierte Arthralgien in der adjuvanten endokrinen Therapie des Mammakarzinoms bei postmenopausalen Frauen: COMPACT (Compliance and Arthralgias in Clinical Therapy). DGS 05.-07.07.2012 Stuttgart/Germany

- Bolten WW et al., COMPliance and Arthralgias in Clinical Therapy (COMPACT): Assessment of the incidence of arthralgia, therapy costs and compliance within the first year of adjuvant anastrozole therapy. Accepted for publication only in the official Congress Abstract Book / USB Stick EULAR 06.-09. 06.2012 BerlinRief W et al., Psychological factors and side effects as predictors of non-adherence in women on adjuvant breast cancer treatment: The COMPACT trial investigating adjuvant anastrozole therapy. EACLPP 27.-30.06.2012, Aarhus/Dänemark

- Hadji P, et al., COMPliance and Arthralgias in Clinical Therapy (COMPACT): Assessment of the incidence of arthralgia, therapy costs and compliance in the first year of adjuvant anastrozole. Accepted for publication only in the official Congress Abstract Book / USB Stick ASCO 01.06.-05.06.2012 Chicago

- Hindenburg H.J. et al., Compliance and Arthralgias in Clinical Therapy (COMPACT) Assessment of the incidence and severity of arthralgia, treatment costs and compliance within the first year of adjuvant anastrozole therapy. DKK 22.- 25.02.2012 Berlin

- Hadji P et al., Compliance and Arthralgias in Clinical Therapy (COMPACT): Assessment of the incidence and severity of arthralgia, treatment costs and compliance within the first year of adjuvant anastrozole therapy. SABCS/06.-10.12.2011, San Antonio

- Hadji P et al., COMPACT (Compliance and Arthralgias in Clinical Therapy): Eine Untersuchung zum Management von Aromatasehemmerassoziierten Arthralgien in der adjuvanten endokrinen Therapie des Mammakarzinoms bei postmenopausalen Frauen. DKFV/20.-22.10.2011, Köln/Germany

- Hadji P et al., COMPACT (COMPliance and Arthralgias in Clinical Therapy): Eine Untersuchung zum Management von Aromatasehemmer-assoziierten Arthralgien in der adjuvanten endokrinen Therapie des Mammakarzinoms bei postmenpausalen Frauen. DGS/23. - 25.06.2011, Dresden, Germany

- Hadji P et al., COMPliance and Arthralgias in Clinical Therapy (COMPACT): Assessment of the incidence of arthralgia, therapy costs and compliance within the first year of adjuvant anastrozole therapy. DGGG/05.-08.10.2010, München, Germany

- Jackisch C et al., Untersuchung zum Management von Aromatasehemmer-assoziierten Arthralgien in der adjuvanten endokrinen Therapie des Mammakarzinoms mit Anastrozol. DGS/01.- 03.07.2010, Hamburg/Germany

- Hadji P et al., Assessment of the incidence of arthralgia, therapy costs and compliance within the first year of Anastrozole therapy. DKK/24.-27.02.2010, Berlin/Germany

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	Assessment of arthralgia scores and patient compliance within the first year of anastrozole treatment, stratified by upfront and switch therapy as well as assessment of the relationship between compliance and arthralgia scores	**Compliance** to anastrozole therapy was assessed based on the information collected by the physician and by the patient at 0, 3, 6 and 9 months after study start. A patient was defined as being 'compliant' when both the physician and the patient rated her compliance to be at least 80% (i.e. she has taken 'almost all' or 'all' of the tablets in the observed period). Each occurrence of **arthralgia** and arthralgia characteristics was assigned to a corresponding time period according to pre-defined time intervals: 4 weeks prior to the start of anastrozole therapy until start of anastrozole treatment and subsequently 0-3, 3-6 and 6-9 months after study start.
Secondary	Efficacy	Incidence of arthralgias and arthralgia characteristics within the first year of anastrozole therapy stratified by upfront and switch therapy and assessment of the relationship of arthralgia incidence and arthralgia characteristics to patient compliance	Arthralgia characteristics were evaluated with RASQ (Rheumatoid Arthritis Symptom Questionnaire - *a 14-item self-reporting questionnaire using a 10 cm visual analogue scale from "no" distress to the "worst possible" distress*). Additional Characteristics of arthralgia were: localization; intensity according to NCI; onset; duration; relationship to study drug.
Secondary	Efficacy	Retrospective assessment of incidence of pre-existing arthralgias before start of anastrozole treatment, stratified by upfront and switch therapy	Assessment was documented by the physician in the electronic Case Report Form (eCRF) and documented by the patient in the patient questionnaire (0 months).
Secondary	Efficacy	Descriptive assessment of arthralgia therapy and of costs of arthralgia therapy, stratified by upfront and switch therapy	Arthralgia management was evaluated from documentation in the eCRF and patient questionnaire and comprised: Medication (drug name, dose, package size, duration); Physiotherapy; Doctor's visits (fields and number of visits).
Secondary	Efficacy	Comparison and validation of the assessment of compliance and of arthralgia therapy using the corresponding data obtained by the sick funds of the patients who consented to data transfer and who were insured by sick funds that joined the respective contract	For a subgroup of patients who signed an additional informed consent form, a comparison of arthralgia therapy as documented by the investigators and the patients to sick fund data is planned on an individual patient level. *Evaluation will have to be performed outside of this report.*

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	Assessment of subjective perception of side-effects by the patients, stratified by upfront and switch therapy	Subjective perception of side-effects was evaluated using the following scores: GASE-P (Generic Assessment of Side Effects), SSAS (Somatosensory Amplification Scale), BMQ (Beliefs about medicines questionnaire).
Secondary	Efficacy	Identification of factors influencing and correlating to treatment-emergent arthralgias (TEA), such as patient characteristics, disease characteristics, duration of anastrozole treatment, subjective perception of side-effects by the patients etc.	Demographic data: age (years), height (cm), weight (kg), Body Mass Index, BMI (kg/m^2), calculated as: $BMI=Weight\ (kg)/[Height(cm)/100]^2$ Disease characteristics: age of patient when entering menopause; previous hormone replacement therapy; specification of hormone replacement therapy; concomitant diseases; primary diagnosis of breast cancer; localization of primary tumor; breast cancer therapies
Secondary	Efficacy	Identification of factors influencing and correlating to patient compliance; for example patient characteristics (age), disease characteristics, concomitant medication, subjective perception of side-effects by the patients, incidence and characteristics of arthralgias (time between start of anastrozole therapy and occurrence, intensity and duration of arthralgias), incidence of AEs etc.	*Variables see above*
Secondary	Efficacy	Comparison of time to progression (TTP) between patients with arthralgias and patients without arthralgias in the first year of anastrozole treatment, stratified by upfront and switch therapy	Time of disease free survival, defined as date of recurrence or progression of the tumor minus date of start of anastrozole therapy.
Secondary	Safety	Assessment of safety and tolerability of anastrozole	All adverse events were coded according to MedDRA dictionary, version 15.0. For any AE as described by the physician(s) the lowest level term was chosen that best matched or approximated the physician's actual description. These lowest level terms were translated into more general terms [so-called preferred terms (PT)], which were classified into a system organ class (SOC). This system organ class was the primary system organ class as given in the MedDRA dictionary.

Study design

This study was an open, non-randomized Non-Interventional 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. As this was an in-practice evaluation study, in accordance with German treatment guidelines the decision to treat with anastrozole was required to be taken prior to offering participation in this program,.

During the study, patients were permitted to receive any further investigations and treatments deemed necessary by their investigators according to current standards of care.

Target subject population and sample size

The patient population included postmenopausal women with hormone-receptor positive primary breast cancer scheduled for adjuvant endocrine treatment. Patients were eligible for inclusion in this NIS if they had been treated with anastrozole either upfront or following two to three years of tamoxifen treatment ("switch"). Patients had to have received anastrozole treatment according to the current Summary of Product Characteristics (SmPC) for at least three and not more than six months before an individual participation in this program was offered.

Based on previous data, it could be assumed that a patient compliance would decrease to approximately 50% during the first year of antihormone therapy, a difference in patient compliance of 6% was judged clinically relevant. In order to identify a statistically significant difference of 6% between two groups (here: upfront vs. switch groups) or between different time points 1119 patients were required per group or time point.

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

Anastrozole, 1 mg p.o daily. There was no comparator drug.

Duration of treatment

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

Statistical methods

Binary, categorical and ordinal parameters were summarized by means of absolute and percentage numbers (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, lower and upper quartile).

Patients were grouped into patients who were treated with anastrozole upfront ('upfront') and those who switched to anastrozole after treatment with tamoxifen ('switch').

All statistical tests were performed two-sided at a 5% level of significance. However, the p-values of all statistical tests must be interpreted only in a descriptive-exploratory way. Two-sided confidence intervals (CIs) are displayed for important variables. Appropriate methods were used to derive CIs, depending on data nature and distribution. All safety and tolerability data (excluding data obtained on arthralgias) are presented in a purely descriptive manner.

Subject population

In 334 study centres 2210 patients were recruited and could be considered for the analysis (1916 upfront patients; 294 switch patients). A total of 539 patients (24.4%) were withdrawn prior to the planned visit 9 months after study start.

Comparison of upfront and switch patients revealed only minor differences. Upfront patients were older than switch patients (64.8 vs 62.1 years) with a slightly higher BMI (27.8 vs 27.0 kg/m2). Status of natural menopause occurred more frequently in the upfront group than in the switch group (90.6% in the upfront group and 84.4% in the switch group).

Summary of efficacy results

Based on the ITT population, during the period between start of anastrozole therapy and study start (enrolment) 81.9% of patients with upfront therapy were assessed to be compliant compared to 78.6% of patients with switch therapy. The difference between groups was statistically not significant (P = 0.221; Fisher's exact test). During 0-3 months after the study start 77.1% of patients with upfront therapy were assessed to be compliant compared to 74.6% of patients with switch therapy (P = 0.377; Fisher's exact test). During 3-6 months after the study start 71.6% of patients with upfront therapy were assessed to be compliant compared to 68.1% of patients with switch therapy (P = 0.308; Fisher's exact test). During the final observational period (6 to 9 months after the start of the study) compliance was significantly higher in the upfront group (66.2% compared to 56.6%; P = 0.009; Fisher's exact test).

Arthralgia RASQ Mean scores were slightly increased from 20.8 mm at enrolment to 25.1 mm after 9 months in the upfront group and from 23.3 mm to 24 mm in the switch group. There was no noticeable difference between groups at any time point (P > 0.05, ANOVA). However, there was a statistically significant association between arthralgia mean scores and non-compliance at 6 months, 9 months and overall (i.e. not considering time at all). 6 months after study start, an increase of the mean scores of arthralgia resulted in a 1.245-fold higher odd to be non-compliant. After 9 months this odds ratio was 1.209 and for the whole study period it amounted to 1.14.

Arthralgias that existed prior to the start of anastrozole therapy were documented for 12.5% of patients. New arthralgias or worsening of existing arthralgias between start of therapy and enrolment into the study occurred with 16.1% of patients. During the first year of anastrozole therapy, new or impaired arthralgias were mainly reported for the knee, the finger and the wrist joint. The majority of new or impaired arthralgias was reported with NCI-grade 1 or 2. Relationship to anastrozole was assumed more frequently in the upfront group than in the switch group. The difference was statistically significant in the periods from 3 to 6 months (12.4% vs 5.7%) and from 6 to 9 months after study start (9.6% vs 5.0%) (P < 0.05, Fisher's exact test).

Increasing age and the presence of swollen joints correlated with reduced patient compliance, whereas increasing intensity of arthralgias and increasing intensity of pain documented by the investigators correlated with increased patient compliance.

The majority of the patients reported a consultation of a doctor because of arthralgias. Gynaecologists, general practitioners or orthopaedic surgeons being consulted more often than rheumatologists.

In both groups, patients arthralgias were most commonly treated with ibuprofen or diclofenac, followed by paracetamol and novaminsulfon. Around 25% of the Upfront-patients and 30% of the Switch patients with arthralgias received physiotherapy, respectively.

Assessment of subjective perception of side-effects by the patients using GASE-P revealed only a slight increase in the number and intensity of symptoms (side effects) for the whole study duration. Concerning the somtosensoric amplification, a constant SSAS mean score about 18 for the whole study period demonstrates that sensitivity to normal somatic and visceral sensations applied moderately.

A statistically significant influence of age (P < 0.0001) and BMI (P = 0.0194) was seen on incidence of treatment-emergent arthralgias (TEA). Increasing age reduced odds of TEA (odds ratio = 0.976) while increasing BMI increased odds of TEA (odds ratio = 1.022, 95% CI = [1.003; 1.040]). Prior hormone replacement therapy,

pre-existing arthralgias, other relevant concomitant diseases and adjuvant chemotherapy were associated with increased odds of treatment-emergent arthralgias (odds ratios > 1.5).

There was no difference in time to progression between patients with and without treatment-emergent arthralgias (P = 0.5454, Log-Rank test).

Summary of safety results

In total, 2292 adverse events were reported in 2210 patients available for the safety analysis, with each event being counted only once per patient. 54% of the Upfront patients and 39.5% of the Switch patients experienced at least one adverse event. 129 of these 2292 events (in 5.8% of the Upfront patients and in 6.1% of the Switch patients) lead to treatment discontinuation.

1426 adverse events were considered to be drug related. Most commonly reported drug related adverse events were: Arthralgia (in 34.7% of the patients: 35.9% Upfront patients, 26.5% Switch patients), hot flush (in 4.6% of the patients: 5.1% Upfront patients, 1.0% Switch patients), fatigue (in 2.6% of the patients: 2.9% Upfront patients, 0.3% Switch patients), hyperhidrosis (in 2.0% of the patients: 2.2% Upfront patients, 0.7% Switch patients), bone pain (in 1.9% of the patients: 2.0% Upfront patients, 1.4% Switch patients), alopecia (in 1.8% of the patients: 1.9% Upfront patients, 1.0% Switch patients). Arthralgia with NCI grade 4 was reported for 0.6% of Upfront patients and 0.7% of Switch patients.

66 serious adverse events (SAEs) occurred when repeated occurrence of the same event in a patient was counted multiple times. 14 of these 66 SAEs were considered drug related (there were 64 serious adverse events when the same event was counted only once per patient with 13 SAEs considered drug related). Drug related SAEs were arthralgia (0.4% in Upfront patients, 0.3% in Switch patients), arthropathy (0.1% in Upfront patients, no event in Switch patients), bone pain (0.1% in Upfront patients, no event in Switch patients), insomnia (0.1% in Upfront patients, no event in Switch patients) and hot flush (0.1% in Upfront patients, no event in Switch patients). Most frequently reported SAEs not considered to be drug related were ‘secondary malignancy’ (0.2% in Upfront patients, 0.3% in Switch patients) and ‘fracture’ (0.2% in Upfront patients, none in Switch patients).

7 patients died due to an adverse event. The events leading to death were 2 cases of ‘death without further specification and one event each of ‘colon carcinoma‘, ‘pain’, ‘multiorgan failure‘, ‘brain metastases‘, ‘malignant ascites‘ and ‘exitus letalis in the context of a decompensated heart failure‘(0.2% in Upfront patients, no event in Switch patients). Please note that the events ‘multiorgan failure‘ and ‘brain metastases‘ occurred in the same patient.

Overall, the nature and frequency of adverse events reported in this study are in line with the known adverse event profile of anastrozole from clinical trials and as specified in the SMPC. No new and unexpected safety findings were noted.