Observation Plan

Drug Substance	Anastrozole
Code	NIS-ODE-ARI-2008/1
	19 Mar 2009 (Version 1.4)

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

Sponsor:

AstraZeneca GmbH
Tinsdaler Weg 183
D-22880 Wedel / Germany
Tel: 04103-708-0

Responsible Medical Officer:

Responsible Statistician:

Planned non-interventional study period:

Q1 2009 – Q4 2010

SYNOPSIS

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

Centre(s) and number of patients planned

Approximately 700 centres in Germany will participate in this in practice evaluation program, including specialised clinics and office based gynaecologists or oncologists.

It is planned to enroll 3212 patients in this NIS.

Program period

Estimated date of first patient enrolled	Q1 2009
Estimated date of last patient enrolled	Q1 2010
Estimated date of last patient completed / NIS end	Q4 2010
Estimated date of analysis of three months data	Q2 2010
Estimated date of final analysis	Q4 2010
Estimated date of finalisation of report	Q2 2011

EXTERNAL ADVISING COMMITTEES

Steering Committee

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Objectives:

Primary objective:

Assessment of arthralgia scores and patients` compliance within the first year of anastrozole treatment[1], stratified by upfront and switch therapy as well as assessment of the relationship between compliance and arthralgia scores.

Secondary objectives

Incidence of arthralgias and arthralgia characteristics within the first year of anastrozole therapy[1] stratified by upfront and switch therapy and assessment of the relationship of arthralgia incidence and arthralgia characteristics to patients` compliance.

Retrospective assessment of incidence of pre-existing arthralgias before start of anastrozole treatment, stratified by upfront and switch therapy.

Descriptive assessment of arthralgia therapy and of costs of arthralgia therapy, stratified by upfront and switch therapy.

The assessment of compliance and of arthralgia therapy will be compared to and validated by the corresponding data obtained by the sick funds of the patients.[2]

Assessment of subjective perception of side-effects by the patients, stratified by upfront and switch therapy.

Identification of factors influencing and correlating to treatment-emergent arthralgias, such as patient`s characteristics (e.g. age, BMI), disease characteristics, duration of anastrozole treatment, subjective perception of side-effects by the patients etc.

Identification of factors influencing and correlating to patients` compliance; for example patient's 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.

Compare 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.

Assessment of safety and tolerability of anastrozole.

The ITT analysis set will be used for the primary analysis of compliance and arthralgia scores. The safety population(s) will be the basis for the analysis of costs and safety analyses and for a secondary analysis of arthralgia scores. Additionally, all women who completed this NIS and who were compliant according to the criteria defined in the protocol for the total duration of 12 months of anastrozole treatment will be analysed separately with regard to the arthragia

characteristics (VAS score, incidence, intensity etc), side-effect management, related costs, perception of side effects etc.

Demographic data and all other important baseline characteristics will be presented for both, the ITT and safety analysis sets. The results will be presented in a descriptive manner.

Other analysis sets may be defined.

[1] The start of the adjuvant treatment with anastrozole is defined by the date of the first tablet intake. If this date is not assessible, the date of the first prescription of anastrozole can be used instead.

[2] This is only applicable to patients who consented to data transfer and who are insured by sick funds who joined the respective contract. Data transferred from the sick funds will include breast-cancer related costs from 12 months before study start up to the end of the study for the respective patient.

Design

This is an open, multi centre NIS.

Target patient population

The patient population will include postmenopausal women with hormone-receptor positive primary breast cancer receiving adjuvant endocrine treatment with anastrozole upfront or following two to three years of tamoxifen therapy ("switch") according to the current SmPC (Appendix C). Patients will have received anastrozole treatment for at least 3 months and up to 6 months before the start of the study.

Randomisation

- No randomisation will be performed in this study.

Outcome variables

Compliance:

Compliance is defined by the percentage number of patients being 'compliant' to anastrozole therapy, based on the following information collected by the doctor at 0, 3, 6 and 9 months after study start:

1) Question about the daily intake of anastrozole (to be answered by the investigator):

"The patient was instructed to take 1 anastrozole tablet per day. However, it's still possible that the intake has sometimes been forgotten. How many tablets, according to your impression of the patient, has the patient actually taken during the last year?"

Scoring:	0 – none	0%
	1 – few	[0% ; 20%]

2 – less than half	[20% ; 40%]	
3 – approximately half	[40% ; 60%]	
4 – more than half	[60% ; 80%]	
5 – almost all		[80% ; 100%]
6 – all		100%.

2) Question about the daily intake of anastrozole (to be answered by the patient in the patient questionnaire)
   "You were instructed to take 1 anastrozole tablet per day. However, it's still possible that the intake has sometimes been forgotten. How many tablets have you actually taken during the last year?"

Scoring:	0 – none	0%	
	1 – few	[0% ; 20%]	
	2 – less than half	[20% ; 40%]	
	3 – approximately half	[40% ; 60%]	
	4 – more than half	[60% ; 80%]	
	5 – almost all		[80% ; 100%]
	6 – all		100%.

3) A patient will only be defined as being 'compliant' when the answer of the doctor **and** the patient score '5' or '6' concerning the question regarding the number of tablets actually taken.

Arthralgias

Arthralgias will be summarized by incidence, localization, onset, duration, intensity, and relationship to study drug, diagnostics and arthralgia management (e.g. medication, physiotherapy, doctor's visits, change of life style etc.). Arthralgia characteristics will be particularly assessed using VAS scores (Appendices E and F).

Perception of side-effects

Subjective perception of side-effects will be evaluated using the following scores: GASE-P (Generic Assessment of Side Effects, Appendices E and F), SASS (Somatosensory Amplification Scale, Appendices E and F), and BMQ (Beliefs about medicines questionnaire, Appendices E and F).

Arthralgia therapy and related costs

Arthralgia therapy will be documented in the eCRF and in the patient questionnaire (for further information, see Chapter 8; e.g., newly prescribed medication, doctor`s visits, diagnostics, hospital admissions). Diagnostic and therapeutic measures will be recorded as standardised patterns in the eCRF and in the patient questionnaire and will be correlated with itemised costs for evaluation purposes. Cost evalulations will be feasible on patient and global level.

Validation of data (arthralgia therapy and compliance) by sick fund data

For patients who signed an additional informed consent form (Appendix C, see chapter 7.3), arthralgia therapy as documented by the investigators and the patients will be compared to sick fund data on an individual patient level by a third party who will combine the study and the sick fund datasets on an individual patient level. The third party will combine the sick fund dataset and the study dataset using the patient insurance number which will be sent to on the additional informed consent (Appendix C). The patient insurance number will be immediately deleted after data combination. Statistical evaluation will only be based on pseudonymised data.

Statistical methods

This population will consist of all patients enrolled into this NIS who have taken at least one anastrozole tablet (with a documented date of 1st intake of anastrozole; if unavailable, date of 1st prescription of anastrozole may be used).

The ITT analysis set will be used for the primary analysis of compliance and arthralgia scores. The safety population(s) will be the basis for the analysis of costs and safety analyses and for a secondary analysis of arthralgia scores. Additionally, all women who completed this NIS and who were compliant according to the criteria defined in the protocol for the total duration of 12 months of anastrozole treatment will be analysed separately with regard to the arthragia characteristics (VAS score, incidence, intensity etc), side-effect management, related costs, perception of side effects etc.

Demographic data and all other important baseline characteristics will be presented for both, the ITT and safety analysis sets. The results will be presented in a descriptive manner.

Other analysis sets may be defined. Details about the definition of these additional analysis sets will be given in the SAP.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this observation plan.

Abbreviation or special term	Explanation
AE	Adverse Event (see definition in Section 8.3.1.1)
AI	Aromatase Inhibitor
AMG	German Drug Law (Arzneimittelgesetz)
ASCO	American Society of Clinical Oncology
ATAC	Anastrozole, tamoxifen alone or in combination-trial
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BKK	Bundesverband der Krankenkassen
BMI	Body Mass Index
BMQ	Beliefs about Medicines Questionnaire
CRF	Case Report Form
CRO	Clinical Research Organisation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
E_2	Estrogen
EC	Ethics Committee (synonymous to Institutional Review Board and Independent Ethics Committee)
ER	Estrogen Receptor
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GWQ	Gesellschaft für Wirtschaftlichkeit und Qualität bei Krankenkassen
ICH	International Conference on Harmonisation
ITT	Intent-To-Treat
IU	International Units
KBV	Kassenärztliche Bundesvereinigung
l	litre
MCa	Mamma Carcinoma
NIS	Non-Intervention Study
odd	Oral Daily Dose
OP	Operation

Abbreviation or special term	Explanation
PgR	Progesterone Receptor
PMS	Post Marketing Surveillance
PRO	Patient Reported Outcome
RCT	Randomised Clinical Trial
SAE	Serious Adverse Event (see definition in Section 8.3.1.1).
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSL	Socket Layer Algorithm
TTP	Time to progression
WBDC	Web Based Data Capture
WOSCOPS	West of Scotland Coronary Prevention Study
+ve	positive

1. INTRODUCTION

Breast cancer is the most prevalent cancer in women (23% of all cancers) and in 2002 was estimated to be the second most common cancer worldwide in terms of new cases (1.15 million) [1]. Despite a reduction in death rates in recent years [2], breast cancer still leads to significant mortality. For the past three decades tamoxifen has been the standard treatment for estrogen receptor (ER)-positive breast cancer. However, data now suggest that the third-generation aromatase inhibitors (AIs), 'Arimidex' (anastrozole), exemestane and letrozole, are more effective than tamoxifen and have the potential to improve outcomes.

The third-generation AIs first became a potential treatment option for postmenopausal women with advanced and early breast cancer in the 1990s. Compared with first- and second-generation AIs, these agents showed increased potency with respect to both aromatase inhibition and subsequent estrogen suppression [3, 4]. Anastrozole and letrozole are both reversible non-steroidal AIs and exemestane is an irreversible steroidal AI. Letrozole is approved as extended adjuvant therapy for women who have already received 5 years' tamoxifen and as first- or second-line treatment for advanced disease. Exemestane, the latest AI to undergo clinical investigation, is approved for the treatment of advanced breast cancer in patients who have progressed following tamoxifen therapy and of early breast cancer after a previous adjuvant treatment with tamoxifen for 2 or 3 years. Anastrozole, however, is the only aromatase inhibitor licensed for upfront treatment of early breast cancer and for therapy of early breast cancer following two to three years of tamoxifen treatment ("switch").

1.1 Medical Background

In the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial, 9366 postmenopausal women with histologically proven operable invasive breast cancer, who had completed primary surgery and chemotherapy (where given), were randomized to receive adjuvant anastrozole (1 mg/day), tamoxifen (1 mg/day) or a combination. After a median of 100 months, disease-free survival, time to recurrence, and time to distant recurrence were improved significantly in the ITT and hormone-receptor-positive populations. Absolute differences in time to recurrence increased over time, showing a larger carry-over effect of anastrozole compared to tamoxifen after five years of adjuvant endocrine therapy.

Long-term safety and tolerability data are particularly important in the adjuvant setting, where patients typically receive five or more years of endocrine therapy. Predefined adverse events in the ATAC trial at 68 months' median follow-up [5], when ≥90% of patients had completed treatment, occurred with similar relative frequency to adverse events at the 33- and 47-month analysis [6, 7] although the absolute incidence of adverse events increased with longer follow-up. Anastrozole was associated with a number of important tolerability benefits over tamoxifen, including significant reductions in the incidence of endometrial cancer (5% vs 17%; p=0.02), thromboembolic events (venous, 2.8% vs 4.5%, p=0.0004; deep venous, 1.6 vs 2.4, p=0.02; respectively), and ischemic cerebrovascular events (2.0% vs 2.8%; p=0.03). Importantly, and due to the current concern about a link between the use of aromatase

inhibitors and cardiovascular toxicity [3, 4, 8, 9], it is reassuring to see that there is no difference in the number of cardiac deaths between anastrozole (n=49) and tamoxifen (n=46). The only adverse events with significantly increased risks on anastrozole therapy compared with tamoxifen were joint disorders (35.6 vs 29.4; p<0.0001) and fractures (11.0 vs 7.7; p<0.0001). Joint symptoms (arthralgias and arthritis) are well-known to limit compliance, and to form a prescription-barrier for doctors. Major risk factors for developing joint symptoms were previous HRT, hormone-receptor positivity, previous chemotherapy, and obesity.

1.2 Compliance Background

In a long-term therapy, where a daily medication has to be self-administered by patients, patients' compliance is likely to affect efficacy. The intended benefits can only be achieved when medication is taken as it was prescribed [10]. Research in various therapeutic fields has shown an attrition of compliance with drug and non-drug treatments over time, even within the highly controlled frame of a randomised clinical trial (RCT). A primary prevention trial of pravastatin in 6595 male patients (WOSCOPS) showed an important reduction in coronary death and non-fatal MI (reduced by 31%) as well as a decrease in overall mortality [11]. However, one third of the patients had stopped taking their treatment after five years.

The situation is even worse after closure of the RCT. Clinical trials provide an environment that favours good compliance with visits and tests scheduled as well as therapies. On returning to routine practice patients often do not take the medication as prescribed, give up therapy after a short period, or are undertreated, decreasing their chances for the best result of the therapy. In the 4S study (Scandinavian Simvastatin Survival Study Group, 1994), simvastatin reduced the risk of coronary death (relative to placebo) by 42%, hospitalisation due to coronary artery disease by 32%, and risk of undergoing a revascularisation procedure by 37%; overall mortality was reduced by 30%. During this trial, the compliance rate was greater than 80%. After completion of the double-blind period however, many patients abandoned therapy. [12].

Compliance with medical recommendations, i.e. the extent to which recommendations are followed, is a way to maintain or improve health and manage symptoms and signs of disease. It supposes that the patient has the requisite knowledge, motivation, skills, and resources to follow the recommendations. According to the sparse research in this domain, the most promising strategies are combinations of interventions, including patient education, contracts, self-monitoring, social support, telephone follow-up, and tailoring, often associated in multi-component strategies [14, 15]. Compliance in the first months of treatment is the most powerful predictor of long-term compliance; however, many studies show a decrease in compliance over time [13].

1.3 Rationale

Anastrozole is available as a 1 mg film-coated tablet. The registered dose is a daily tablet, daily for five years in the absence of intolerable side-effects or recurrence of disease. Anastrozole is highly effective in inhibiting in vivo aromatization. Pharmacodynamic data from Phase I clinical studies in postmenopausal female volunteers and patients with advanced

breast cancer demonstrate maximal suppression of plasma estrogens occurring after 3-4 days of anastrozole treatment (0.5-1.0 mg) and no recovery in estradiol was apparent for up to 144 hours after the last dose [16, 17, 18]. Thus individual cases of missed tablets are not expected to translate into meaningful biological or clinical effects. However, the most important requirement for the effectiveness of an oral therapy self-administered without medical supervision is optimal compliance i.e. the extent to which a patient adheres to the recommended therapy. Rates of compliance for different therapies of chronic diseases are reported in the literature, vary widely and irrespective of disease are low, not exceeding 40-50% within a few months after beginning of treatment [19]. Only a few reports have evaluated the rate of compliance in the adjuvant therapy of breast cancer. Usually patients with the potential to become non-compliant are not excluded from randomised clinical study participation. A common withdrawal criterion is failure to comply with the protocolled dosing schedule by less than 80%.

The existing data assessing compliance was mainly accumulated in RCTs. One report investigating the compliance to adjuvant tamoxifen therapy in 2378 American women with receptor positive breast cancer documented that 23% of patients were non-compliant after the first year of therapy. Only 50% of the total population were considered compliant after 4 years [20]. These data are supported by a smaller randomised trial that monitored compliance to tamoxifen over a 3-month period using an electronic monitoring device. Waterhouse and co-workers demonstrated that 75% of patients did not adhere to an 80% compliance-level in this study [21]. Compliance data highlight the fact that persistence on any therapeutic intervention for a period of years is significantly influenced by the treatment interval, the route of administration, the number as well as the severity of side effects and the degree of influence on the day to day routine. Additionally, patient's motivation and the knowledge about the individual disease seemed to be a significant determinate [21]. Partridge et al. noted that age, race and regular contact with an oncologist were factors which correlated with patient compliance to tamoxifen [20].

In this Non-Intervention Study (NIS) all participating patients will receive standard routine care for breast cancer and information material with general background information on breast cancer, endocrine treatment, coping with the diagnose and lifestyle in order to enhance compliance [22].This NIS aims to assess incidence and characteristics of arthralgias as a therapy-limiting and compliance-limiting side-effect, and assesses whether the incidence and severity of arthralgias is different in upfront anastrozole therapy and in anastrozole therapy following two to three years of tamoxifen treatment. Furthermore, compliance will be assessed and compared in patients experiencing arthralgias and patients not experiencing arthralgias. Arthralgia incidence and characteristics will be correlated to patient`s compliance, and factors influencing arthralgias and compliance will be identified. Arthralgia characteristics will be particularly assessed using a validated VAS scale (Appendices E and F). Subjective perception of side-effects will be evaluated by psycho-oncologic scales (Appendices E and F). Costs of arthralgia therapy, as well as all costs of breast cancer therapy will be assessed and described in a descriptive manner. This study is part of a cooperation project with the GWQ (an organization including currently 19 sick funds). For patients who are insured in one of these sick funds and who consented to transfer of pre-defined data, study data will be compared to and validated by sick fund data.

2. TYPE OF STUDY

This study is a Non-Interventional Study (NIS), called 'nicht-interventionelle-Beobachtungsstudie' in Germany according to the German Drug Law (AMG, §67(6)), i.e. a specific type of Post Marketing Surveillance (PMS) study. It will be 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.

An ethics approval will be requested by the ethics committee in Marburg. The study will be announced to the Federal Institute for Drugs and Medical Devices (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte), to the German association of Statutory Health Insurance Physicians (KBV, Kassenärztliche Bundesvereinigung), and to the German Association of Health Insurance Funds (BKK, Bundesverband der Krankenkassen).

3. OBJECTIVES

Objectives:

Primary objective:

Assessment of arthralgia scores and patients` compliance within the first year of anastrozole treatment[1], stratified by upfront and switch therapy as well as assessment of the relationship between compliance and arthralgia scores.

Secondary objectives

Incidence of arthralgias and arthralgia characteristics within the first year of anastrozole therapy[1] stratified by upfront and switch therapy and assessment of the relationship of arthralgia incidence and arthralgia characteristics to patients` compliance.

Retrospective assessment of incidence of pre-existing arthralgias before start of anastrozole treatment, stratified by upfront and switch therapy.

Descriptive assessment of arthralgia therapy and of costs of arthralgia therapy, stratified by upfront and switch therapy.

The assessment of compliance and of arthralgia therapy will be compared to and validated by the corresponding data obtained by the sick funds of the patients.[2]

Assessment of subjective perception of side-effects by the patients, stratified by upfront and switch therapy.

Identification of factors influencing and correlating to treatment-emergent arthralgias, such as patient`s characteristics (e.g. age, BMI), disease characteristics, duration of anastrozole treatment, subjective perception of side-effects by the patients etc.

Identification of factors influencing and correlating to patients` compliance; for example patient's 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.

Compare 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.

Assessment of safety and tolerability of anastrozole.

The ITT analysis set will be used for the primary analysis of compliance and arthralgia scores. The safety population(s) will be the basis for the analysis of costs and safety analyses and for a secondary analysis of arthralgia scores. Additionally, all women who completed this NIS and who were compliant according to the criteria defined in the protocol for the total duration of 12 months of anastrozole treatment will be analysed separately with regard to the arthragia characteristics (VAS score, incidence, intensity etc), side-effect management, related costs, perception of side effects etc.

Demographic data and all other important baseline characteristics will be presented for both, the ITT and safety analysis sets. The results will be presented in a descriptive manner.

Other analysis sets may be defined.

[1] The start of the adjuvant treatment with anastrozole is defined by the date of the first tablet intake. If this date is not assessible, the date of the first prescription of anastrozole can be used instead.

[2] This is only applicable to patients who consented to data transfer and who are insured by sick funds who joined the respective contract. Data transferred from the sick funds will include breast-cancer related costs from 12 months before study start up to the end of the study for the respective patient.

Outcome variables

Compliance:

Compliance is defined by the percentage number of patients being 'compliant' to anastrozole therapy, based on the following information collected by the doctor at 0, 3, 6 and 9 months after study start:

1) Question about the daily intake of anastrozole (to be answered by the investigator):

”The patient was instructed to take 1 anastrozole tablet per day. However, it’s still possible that the intake has sometimes been forgotten. How many tablets, according to your impression of the patient, has the patient actually taken during the last year?”

Scoring:		
	0 – none	0%
	1 – few	[0% ; 20%]
	2 – less than half	[20% ; 40%]
	3 – approximately half	[40% ; 60%]
	4 – more than half	[60% ; 80%]
	5 – almost all	[80% ; 100%]
	6 – all	100%.

2) Question about the daily intake of anastrozole (to be answered by the patient in the patient questionnaire)
”You were instructed to take 1 anastrozole tablet per day. However, it’s still possible that the intake has sometimes been forgotten. How many tablets have you actually taken during the last year?”

Scoring:		
	0 – none	0%
	1 – few	[0% ; 20%]
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	3 – approximately half	[40% ; 60%]
	4 – more than half	[60% ; 80%]
	5 – almost all	[80% ; 100%]
	6 – all	100%.

3) A patient will only be defined as being ‘compliant’ when the answer of the doctor **and** the patient score ‘5’ or ‘6’ concerning the question regarding the number of tablets actually taken.

Upon receipt of sick fund data, for patients insured in the GWQ and who consented to data exchange, compliance data obtained in this NIS will be compared to the percentage of prescriptions actually received by the pharmacies.

Arthralgias

Arthralgias will be summarized by incidence, localization, onset, duration, intensity, and relationship to study drug, diagnostics and arthralgia management (e.g. medication, physiotherapy, doctor’s visits, change of life style etc.). Arthralgia characteristics will be particularly assessed using VAS scores (Appendices E and F).

Perception of side-effects

Subjective perception of side-effects will be evaluated using the following scores: GASE-P (Generic Assessment of Side Effects, appendices E and F), SASS (Somatosensory

Amplification Scale, appendices E and F), and BMQ (Beliefs about medicines questionnaire, appendices E and F).

Arthralgia therapy and related costs

Arthralgia therapy will be documented in the eCRF and in the patient questionnaire (for further information, see Chapter 8; e.g., newly prescribed medication, doctor`s visits, diagnostics, hospital admissions). Diagnostic and therapeutic measures will be recorded as standardised patterns in the eCRF and in the patient questionnaire and will be correlated with itemised costs for evaluation purposes. Cost evalulations will be feasible on patient and global level.

Validation of data (arthralgia therapy and compliance) by sick fund data

For patients who signed an additional informed consent form (Appendix C, see chapter 7.3), arthralgia therapy as documented by the investigators and the patients will be compared to sick fund data on an individual patient level by a third party who will combine the study and the sick fund datasets on an individual patient level. The third party will combine the sick fund dataset and the study dataset using the patient insurance number which will be sent to on the additional informed consent (Appendix C). The patient insurance number will be immediately deleted after data combination. Statistical evaluation will only be based on pseudonymised data.

4. PRODUCT-SPECIFIC INFORMATION ON ANASTROZOLE

Anastrozole has been approved in Germany (Arimidex®). The current summary of product characteristic (SmPC, "Fachinformation") can be found in Appendix C of this observational plan.

Anastrozole is contraindicated for patients with severe renal function disorders (Creatinine clearance < 20 ml/min) or with moderate or severe disorders of hepatic function.

5. CENTRE SELECTION AND PLANNED NUMBER OF CENTRES

This NIS study is a non-interventional, multi-centre, observational study with approximately 700 specialised clinics and office based gynaecologists or oncologists. Study Centres will be selected in concern of the criteria of the medical experiences and the knowledge of the disease of study investigators.

6. PATIENT SELECTION AND PLANNED NUMBER OF PATIENTS

Patients are eligible for inclusion in this NIS if they have taken anastrozole either upfront or following two to three years of tamoxifen treatment ("switch") for at least three and not more than six months prior to offering an individual participation in this program. Treatment should follow local therapy guidelines and standard practice. Treatment decisions for patients participating in this study including assessments or supportive therapy during follow-up visits will also follow guidelines and remain independent of the program.

The patient population will include postmenopausal women with hormone-receptor positive primary breast cancer scheduled for adjuvant upfront endocrine treatment with anastrozole or following two to three years of tamoxifen treatment ("switch") according to the current SmPC (Appendix C). Patients will have taken anastrozole for at least three months and not more than six months before the start of the study.

It is planned to enrol and document 3212 patients in this NIS. Further details regarding the objectives and the sample size consideration can be found in Section 3 and 11.5..

6.1 Inclusion and exclusion criteria

Based on the current version of the SmPC for anastrozole patients participating in this study must meet all of the following criteria:

1. Provision of Written Informed Consent

2. Postmenopausal women aged 18 years or older;
   Postmenopause is defined as
   - Natural menopause with menses >1 year ago or
   - Serum FSH (> 20 IU/ l), and E2 levels in the postmenopausal range or
   - patients who had bilateral oophrectomy

3. Histologically / cytologically confirmed primary diagnosis of early breast cancer (M0) with hormone sensitive tumour (ER+ve and/or PgR+ve)

4. Patients, who underwent breast cancer surgery and, if applicable, radiation therapy and/ or neo/adjuvant chemotherapy and have taken adjuvant endocrine treatment with anastrozole (upfront or following two to three years of tamoxifen treatment) for at least 3 month and for a maximum of 6 months

5. Patient is considered suitable for treatment with an oral therapy.

6. Ability to organize the daily intake of drugs

7. Ablility to read and understand German

8. In case of a previous therapy with tamoxifen (switch-therapy), duration of tamoxifen treatment for at least two and up to three years.

Any of the following is regarded as a criterion for exclusion from the program:

1. Patients, who are unable to provide written consent

2. Concomitant treatment with drugs known to affect sex hormonal status and Tamoxifen

3. Known hypersensitivity to anastrozole or any excipients of the tablet. The contraindications, warning notices and measures of precaution of this product, as notified in the product information, have to be respected

2. Patients with ductal carcinoma in situ (DCIS) without primary diagnosis of early breast cancer (M0)

3. Evidence of any significant clinical disorder or laboratory finding which in the opinion of the investigator, makes it undesirable for the patient to participate in the program

4. Previous enrolment in the present program

5. Participation in any other clinical trial within 30 days of enrolment

8. Involvement in the planning and conduct of the program (applies to both AstraZeneca staff or staff at a participating site or at the CRO).

7. PROGRAM PLAN AND PROCEDURES

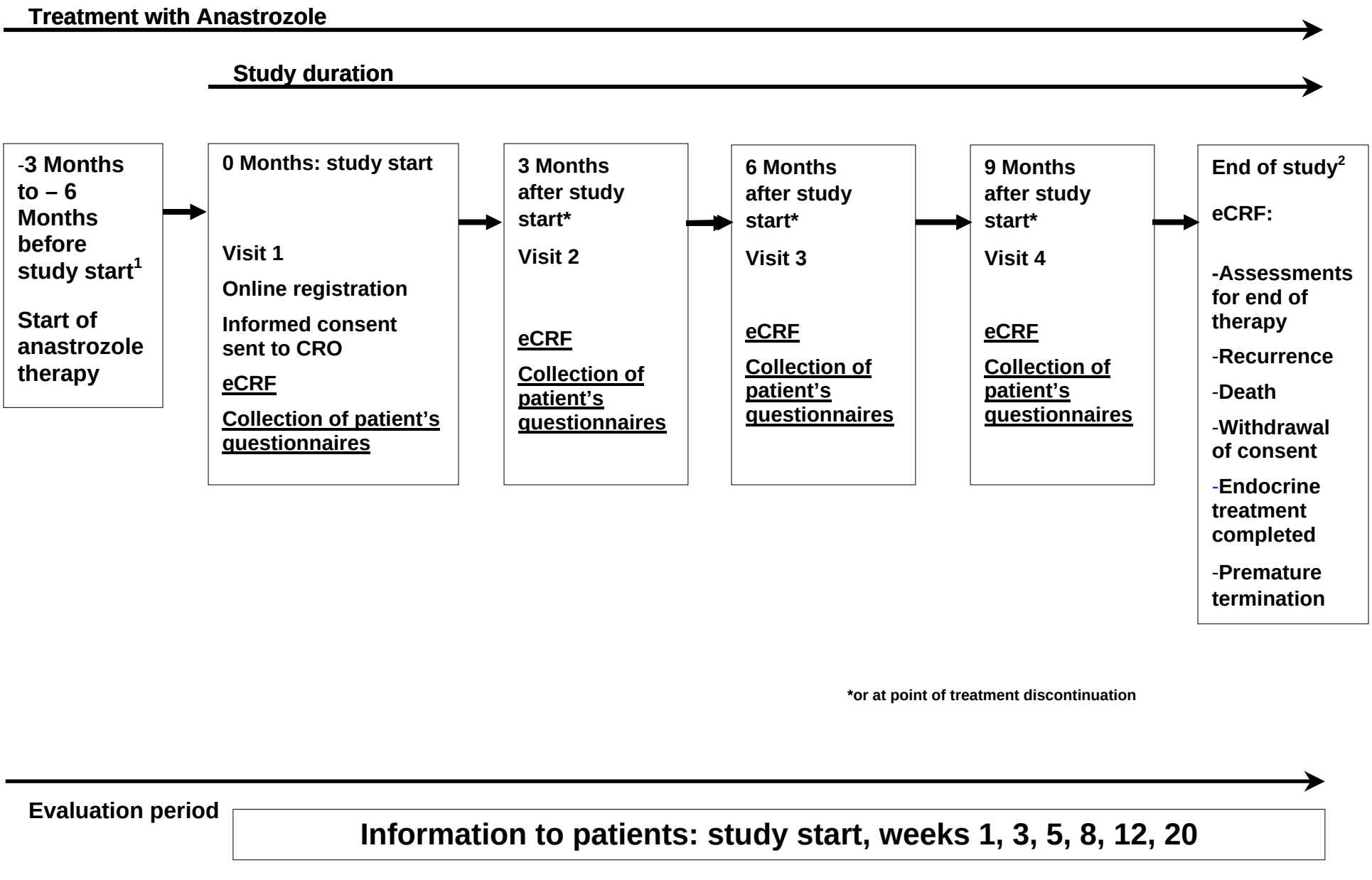
7.1 Overall design and flow chart

This is an open, multicentre NIS.

It is planned to enrol subjects into this NIS between Q1 2009 and Q1 2010. Based on the plan outlined below, it is assumed that the last subject will be enrolled in Q1 2010 and subsequently documented until Q4 2010.

The treatment with anastrozole can be stopped at any time.

Furthermore it is expected, that the last completed eCRF will be filled in Q4 2010. It is planned to close all centres until end of Q1 2011 (i.e. the fees for all participating centres are paid).


Treatment with Anastrozole
Study duration
-3 Months to – 6 Months before study start[1]
Start of anastrozole therapy
0 Months: study start
Visit 1
Online registration
Informed consent sent to CRO
eCRF
Collection of patient's questionnaires
3 Months after study start*
Visit 2
eCRF
Collection of patient's questionnaires
6 Months after study start*
Visit 3
eCRF
Collection of patient's questionnaires
9 Months after study start*
Visit 4
eCRF
Collection of patient's questionnaires
End of study[2]
eCRF:
-Assessments for end of therapy
-Recurrence
-Death
-Withdrawal of consent
-Endocrine treatment completed
-Premature termination
*or at point of treatment discontinuation
Evaluation period
Information to patients: study start, weeks 1, 3, 5, 8, 12, 20

1 The start of the adjuvant treatment with anastrozole is defined by the date of the first tablet intake. If this date is not available, the date of first prescription will be taken.

[2] The end of participation in this NIS is defined as recurrence or death or withdrawal of informed consent is documented via WBDC. Patients who stop endocrine therapy (i.e. do not take further treatment) or patients who switch to an adjuvant endocrine therapy with tamoxifen or a different aromatase inhibitor or patients considered 'lost to follow-up' (i.e.: can no longer be contacted) will be documented as premature terminations. Otherwise this NIS terminates after completion of 12 (15) months observation period (12 respectively 15 months observation period results from time slot for inclusion, minimum 3 and maximum 6 months of anastrozole therapy prior to enrolment)

7.2 Program plan

	3 – 6 months before study start	Study start	3, 6, and 9 months after study start
Start of adjuvant treatment with anastrozole (upfront or switch following tamoxifen treatment)	X		
Written Informed consent		X[1]	
Registration inclusion/exclusion criteria (online eCRF)		X	
Activation of the further online documentation forms		X[2]	
Baseline documentation (online eCRF; see chapter 8)		X	
Follow-up documentation (online eCRF; see chapter 8)			X
Entrance-Questions eCRF (status activates applicable modules)			X
AE/SAE – module (eCRF)		X	X [3, 4]
Therapy continuation module (eCRF)			X [3,]
Therapy discontinuation module (eCRF)			X [3, 5,]
Recurrence module (eCRF)			X [3, 5,]
Death module (eCRF)			X [3, 5,]
Consent withdrawn module (eCRF)			X [3, 5,]
Treatment change module (eCRF)			X [3, 5,]
Patient's questionnaires		X[6]	X[7]

[1] Patient's written Informed Consent must be obtained before registration of the patient for the program, for details please see Section 7.3. A copy of the Patient information and Informed Consent Form can be found in Appendix B.

[2] Activation of the further online documentation forms will take place within a few hours after online registration on the same day during normal office working time (9 – 16 h). If the online registration was performed in the evening, on a weekend or a holiday, activation of the further online documentation forms will take place on the next working day. For details please see Section 7.4.

[3] Completion if applicable. The e-documentation at 3, 6, and 9 months starts with entrance questions concerning patient's status. These questions activate other relevant documentation-modules.

[4] SAE must be reported to AstraZeneca drug safety within 1 day of notification, for details concerning SAE please see Sections 8.3 and 8.3.1.3.

[5] Recurrence, death, withdrawal of consent, treatment discontinuation and switch to an adjuvant endocrine treatment with tamoxifen or a different aromatase inhibitor must be documented immediately. If one of these events is documented the sending of patient material will be stopped.

[6] Patient's questionnaires "Start".

[7] Patient's questionnaires "Follow up".

7.3 Informed consent and patient data

The investigator(s) at each clinic will ensure that the patient is given full and adequate oral and written information about the nature and purpose of the NIS as well as the use of patient's data and storage of patient's names and addresses during the program. The patients must also be notified that they are free to discontinue from the program at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's informed consent contains the full name of the patient and her address and the name of the investigator. The informed consent form must be signed and dated by the patient and the investigator. The patient's signed and dated informed consent as well as investigators signature must be obtained before registration. The investigator(s) at the clinic or the office based physician must store the original, signed Informed Consent Form according to legal requirements. A second original copy of the signed Informed Consent Form must be given to the patient. A copy of the patient's information consent form can be found in Appendix B.

A copy of the completed and signed patient's informed consent must be sent by fax to . The informed consent will be stored by until the end of the NIS (final analysis completed). After completion of the program all Informed Consent Forms will be destroyed by . The destruction must be documented and confirmed in written form.

Patient names and addresses are required for the shipment of information material to patients. Furthermore, upon consent by the patients, may contact the patients per mail in case the patient questionnaire was not received by (at maximum, one written contact per patient documentation will be allowed).

For the handling of patient names and addresses a separate database will be used, as well as for the information obtained by the sick fund. This database will be operated within the facilities of only. The patients` address database will be linked through the registration number with the study database. Links to other databases will not be implemented. At the end of the NIS (final analysis completed) all patient names and addresses must be deleted from this database. The deletion must be confirmed in written form.

The sponsor of this NIS has no access to patient names and addresses.

Patients, who are insured by a sick fund organized by "Gesellschaft für Wirtschaftlichkeit und Qualität bei Krankenkassen" (GWQ) are asked to take part for special settlement informations by their sick fund. For this information it is necessary to get the sick fund and the insurance policy number. In addition to the informed consent for the main COMPACT program (Appendix B-1), an additional informed consent form will be signed (Appendix B-2). Patients will be informed that the participation at the special settlement is not mandatory for the participation at the COMPACT program. Patients who sign the additional Informed Consent Form agree that their sick fund data about breast-cancer related costs and arthralgia therapy will be combined with the study datasets by a third party using the patient

sick fund and insurance number which will be sent to on the additional informed consent (Appendix B-2). Patients agree that data transferred from the sick funds will concern data from 12 months before study start up to the end of the study for the respective patient The patient insurance number will be immediately deleted after data combination.

A copy of the completed and signed additional patient's informed consent must be sent by fax even to The informed consent will be stored by until the end of the NIS (final analysis completed). After completion of the program all Informed Consent Forms will be destroyed by .

7.4 Registration of patients

Patients meeting all eligibility criteria and having given written informed consent (Appendix B) will be enrolled by the site using an online registration form. Registration will be possible 24 hours a day via the COMPACT-webpage: www. compact-programm.de

Registration

For the registration of a patient

- a copy of the signed informed consent form must be faxed to , to

and

- the registration form must be completed online via the COMPACT-webpage: www.compact-programm.de

If patients take part in the additional information program from the sick fund

- a copy of the signed additional informed consent form must be faxed to

7.5 Information

Patients will undergo standard routine care for breast cancer. Additionally, information will be provided to patients by mail. The information material includes patient support materials (letters and brochures) with general background information on breast cancer, coping with the diagnosis, lifestyle and diet. Additionally patient questionnaires will be send at the start of the study and 3, 6 and 9 months after study start. Table 1 provides an overview of the topics of the patient support materials, questionnaires and the timing of the mailings. The information packages will be sent to the patients at the indicated time points after the registration of the patient.

Table 1 Patient materials packages, mailing frequency and themes

Time point of mailing	Patient's material
Week 0	**Letter:** "Die Antihormontherapie – Ihr starker Begleiter" („Antihormone therapy - your strong companion") **Brochure 1** „Alle Chancen nutzen" („Taking all chances")
Week 1	**Brochure 2 "**Was Sie über Nebenwirkungen des Aromatasehemmers wissen sollten" („What you should know about side effects of aromatase inhibitors")
Week 3	**Letter:** "Was hilft, wer hilft - Partner und Verbündete" („What helps, who helps – partner and leagues") **Brochure 3** „Was Sie über Kommunikation wissen sollten" („What you should know about communication")
Week 5	**Brochure 4** "Was Sie über Fatigue-Syndrom und Lymphödem wissen sollten" („What you should know about Fatigue Syndrome and Lymphedema")
Week 8	**Letter:** "Bewusstes Leben - der eigene Körper" („Conscious life – your own body") **Brochure 5** „Was Sie über Umgang mit Ängsten wissen sollten" („Dealing with anxieties, what you should know")
Week 12 (month 3)	**Brochure 6** "Was Sie über Brustkrebs und Sexualität wissen sollten" („What you should know about breast cancer and sexuality")
Week 20	**Letter:** "Kraft & Lebensenergie - der Blick nach vorn" („Power & Vitality – looking ahead") **Brochure 7** „Was Sie über regelmäßige Bewegung und den Umgang mit Ängsten wissen sollten" („Regular exercise and dealing with anxieties, what you should know")

Mailing of the patient materials will be stopped:

- if breast cancer recurrence or patient's death is documented by the investigator via WBDC

- or if stop of adjuvant endocrine treatment (no further continuation of adjuvant treatment at all) or switch to a different adjuvant endocrine treatment with tamoxifen or a different aromatase inhibitor is documented by the investigator via WBDC

- or if patient withdraws consent (documented by the investigator via WBDC)

- or if is notified either by physician or by patient that the patient does not wish to receive further mailings.

Patient materials will be sent to the patients by mail. The mailing of the appropriate patient material packages at the appropriate time points will be coordinated and organised by
.

7.6 Discontinuation of patients from program

Patients may discontinue participation in this program at any time. Specific reasons for discontinuing a patient from this program are:

- Withdrawal of informed consent
- Breast cancer recurrence
- Stop of adjuvant endocrine treatment (no further continuation of adjuvant treatment at all) or switch to an adjuvant endocrine treatment with tamoxifen or a different aromatase inhibitor

Patients should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. For these cases, the investigator has to complete the consent withdrawal form and the respective forms in the eCRFs.

7.7 Concomitant treatment(s)

Any medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). However possible drug interactions as specified in the current SmPC should be taken into account. A copy of the current SmPC for anastrozole can be found in Appendix C.

8. DOCUMENTATION

8.1 Patient documentation by investigator

The following data will be collected via web based data capture (WBDC) by the investigator or a designated delegate.

8.1.1 Documentation at registration

The following data should be documented at registration/enrolment

Demographics	Year of birth
Patient number	
Patient insured in a sick fund part of GWQ?	Yes; no
Informed consent	
Inclusion / exclusion criteria	
Was the patient identified for anastrozole therapy 1mg / day?	Yes; no
Date of the 1st prescription	
Start date of anastrozole therapy	
Breast centre that performed surgery	Name Address
Investigator details	Fax number E-mail address Name

8.1.2 Documentation at baseline

The following data should be documented at baseline:

Demographics	Height (cm) Weight (kg) BMI
Menopausal status	
Age of patient when entering menopause	
Did the patients receive any hormone replacement therapy before?	Yes, no; if yes => duration of hormone replacement therapy?
Specification of hormone replacement therapy	Estrogen only (dose of estrogen); Estrogen-gestagen combination (dose of estrogen)
Concomitant diseases	Answers for each listed point (no, yes – please specify, unknown) Cardio-circulatory system

	vascularly system skeleton, musculature (i.e. rheumatoid arthritis, arthralgias, osteoarthritis, back pain, capral tunnel syndrome; soft tissue rheumatism; other musculature and joint discomfort) if arthralgias occurred => pre-existing arthralgias before anastrozole therapy? => if yes: intensity? localisation? duration?; => any arthralgia occurrence after the start of anastrozole therapy? if yes => Arthralgia AE module Urogenital system Central nervous system Gastrointestinal system Metabolic diseases Hot flushes Headache / migraine Other
Primary diagnosis of breast cancer	Date of primary diagnosis
Number of tablets currently taken by patient per day	
Localisation of primary tumour	
Anastrozole indication	Upfront or following tamoxifen treatment if following tamoxifen treatment: duration of tamoxifen therapy
Breast cancer therapies	Performance of post-operative radiation therapy (no, yes) Performance of neo-adjuvant chemotherapy (CHT) (no, yes; number of cycles) Performance post-operative chemotherapy (no, yes; number of cycles)
Treatment compliance: doctor`s assessment	Estimation of compliance by doctor`s judgement: "How many tables have been taken in the observed period?" (none, few, less than half, appr. half, more than half, almost all, all)
Concomitant medication	No, yes => please specify

Arthralgia – Module (to be filled in in case of arthralgia occurrence during anastrozole therapy)	
Arthralgia questionnaire	Arthralgia onset during anastrozole therapy (no, yes, unknown – if yes : localisation, swelling, pain intensity; duration, relationship to study drug) Therapy of arthralgias: no, yes – please specify. Assessment of treatment with medication (drug name, dose, package size, duration (start-end) Doctor`s visits (including doctor`s specification) Diagnostics? if yes => specify Physiotherapy? if yes => specify Adjuvants? if yes => specify Lifestyle changes? if yes => specify

8.1.3 Documentation after 3, 6, and 9 months after study start

The following patient data should be documented after 3, 6, and 9 months after study start or at the time point of treatment discontinuation:

Observation interval	Date of last examination Date of documentation (current date)
Date of observation	
Patient lost to follow-up status	If the patient does not attend follow-up visits, can she be contacted (yes, no – lost to follow-up)
Demographics	Weight (kg)
Occurrence of adverse events	(no, yes) ⇒ AE/SAE-module
Status of breast cancer disease	Loco-regional recurrence / contralateral recurrence / distant metastasis (if yes: date of recurrence / localisation?)
Survival status	(alive, died) ⇒ Survival –module
Continuation of anastrozole therapy (yes, no)	Yes ⇒ Treatment continuation-module No ⇒ Treatment discontinuation module Change of endocrine therapy ⇒ Switch module
Patient continuation of participation in COMPACT	(Yes, no – consent withdrawn, no – died, no – other reasons) ⇒ Consent withdrawal-module
Concomitant medication	No, yes => please specify

The following data should be documented after 3, 6, and 9 months of endocrine therapy or at the time point of treatment discontinuation as indicated and applicable by patient's status:

Treatment continuation – Module (continuation of anastrozole therapy)	
Treatment compliance: doctor`s assessment	Estimation of compliance by doctor`s judgement: "How many tables have been taken in the observed period?" (none, few, less than half, appr. half, more than half, almost all, all)
Number of medicines / tablets or capsules per day	
Anastrozole prescriptions / sample packages	Number and package size
Was anastrozole intake stopped / taken irregularly?	if yes => reason?
Concomitant medication	No, yes => please specify

Arthralgia – Module (to be filled in in case of arthralgia occurrence during anastrozole therapy)	
Arthralgia questionnaire	Arthralgia onset during anastrozole therapy (no, yes, unknown – if yes : localisation, swelling, pain intensity; duration, relationship to study drug) Therapy of arthralgias: no, yes – please specify. Assessment of treatment with medication (drug name, dose, package size, duration (start-end) Doctor`s visits (including doctor`s specification) Diagnostics? if yes => specify Physiotherapy? if yes => specify Adjuvants? if yes => specify Lifestyle changes? if yes => specify

Treatment discontinuation – Module (discontinuation of anastrozole therapy)	
Treatment compliance: doctor`s assessment	Estimation of compliance by doctor`s judgement: "How many tables have been taken in the observed period?" (none, few, less than half, appr. half, more than half, almost all, all)
Questions on arthralgias and	assessment of arthralgia occurrence during therapy with

related costs	anastrozole (no, yes, unknown - if yes : localisation, swelling, pain intensity: mild/moderate/severe; duration, relationship to study drug: certain, probable, possible, unlikely, not related; serious: yes/no) Therapy of arthralgias: no, yes – please specify. Assessment of treatment with medication (drug name, dose, package size, duration (start-end) Action in concern of the therapy with anastrozol Outcome Relationship to anastrozole therapy, and treatment with medication A reason to discontinuate the therapy with anastrozol? SAE?
Discontinuation of treatment with anastrozole	Date of last intake, unknown Reasons for discontinuation (recurrence, death, patient's wish, physician's recommendation and specification of reasons, other, interactions with concomitant medication, AE – worsening of a concomitant disease: (hot flushes, headache, joint pain/arthritic complains (fingers, hands, arm, shoulder/ feet, knees, hip / spine), other) AE – new: (hot flushes, headache, joint pain/arthritic complains (fingers, hands, arm, shoulder/ feet, knees, hip / spine), other)
Continuation of other endocrine treatment	(no) (yes – change of endocrine therapy which drug: tamoxifen, letrozole, exemestane, other - specification)

Switch – Module (continuation of endocrine therapy with tamoxifen or a different aromatase inhibitor)	
Continuation of other endocrine treatment	(no) (yes – change of endocrine therapy which drug: tamoxifen, letrozole, exemestane, other - specification)
Discontinuation of treatment	Date of last intake, unknown Reasons for discontinuation (recurrence, death, patient's wish, physician's recommendation and specification of reasons, other, interactions with concomitant medication, AE – worsening of a concomitant disease: (hot flushes,

	headache, joint pain/arthritic complains (fingers, hands, arm, shoulder/ feet, knees, hip / spine), other) AE – new: (hot flushes, headache, joint pain/arthritic complains (fingers, hands, arm, shoulder/ feet, knees, hip / spine), other)

Death - Module	
	Date of death Reason of death (due to tumour and complications and progression, due to tumour and adverse event, not due to tumour, dependency to tumour not evaluable) Reason of death unknown, specification possible

Consent withdrawal - Module	
	Date consent withdrawn Reason for consent withdrawn (friends, family advise not to participate, patient refusal to complete questionnaires, patient rejecton of information material, patient no longer wishes to support research, unknown, other) Patient agreement to complete a final questionnaire (no/yes)

8.2 Patient documentation

The following data will be collected from patients using patient questionnaires. Patient questionnaires will be provided on paper and will be send to the patient by .

8.2.1 Documentation at start

The following data will be filled in by before shipment to the patient:

Centre number	
Patient number	
Demographics	Year of birth

The patient will be asked to complete the following questions:

Observation interval	Date of assessment
Personal data	Marital status? (married / living with partner; married / living apart; single; divorced; widowed)

	Living in a relationship? (no; yes => for how many years?) Do you have any children? (no, yes => how many?) How many persons are currently living in your household? Do you need regular help to do your housekeeping and for your daily routine? (no, yes)
Education and profession	Graduation from school? (none; "Hauptschulabschluss"; "Realschulabschluss"; „Fachhochschulreife oder Abitur"; others) Job training? (none; apprenticeship; full-time vocational school; technical / professional school; advanced technical college; university; others) Employment? (full-time; part-time; unemployed; retired; housewife; on sick leave; others)
Medication intake	Daily intake of drugs/tablets apart from the prescribed anti-cancer agent? Number of drugs and tablets per day? (none, unknown) Self reported medication intake (questions from reference): Do you occasionally forget taking of your medicine ? (yes, no) Are you occasionally neglectful concerning your medicine intake? (yes, no) When you feel better, do you occasionaly stop taking your medicine? (yes, no) Sometimes when you feel worse, do you stop taking your medicine? (yes, no) Self reported medication intake: There are several types of patients in concern of medication intake. Which of the following describes you best? Intake of medicines takes place… - never, although the doctor prescribed it. - don't like it, only if I remembered it - irregularly, forgotten it over and over - at start regulary, later less - always How do you feel about taking your medication? - never mind

	- don't like it Why don't you like taking your medication? - difficulties in swallowing tablets - disturbs my daily routine - reminds me of my disease - other Compliance to anastrozole: You were supposed to take one tablet anastrozole per day. However, daily medication intake may be forgotten. How many anastrozole tablets did you actually take from the start of anastrozole therapy until today: - none - few - less than half - almost the half - more than half - almost all - all
Breast cancer and therapy	Do you have the feeling that you have a voice in concern of your breast cancer medication? (no, few, satisfactory, good) Were the effects of the anti-hormone therapy and the scheduled drug explained to you? (no, few, satisfactory, good) Were the side effects of the anti-hormone therapy and the scheduled drug explained to you ? (no, few, satisfactory, good) Did you receive any sample of anastrozol? (no, yes, if yes, how many?, I don't know)
Questions on arthralgia occurrence, characteristics and management	Did you experience any arthralgias? (yes, no) Did you experience any arthralgias before the start of anastrozole treatment? (no, yes => which medication did you take?) Did you experience any arthralgias since you started anastrozole treatment? (no, yes) Which medication did you take because of arthralgias? Did you consult any doctor because of arthralgias, and in which field did the doctor specify? (general practitioner,

	number of times; internist, number of times; orthopedist, number of times; rheumatologist, number of times; pain therapist, number of times; gynaecologist, number of times) Which diagnostic measures did you undergo during your doctor`s visit? (X-ray, CT, MRT, Ultrasound) Were you admitted to hospital due to arthralgias? Did you receive any physiotherapy? (yes, no, if yes => therapy method; number of prescribed therapies) Performance of any regular sportive action? If yes, how often? VAS scale: Rheumatoid Arthritis Symptom Questionnaire (see appendix E)
Questions about medication side effects	GASE-P: Generic Assessment of Side Effects (appendix E)
Somatosensory amplification of side-effects	SASS, Somatosensory Amplification Scale (appendix E)
Patient`s belief about medicines	BMQ, Beliefs about medicines questionnaire (appendix E)

8.2.2 Documentation at 3, 6 an 9 months after study start

The following data should be documented after 3, 6 and 9 months after study start or at the time point of treatment discontinuation

Demographics	Year of birth
Observation interval	Date of assessment
Demographics	Year of birth

Observation interval	Date of assessment
Medication intake	Daily intake of drugs/tablets apart from the prescribed anti-cancer agent? Number of drugs and tablets per day? (none, unknown) Self reported medication intake (questions from reference): Do you occasionally forget taking of your medicine ? (yes,

	no) Are you occasionally neglectful concerning your medicine intake? (yes, no) When you feel better, do you occasionally stop taking your medicine? (yes, no) Sometimes when you feel worse, do you stop taking your medicine? (yes, no) How do you feel about taking your medication? - never mind - don't like it Why don't you like taking your medication? - difficulties in swallowing tablets - disturbs my daily routine - reminds me of my disease - other Compliance to anastrozole: You were supposed to take one tablet anastrozole per day. However, daily medication intake may be forgotten. How many anastrozole tablets did you actually take from the start of anastrozole therapy until today: - none - few - less than half - almost the half - more than half - almost all - all
Questions on arthralgia occurrence, characteristics and management	Did you experience any arthralgias during the past threee months? (yes, no) Did the arthralgia intensity change during the past three months? (yes, the intensity decreased; yes, the intensity increased; no) Which medication did you take because of arthralgias? Did you consult any doctor because of arthralgias, and in which field did the doctor specify? (general practitioner, number of times; internist, number of times; orthopedist, number of times; rheumatologist, number of times; pain

	therapist, number of times; gynaecologist, number of times) Which diagnostic measures did you undergo during your doctor`s visit? (X-ray, CT, MRT, Ultrasound) Were you admitted to hospital due to arthralgias? Did you receive any physiotherapy? (yes, no, if yes => therapy method; number of prescribed therapies) Performance of any regular sportive action? If yes, how often? VAS scale: Rheumatoid Arthritis Symptom Questionnaire (see appendix F)
Questions about medication side effects	GASE-P: Generic Assessment of Side Effects (appendix F)
Somatosensory amplification of side-effects	SASS, Somatosensory Amplification Scale (appendix F)
Patient`s belief about medicines	BMQ, Beliefs about medicines questionnaire (appendix F)

8.3 Safety measurements and variables

The methods for collecting safety data are described below.

8.3.1 Adverse events (AE)

8.3.1.1 Definitions of AE

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg nausea, chest pain), signs (eg tachycardia, enlarged liver) or the abnormal results of an investigation (eg laboratory findings, electrocardiogram).

A serious adverse event (SAE) is an AE occurring during the treatment period with anastrozole, that fulfils one or more of the following criteria:

- results in death,
- is immediately life-threatening,
- requires in-patient hospitalisation or prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity,
- is a congenital abnormality or a birth defect,
- is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

An unexpected adverse event is an AE not mentioned in the SmPC (see Appendix C).

8.3.1.2 Documentation of AE

All adverse events occurring during the observational period should be documented on the corresponding subject-related AE CRFs. However, events and symptoms which are related to a worsening of the underlying disease to be treated with anastrozole should not be documented as AE.

For each AE, the following information should be given:

- description of adverse event,
- start date of AE,
- stop date of AE,
- maximum intensity of AE [mild, moderate, severe],
- action taken on anastrozole [none, dose reduction, temporarily stopped, stopped],
- outcome [recovered, not yet recovered, permanent disability, death, unknown],
- causality/relationship to anastrozole [no, yes],
- AE serious [no, yes]

8.3.1.3 Reporting of serious adverse events

All SAEs occurring during the observational period must be reported, whether or not considered causally related to anastrozole. However, serious events which are related to a worsening of the underlying disease to be treated with anastrozole should not be documented as a SAE.

When the physician becomes aware of a SAE during the course of the NIS, the physician must immediately (within 24 hours) inform the Patient Safety Department of AstraZeneca GmbH, must document all relevant data on the SAE form (Formblatt “Bericht über unerwünschte Arzneimittelwirkungen”, Appendix D), and must send this form to:

AstraZeneca GmbH
Patientensicherheit
D-22876 Wedel
phone: +49 (0)4103 708-0
fax: +49 (0)4103 708-3882

9. CONDUCT OF THE NIS AND QUALITY ASSURANCE

Before the start of the NIS, each participating physician will be informed in detail about the objectives design and conduct of this NIS, the collection and handling of Informed Consent, the WBDC system, the handling of serious AEs, contact personnel and all other relevant aspects of this NIS. Each participating centre will receive a binder containing the necessary documents and information.

The participation of the physician must be confirmed by signing and dating the project-specific contract between the centre and AstraZeneca GmbH. This contract needs to be signed off by the following persons: participating physician and the AZ representative. The contract needs to be signed in two copies. One signed copy will be retained by the centre and the second signed copy will be filed by AstraZeneca.

Upon completion of the eCRF the investigator declares using a electronic signature form that all data recorded for a patient has been reviewed and are accurate. The digital signature comprises: i. time stamp (date and time of signature), ii. user details (user name and password). The WBDC system is compliant with the FDA (Food and Drug Administration) Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures.

The end of this NIS is defined as the date when the last patient completed the visit scheduled nine months after start of the study.

10. DATA MANAGEMENT

The data management for this NIS will be performed by

The following chapters describe the software employed and measures applied for data security.

NIS data are recorded, processed and stored using the following software tools.

a. CRF database (Location:)
b. Patient address database (Location:)
c. AstraZeneca SAE database (Sapphire, location: AstraZeneca)
d. Statistical analysis SAS® (Location:)

Wherever applicable, current GCP guidelines (Good Clinical practice), actual technical standards and guidelines are observed.

10.1 Employed software

CRF database

For data capturing and data management of this NIS, a web-based validated software (WBDC) will be employed. The software consists of the following modules:

a) **Administration:** Administration of sites (clinics / office based physicians) by system administrator and project management. Within the individual sites the following system users are defined: Investigator and study nurse. All access rights are administered in a role-based security system.

b) **Forms / Form validator:** Electronic Case Report Forms (eCRFs) for data capture including online validation of CRFs during data capture, e. g. check on range, plausibility, type mismatch.
In addition to the system based plausibility checks, a formal query process will be implemented to resolve inconsistencies in SAE data.

c) **Reports:** Dynamic report generator, e.g. reports for investigators on CRF status;

d) **Database:** Relational database for data management. The data from the relational database will be retrieved using the export engine of and thereafter converted into SAS data sets for further validation and analysis.

The employed technology and technical requirements for data entry on site are as follows:

a) The used software is completely server-based, i.e. all program processes are executed centrally on a web or database server.

b) Data are saved exclusively in the central database server. This server is located in the facilities of .

c) For system access, users require a conventional desktop computer with internet access.

A reconciliation of SAE data will be performed every 6 months (after first subject in) to ensure that critical data related to serious adverse events are consistent in the Global safety-database, which is operated by AstraZeneca Drug Safety, and the CRF database. If necessary, discrepancies will be discussed and/or clarified with the participating centres.

Patient address database

For the handling of shipments of patient materials to patients a separate database will be set up, which will contain patient names and addresses. This database will be operated within the facilities of . Only authorized personnel will have access to this database.

A relational database will be used for this purpose. The patients address database will be linked through the randomization number with the eCRF database. Links to other databases will not be implemented.

The sponsor will not have access to the data stored in the patient address database.

Statistical analysis (SAS)

For statistical analysis the program SAS® will be used.

Data from the CRF database will be transformed into SAS data sets, which will form the basis for the statistical analysis

The date of the final data retrieval from the CRF database will be documented.

10.2 Data security and storage

Data security

For client / server communication via the Internet only encrypted transmissions are applied. State of the art encryption technology is used exclusively. For data transmission in this NIS an encryption level (128-bit) is employed by means of the Secure Socket Layer Algorithm (SSL).

In addition, the server identifies itself to the client workstation by means of a digital server certificate issued by an authorised certification authority. By this, it is ensured that data are sent only to the server of .

Data are protected from potential virtual attacks and physical damage.

According to the role of the participating personnel in this NIS (see section 10.1) individual authorisations to the system are granted. Views on data or reports as well as edit or read only rights are controlled with individual passwords. Access authorisation to the CRF databases is granted individually to investigators and program personnel by means of user accounts.

The project management of the CRO has a read-only access to all patient data stored in the CRF database.

Storage

will store all paper documents (facsimile of signed Informed Consent Forms) and all electronically recorded data (i.e. patient address database, CRF database and SAS files) until the completion of this NIS.

At the end of the NIS (final analysis completed) all copies of the signed Informed Consent Forms will be destroyed by . The destruction must be documented and confirmed in written form by .

At the end of the NIS (final analysis completed) all electronically stored data (names and addresses) in the patient address database will be deleted. The deletion must be documented and confirmed in written form by . When the data is deleted from the patient address database all data stored in the CRF database will automatically be anonymised.

After accomplishment of this NIS all electronically captured data during the performance of this NIS, including a copy of the CRF database and the SAS-dataset will be handed over to AstraZeneca and to the principal investigator.

For archiving purposes investigators may receive a hardcopy or a CD-ROM with the data of the enrolled patients at their site.

Provision is made to ensure the readability of electronically stored data over the required storage period.

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The statistical analysis and reporting of this NIS will be performed by DSH statistical services under the supervision of and in close collaboration with AstraZeneca GmbH.

This section is focused on the first statistical analysis, i.e. after all patients were observed for at least three months. The final statistical analysis (after all patients were observed for 9 months) will be performed in the same way, but using the data in a cumulative way.

11.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) covering details of all methods used to analyze the various parameters will be prepared before database lock of the 3 months data. The SAP will be reviewed, and if needed, updated before this first data base lock.

The disposition of patients with regard to

- the number of patients enrolled,
- the number of patients treated with anastrozole (upfront and following two to three years of tamoxifen treatment),
- the number of patients who discontinued prematurely from the anastrozole therapy within the study period,
- the number of patients who discontinued prematurely from this NIS within the present observational period,
- the number of patients who completed the NIS up to 3, 6, and 9 months after study start,
- the number of patients who are still taking anastrozole up to the time point of the present statistical analysis of this NIS

will be displayed by specialized clinic (including overall). The disposition of the patients in the subsequent final analysis will be displayed in the same way.

Patients without any documented start of an endocrine therapy (e.g. missing information on prescriptions) will be excluded from all statistical analyses, but will be displayed in all data listings.

All treated patients who discontinued prematurely from the anastrozole therapy and/or the NIS (according to the corresponding CRFs) will be listed by clinic; at least the time-point of discontinuation, the main reason for discontinuation and relevant data of exposure to anastrozole will be presented.

The following text refers to more general statistical key-principles based on the statistical analysis data sets, i.e. the intent-to-treat population and the safety population:

Binary, categorical and ordinal parameters will be summarized by means of absolute and percentage numbers (including 'missing data' as valid category at Visit 1). Numerical data will be summarized by means of standard statistics (i.e. number of available data, mean, standard deviation, minimum, median, maximum, lower and upper quartile). Wherever useful, the summary statistics will be presented by specialized clinic (including overall) and/or visit.

In addition, adequate figures (e.g. bar charts, Box-Whisker-Plots) may be presented to summarize the results for some parameters also in a graphical way.

All statistical tests will be performed two-sided at a 5% level of significance. However, the p-values of all statistical tests will be interpreted only in a descriptive-exploratory way. Two-sided confidence intervals will be displayed for important variables. Appropriate methods will be used to derive confidence intervals, depending on data nature and distribution. All safety and tolerability data (excluding data obtained on arthralgias) will be presented in a purely descriptive manner. Data from patients, who stopped anastrozole treatment and continued adjuvant endocrine treatment with a different medication will be presented in descriptive way only.

All statistical analyses will be performed using the SAS® system.

11.2 Description of outcome variables

The co-primary objective of this NIS will be the evaluation of arthralgia scores and patients` compliance. Secondary, arthralgia management and related costs (health economic evaluation) as well as the perception of side-effects will be evaluated. Data concerning arthralgia management will be compared to and validated by data obtained by the GWQ.

Compliance:

Compliance is defined by the percentage number of patients being 'compliant' to anastrozole therapy, based on the following information collected by the doctor at 0, 3, 6 and 9 months after study start:

1) Question about the daily intake of anastrozole (to be answered by the investigator):

"The patient was instructed to take 1 anastrozole tablet per day. However, it's still possible that the intake has sometimes been forgotten. How many tablets, according to your impression of the patient, has the patient actually taken during the last year?"

Scoring:	0 – none	0%
	1 – few	[0% ; 20%]
	2 – less than half	[20% ; 40%]
	3 – approximately half	[40% ; 60%]
	4 – more than half	[60% ; 80%]

5 – almost all	[80% ; 100%]
6 – all	100%.

2) Question about the daily intake of anastrozole (to be answered by the patient in the patient questionnaire)
”You were instructed to take 1 anastrozole tablet per day. However, it’s still possible that the intake has sometimes been forgotten. How many tablets have you actually taken during the last year?”

Scoring:		
	0 – none	0%
	1 – few	[0% ; 20%]
	2 – less than half	[20% ; 40%]
	3 – approximately half	[40% ; 60%]
	4 – more than half	[60% ; 80%]
	5 – almost all	[80% ; 100%]
	6 – all	100%.

3) A patient will only be defined as being ‘compliant’ when the answer of the doctor **and** the patient score ‘5’ or ‘6’ concerning the question regarding the number of tablets actually taken.

Arthralgias

Arthralgias will be characterized by VAS scores containing 14 items.

Arthralgias will be summarized by incidence, localization, onset, duration, intensity, and relationship to study drug, diagnostics and arthralgia management (e.g. medication, physiotherapy, doctor’s visits, change of life style etc.). Arthralgia characteristics will be particularly assessed using VAS scores (Appendices E and F).

Perception of side-effects

Subjective perception of side-effects will be evaluated using the following scores: GASE-P (Generic Assessment of Side Effects, appendices E and F), SASS (Somatosensory Amplification Scale, appendices E and F), and BMQ (Beliefs about medicines questionnaire, appendices E and F).

Arthralgia therapy and related costs

Arthralgia therapy will be documented in the eCRF and in the patient questionnaire (for further information, see Chapter 8; e.g., newly prescribed medication, doctor`s visits, diagnostics, hospital admissions). Diagnostic and therapeutic measures will be recorded as standardised patterns in the eCRF and in the patient questionnaire and will be correlated with itemised costs for evaluation purposes. Cost evalulations will be feasible on patient and global level.

Each occurrence of arthralgia will be assigned to the corresponding time interval according to 0-3, 3-6, 6-9, 9-12 and 12+ months after the start of anastrozole treatment (i.e. post treatment start).

Validation of data (arthralgia therapy and compliance) by sick fund data

For patients who signed an additional informed consent form (Appendix C, see chapter 7.3), arthralgia therapy as documented by the investigators and the patients will be compared to sick fund data on an individual patient level by a third party who will combine the study and the sick fund datasets on an individual patient level. The third party will combine the sick fund dataset and the study dataset using the patient insurance number which will be sent to on the additional informed consent (Appendix C). The patient insurance number will be immediately deleted after data combination. Statistical evaluation will only be based on pseudonymised data.

11.3 Description of analysis sets

The following analysis data sets will be used in the statistical analysis:

Safety population:

This population will consist of all patients enrolled at Visit 1 into this NIS who have taken at least one anastrozole tablet (with a documented date of 1st intake of anastrozole; if unavailable, date of 1st prescription of anastrozole may be used).

Intention-to-Treat (ITT) population:

This population will consist of all documented patients from the safety population for whom – based on CRF documentation - a determination of their compliance and/or incidence of arthralgias within the first 3 months after study start is possible.

Other analysis sets may be defined. Details about the definition of these additional analysis sets will be given in the SAP.

The ITT analysis set will be used for the primary analysis of compliance and arthralgias. The safety population will be the basis for the safety analyses and an additional secondary analysis of athralgias.

Demographic data and all other important baseline characteristics will be presented for both, the ITT and safety analysis sets. The results will be presented in a descriptive way.

11.4 Method of statistical analysis

In this section, only the important statistical aspects of the statistical analysis of the outcome variables and the adverse events are presented. Details regarding the analysis will be presented in the SAP.

11.4.1 Outcome variables

The objectives outlined in chapter 3 will be analysed as follows:

Primary objective:

Assessment of arthralgia scores and patients` compliance within the first year of anastrozole treatment[1], stratified by upfront and switch therapy as well as assessment of the relationship between compliance and arthralgia scores.

The absolute number and percentage of compliant patients will be calculated. Groups will be compared with Fisher's exact test

From the arthralgia scores an overall score will be calculated (sum of 14 single item scores divided by 14). Groups will be compared using t-test.

Relationship between compliance and arthralgia scores will be assessed using logistic regression analysis.

Of primary interest are the 3 months data (data obtained within the first three months of anastrozole therapy). Secondarily, the other time points will be evaluated.

Secondary objectives:

Incidence of arthralgias and arthralgia characteristics within the first year of anastrozole therapy[1] stratified by upfront and switch therapy and assessment of the relationship of arthralgia incidence and arthralgia characteristics to patients` compliance.

The absolute number and percentage of patients with at least on event of arthralgia within pre-defined intervals (0-3, 3-6, 6-9, 9-12 and 12+ months after the start of anastrozole treatment) will be calculated.

Characteristics of arthralgias within each time interval will be evaluated descriptively stratified by upfront and switch therapy:

- Maximum intensity, localization, relationship to study drug, diagnostics and arthralgia management presenting number and percentage of each category.

- Time between start of anastrozole therapy and first incidence of arthralgia will be analysed using the Kaplan-Meier method.

Maximum duration of arthralgias will be evaluated descriptively, presenting standard statistics.

Retrospective assessment of incidence of pre-existing arthralgias before start of anastrozole treatment, stratified by upfront and switch therapy.

The absolute and percentage number of patients with pre-existing arthralgias will be calculated stratified by upfront and switch therapy.

Descriptive assessment of arthralgia therapy and of costs of arthralgia therapy, stratified by upfront and switch therapy.

Evaluation will be performed descriptively with standard statistics and associated with cost modules of sick funds.

The assessment of compliance and of arthralgia therapy will be compared to and validated by the corresponding data obtained by the sick funds of the patients.[2]

For the subgroup of patients who consented to the data transfer of her sick funds data related to compliance and arthralgia therapy will be analyzed for correlation to the transferred data and described descriptively with standard statistics.

Assessment of subjective perception of side-effects by the patients, stratified by upfront and switch therapy.

Scores of GASE-P and SASS will be evaluated by presenting number and percentage of each category stratified by upfront and switch therapy. Groups will be compared using chi-square test.

Identification of factors influencing and correlating to treatment-emergent arthralgias, such as patient`s characteristics (e.g. age, BMI), disease characteristics, duration of anastrozole treatment, subjective perception of side-effects by the patients etc.

Patient characteristics, disease characteristics and duration of anastozole treatment will be described descriptively stratified by the occurrence of treatment-emergent arthralgias. A possible influence will be analyzed using logistic regression.

Identification of factors influencing and correlating to patients` compliance; for example patient's 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.

Evaluation will be performed in the same way as described for the previous criterion.

Compare 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 between start of anastrozole therapy and progression of disease will be analysed using the Kaplan-Meier method comparing patients with arthralgias to patients without arthralgias and upfront therapy to switch therapy.

Assessment of safety and tolerability of anastrozole.

The safety analysis will be descriptive and comprise all documented adverse events.

The ITT analysis set will be used for the primary analysis of compliance and arthralgia scores. The safety population(s) will be the basis for the analysis of costs and safety analyses and for a secondary analysis of arthralgia scores. Additionally, all women who completed this NIS and who were compliant according to the criteria defined in the protocol for the total duration of 12 months of anastrozole treatment will be analysed separately with regard to the arthragia characteristics (VAS score, incidence, intensity etc), side-effect management, related costs, perception of side effects etc.

[1] The start of the adjuvant treatment with anastrozole is defined by the date of the first tablet intake. If this date is not assessible, the date of the first prescription of anastrozole can be used instead.

[2] This is only applicable to patients who consented to data transfer and who are insured by sick funds who joined the respective contract. Data transferred from the sick funds will include breast-cancer related costs from 12 months before study start up to the end of the study for the respective patient.

11.4.2 Adverse events

All adverse events (AE) as documented by the physician(s) on the AE eCRF or on the SAE eCRF will be taken into account in the AE analysis. Information from other eCRF pages will be screened for possible AEs. However, events and symptoms which are related to a worsening of the underlying disease to be treated with anastrozole, will not be considered as (S)AEs in the statistical analysis.

Due to the different level of information related to the events, the AE analysis will be performed in two different ways:

- taking only adverse events from the corresponding AE and/or SAE section into account,
- taking adverse events from the AE and/or SAE section but also the additional events from other sections of the eCRF.

However, for all adverse events not documented in the AE and/or SAE section, no additional information (e.g. intensity, causality, etc.) as requested on the AE eCRF will be available.

General principles:

Only adverse events with a date/time of onset later or equal to the start date of the anastrozole therapy (or, if not exactly known, the date of 1st prescription of anastrozole) will be taken into account in the AE analysis. All AEs with a date/time of onset before this start date or with missing information on date/time of onset will be listed but not taken into account in the AE analysis.

To ensure consistency of AE and SAE data, a so-called reconciliation between adverse event information in the study data base and information in the Drug Safety data base of the sponsor will be performed before the start of the AE analysis.

All AEs as described by the participating physician(s) will be coded using the lowest level terms (LLT) from the latest installed version of the MedDRA Dictionary (V. 11.1 or higher).

For any AE as described by the physician(s) the lowest level term will be chosen that best matches or approximates the physician's actual description. These lowest level terms will be translated into more general terms [so-called preferred terms (PT)], which will be classified into a system organ class (SOC). This system organ class will be the primary system organ class as given in the MedDRA dictionary.

If a patient has experienced more than one AE and at least one of the AEs is considered by the physician as being related to the anastrozole therapy, the patient will be counted as having had a drug-related AE. The same AE (i.e., the same preferred term) reported more than once for a single patient will be counted as one AE. If an AE occurs more than once for a single patient, the AE with the highest reported causality ranking to anastrozole (worst case) will be used in the AE analysis.

An overview table will be presented with the number (and percentage) of patients with at least one AE, with at least one SAE, with AEs leading to treatment discontinuation, with drug-related AEs as well as the number of patients who died during the NIS.

Serious adverse events:

Patients with serious adverse events (SAEs) will be listed and the following variables will be included: SAE description (as reported by the physician), MedDRA ‘preferred term’, MedDRA ‘primary system organ class’, start/stop dates, start/stop days relative to the first day of administration of anastrozole, relationship to anastrozole according to the physician and outcome.

Incidence of adverse events:

The number (%) of patients with at least one AE will be presented in a number of frequency tables:

- by MedDRA primary system organ class,
- by MedDRA primary system organ class and per MedDRA 'preferred term' within the various MedDRA primary system organ classes.

11.5 Justification of sample size

Based on previous data, it can be assumed that a patients´ compliance will decrease to approximately 50% during the first year of antihormone therapy, a difference in patients` compliance of 6% will be judged clinically relevant. In order to recognize a statistically significant difference of 6% between two groups or between different time points 1119 patients are required per group or time point.

In the following table the sample size which is needed to detect a difference of 6% is presented with the corresponding odds ratios starting with an event rate of 44% for a standard group.

Two group continuity corrected chi-square test of equal proportions (odds ratio = 1) (equal n's, 2-sided test, α= 0.05, Power = 80%)

Group 1 proportion, π_1		I
0,44	**Proportion, π_2**	0,5
	Odds ratio, $\psi = \pi_2 (1 - \pi_1) / [\pi_1 (1 - \pi_2)]$	1,273
	n per group	1119

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In a newly performed study a mean arthralgia score of 4 was found with a standard deviation of 1.86. Assuming a standard deviation (sd) of 2 and a difference of 10% between 2 groups a sample size of 394 in each group will have 80% power to detect a difference in means of -0,4 (the difference between a Group 1 mean, μ_1, of 4 and a Group 2 mean, μ_2 of 4,4) assuming that the common standard deviation is 2 using a two group t-test with a 0,050 two-sided significance level.

In the following table the sample size which is needed to detect a difference of 10% in the arthralgia score is shown for the t-test.

Comparison of equal means (2-sided test, α= 0.05, Power = 80%)

	t-test
Group 1 mean, μ_1	4,000
Group 2 mean, μ_2	4,400
Difference in means, $\mu_1 - \mu_2$	-0,400
Common standard deviation, σ	2,000
Effect size, $\delta = \lvert \mu_1 - \mu_2 \rvert / \sigma$	0,200
n per group	394

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Based on previous non-interventional trials, approximately 25 to 40% of the patient documentation will not be accessible. Therefore, assuming a drop-out rate of 30%, 3212 patients will be enrolled to ensure a sufficient number of evaluable patients.

12. ETHICS

12.1 Ethics review

The observation plan, the final version of the Informed Consent Form and all written information material for patients must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate. The sponsor will notify other Ethics Committees, which are responsible for the participating centres, about this NIS and will provide a copy of the master EC approval.

The sponsor is responsible for informing the Ethics Committee of any amendments in the observation plan, the Informed Consent Form or the written information material for patients in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the program.

12.2 Patient data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their NIS data by the investigator and by those persons who need that information for the purposes of the NIS. Pursuant to this wording , patients will agree to the collection and use of their names and addresses for the duration of this NIS.

The Informed Consent Form will explain that NIS data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by or AstraZeneca will be identified by randomisation number. It will also be explained that will keep a copy of the signed Informed Consent Form and will store patient names and addresses in a computer database until the end of this NIS, and

that the sponsor will not have access to these data and that copies will be destructed and electronic data will deleted at the end of this NIS (for further details see Section 7.3 and 10.1).

13. ARCHIVING

After completion of this NIS all collected and anonymous data (patient questionnaires and database set) will be handed over by to AstraZeneca. AstraZeneca is responsible for archiving the data according to local legal requirements and AstraZeneca SOPs.

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