Revised Clinical Study Protocol

Drug Substance Anastrozole

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A prospective randomised, open, multicentre, phase III study to assess different Durations of Anastrozole therapy after 2 to 3 years Tamoxifen as Adjuvant therapy in postmenopausal women with breast cancer.

Sponsor: Maastricht UMC+, P.O. Box 5800 AZ Maastricht, The Netherlands

The study is accepted as a BOOG study under number 2006-01. BOOG, P.O. Box 9236, 1006 AE Amsterdam, The Netherlands

The following Amendment(s) and Administrative Changes are included in this revised protocol:

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1	23 January 2007		
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A prospective randomised, open, multicentre, phase III study to assess different Durations of Anastrozole therapy after 2 to 3 years Tamoxifen as Adjuvant therapy in postmenopausal women with breast cancer.

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PROTOCOL SYNOPSIS

Objectives

Primary objective:

To assess the disease free survival (DFS) with 6 years of adjuvant anastrozole compared with the current standard treatment of 3 years of adjuvant anastrozole in postmenopausal hormone sensitive breast cancer patients, subsequent to 2 to 3 years of adjuvant tamoxifen treatment.

Secondary objectives:

Secondary objectives of the study are:

1. To compare the incidence of contralateral breast cancer after 6 years versus 3 years adjuvant anastrozole, subsequent to 2 to 3 years of tamoxifen.

2. To compare overall survival (OS) in patients treated with 6 years versus 3 years of adjuvant anastrozole, subsequent to 2 to 3 years of tamoxifen.

3. To compare toxicity of 6 years versus 3 years of adjuvant anastrozole in postmenopausal hormone sensitive breast cancer patients, subsequent to 2 to 3 years of tamoxifen.

4. To determine regional differences in the initial treatment of breast cancer retrospectively by collecting baseline information on initial therapies. Aspects of the initial treatment that will be investigated are e.g. the kind of surgery performed (breast saving or mastectomy) and whether or not chemotherapy is given and which chemotherapy was used in postmenopausal patients in relation to the primary tumour and patient characteristics.

5. To compare the cost effectiveness of 3 years versus 6 years of adjuvant anastrozole therapy, after subsequent 2 to 3 years of adjuvant tamoxifen treatment.

6. To assess patterns of care in The Netherlands in prevention, detection and treatment of osteoporosis in postmenopausal women with breast cancer treated with adjuvant anastrozole.

- To assess differences in management of bone health (DEXA scans, vitamin D / Calcium, bisphosphonates) in postmenopausal women with breast cancer treated with adjuvant anastrozole, between medical oncologists, surgeons, radiotherapists and nurse practitioners.

- To assess loco regional differences in the Netherlands in management of bone health in postmenopausal women with breast cancer treated with adjuvant anastrozole.

- To assess rate of compliance to Dutch guidelines on prevention, detection and treatment of osteopenia and osteoporosis in postmenopausal women with breast cancer throughout the period of treatment with adjuvant anastrozole and over time with new breast cancer guidelines.

- To relate the number of osteoporotic fractures during and following treatment with adjuvant anastrozole with the compliance to osteoporotic guidelines.

- To analyse the impact of prolonged anastrozole treatment on BMD and to analyse the impact of short versus prolonged treatment (6 versus 3 years anastrozole) on pattern of care.

- To analyse occurrence of distant (bone) metastases in relation to occurrence of osteopenia and osteoporosis, and in relation to use of supplements and therapy for reduced BMD.

Study design

A prospective, randomised, open, multicentre, phase III study, comparing 3 years versus 6 years of adjuvant anastrozole. This could lead to patients receiving either a total of 5 to 6 years adjuvant therapy or a total of 8 to 9 years adjuvant therapy, including the 2 to 3 years adjuvant tamoxifen.

Statistical methods

This study will be conducted in approximately 1900 subjects, recruited in The Netherlands. Because after randomisation all subjects receive the same therapy for 3 years, differences between both treatment groups will appear starting 3 years after randomisation. At that time, in both groups 91% of all subjects are expected to be disease-free (Coombes R.C. et al 2004). It is assumed that 3 years later this rate has decreased to 80% in the control group, implying a 3-years adapted DFS (see section 6.2) rate of 90% for that period. This study is designed to detect an increase to 94% of this 3-years DFS in the anastrozole group, corresponding with a hazard ratio of 0.60. Originally, we designed the trial with a statistical power of 80 percent and a two-sided alpha level of 0.04 (correcting for one interim analysis), requiring 770 disease-free subjects in the treatment/control group of the trial, implying 850 assessable subjects to be randomised. Accounting for approximately 10% drop-out, 950 subjects per group were decided to be included in this study. Kaplan-Meier survival curves will be used for the graphical representation of the therapy's effect on parameters of primary and secondary survival objectives (DFS and OS). Differences between the two treatment groups will be tested with the log-rank test (for DFS and OS) combined over the non-empty strata and logistic regression (for occurrence of contra lateral breast cancer) adjusted for the stratification factors. Hazard ratios and corresponding 95% confidence intervals (CIs) will be estimated with the Cox proportional-hazard model adjusted for stratification factors. We will not perform an interim analysis of DFS and OS for the ITT population, as we do not expect a relevant difference at this early time point because of the recent results from ATLAS and aTTOM trials. Therefore, the final analysis will be evaluated at a significance level of 0.05, increasing the power to 82 percent.

For monitoring the quality of the study, an interim report will be made. A DSMB will evaluate this report according to instructions provided in the DSMB charter.

Target subject population

Postmenopausal female patients with hormone receptor positive breast cancer who have already received 2 to 3 years of adjuvant tamoxifen, and who never had signs of loco-regional recurrences or distant metastasis. Chemotherapy and/or radiotherapy before or after local surgical treatment is allowed.

Study period

Estimated date of first subject enrolled: March 2006

Estimated date of last subject completed: 31 December 2013

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.3.1.1)
ADFS	Adapted Disease Free Survival
AOS	Adapted Overall Survival
CRF	Case Report Form
CSA	Clinical Study Agreement
DFS	Disease Free Survival
ECG	Electrocardiogram
ER	Estrogen Receptor
GCP	Good Clinical Practice
HR	Hazard Rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
N	Node
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.3.1.1).
OS	Overall Survival
PgR	Progesteron Receptor
RFS	Relapse Free Survival
SAE	Serious adverse event (see definition in Section 4.3.1.1).
SDV	Source Data Verification

1. INTRODUCTION

1.1 Background

In the western world breast cancer is the most common malignancy in women. In the Netherlands annually approximately 12.000 women are diagnosed with breast cancer and each woman has a chance of more than 10% to develop breast cancer in her life.

In early detected disease lesions, the chance of loco-regional cure is high. However, microscopic disease may already have spread before loco-regional therapy was applied. If this microscopic disease remains untreated, it could develop into a life-threatening clinical recurrence. Although the risk of recurrence is greatest during the first years after diagnosis, it is still substantial in the following decade (EBCTCG 2005).

During the last decade the prognosis for women with breast cancer has improved due to implementation of systemic treatment. The dependence of 60% to 70% of breast cancers on estrogens for their continued growth has long been recognised. Several systemic therapies have been developed to deprive the breast cancer of this stimulus. Drug therapy can achieve this goal either by reducing circulating concentration of estrogens with an aromatase inhibitor and/or ovarian ablation, or by antagonising the effects of estrogens on the tumour with an anti-estrogen.

For many years the standard endocrine adjuvant treatment for breast cancer in postmenopausal women with a hormone receptor positive tumour was 5 years treatment with the anti-estrogen tamoxifen. Due to recently published study results concerning 7 adjuvant studies, all comparing the standard adjuvant treatment of 5 years tamoxifen with a regime consisting of an aromatase inhibitor, the standard adjuvant treatment has changed to include an aromatase inhibitor (mammacarcinoom richtlijn 2005, Winer E.P et al 2005, Köberle D. and Thürlimann B. 2005). Two major studies compare 5 years of adjuvant tamoxifen with 5 years adjuvant aromatase inhibitor. In the ATAC study, with a follow-up of 68 months, anastrozole gives a relapse free survival hazard rate (RFS HR) of 0.74 compared with tamoxifen for receptor-positive patients (Howell A. et al 2004). The BIG1-98 study, comparing tamoxifen and letrozole with a median follow-up of 26 months, confirms these results showing a RFS HR of 0.72 (Thürlimann B. et al 2005). Three studies show that switching to an aromatase inhibitor after 2 to 3 years tamoxifen, for a total adjuvant treatment of 5 years, gives a better RFS HR, ranges from 0.70 (Coombes R.C. NEJM 2004), to 0.60 and 0.42 (Jakesz R. et al 2005, Boccardo F. et al 2005), then 5 years tamoxifen. There are two studies showing that switching patients to an aromatase inhibitor after 5 years of adjuvant tamoxifen gives a RFS HR advantage of 0.57 and 0.64 (Goss P. et al 2004, Jakesz R. et al 2005 6a).

The Dutch EBRO guideline version 3.0 regarding breast cancer (mammacarcinoom richtlijn 2005) advises switch to an aromatase inhibitor after 2 to 3 years of adjuvant tamoxifen in patients who already use tamoxifen, for a total duration of 5 years endocrine treatment. For newly diagnosed patients, sequential therapy with tamoxifen followed by an aromatase-

inhibitor is advised for hormone receptor positive Her2neu receptor negative breast cancer, whereas upfront aromatase inhibitors is recommended for hormone receptor positive Her2neu positive breast cancer. Of note, the evidence for using these selection criteria for the first (sequential) versus the second (upfront) strategy should be considered as circumstantial.

1.2 Rationale for this study

The standard endocrine adjuvant treatment is given for a duration of 5 years. However, data from the Oxford Overview (EBCTCG 2005) shows that there are as many recurrences during years 6 through 15 after primary surgery as between years 1 through 5 in women treated with tamoxifen versus controls. The risk of recurrence of breast cancer beyond 5 years is approximately 4% per year for women with node positive disease at the time of primary surgery and approximately 2% per year for women with node negative disease. Therefore it is important to undertake trials with additional randomisations beyond 5 years of endocrine treatment because past experience would suggest that these women will remain at a relatively high risk of recurrence (Pritchard KI 2005).

Previously extended adjuvant treatment beyond 5 years of tamoxifen has been studied. In a trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP-B14), patients that already received 5 years of tamoxifen were randomised to receive an additional 5 years of either placebo or tamoxifen. Unexpectedly, women who continued to receive tamoxifen therapy after 5 years had worse outcomes when compared to women in whom it was discontinued at 5 years (Fisher B et al 2001). Based on these data, it was worldwide recommended at that time to limit the use of adjuvant tamoxifen treatment to 5 years.

Emergence of tamoxifen resistance is one of the proposed causes of this detrimental outcome. However, extended adjuvant treatment may still be beneficial in case resistance could be avoided, for instance by sequentially using a non-cross resistant alternative endocrine treatment. Aromatase inhibitors have demonstrated efficacy after tamoxifen resistance (Buzdar A.U. et al 1998, Robertson J.F.R. et al 2003) and are therefore candidates to be investigated in the setting of prolonged adjuvant endocrine therapy for hormone sensitive breast cancer. Two studies recently demonstrated that an extended treatment with an aromatase inhibitor for 2 or 3 more years, after 5 years of adjuvant treatment with tamoxifen, leads to an improved DFS (Goss P. et al 2004, Jakesz R. et al 2005 6a).

According to the ASCO Technology Assessment Panel neither the optimal timing nor duration of aromatase inhibitor therapy is established (Winer E.P et al 2005). There are no studies investigating extended adjuvant therapy after 5 years, in patients that were switched to an aromatase inhibitor after prior tamoxifen treatment. It is currently unknown what the optimal length of aromatase inhibitor therapy is after 2 to 3 years of adjuvant tamoxifen therapy in postmenopausal hormone sensitive breast cancer patients.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to assess the DFS with 6 years of adjuvant anastrozole compared with the current standard treatment of 3 years of adjuvant anastrozole in postmenopausal hormone sensitive breast cancer patients, subsequent to 2 to 3 years of adjuvant tamoxifen treatment.

2.2 Secondary objectives

The secondary objectives of the study are:

1. To compare the incidence of contralateral breast cancer after 6 years versus 3 years adjuvant anastrozole, subsequent to 2 to 3 years of tamoxifen,

2. To compare the overall survival (OS) in patients treated with 6 years versus 3 years of adjuvant anastrozole, subsequent to 2 to 3 years of tamoxifen.

3. To compare toxicity of 6 years versus 3 years of adjuvant anastrozole in postmenopausal hormone sensitive breast cancer patients, subsequent to 2 to 3 years of tamoxifen.

4. To determine regional differences in the initial treatment of breast cancer retrospectively by collecting baseline information on initial therapies. Aspects of the initial treatment that will be investigated are e.g. the kind of surgery performed (breast saving or mastectomy) and whether or not chemotherapy is given and which chemotherapy was used in postmenopausal patients in relation to the primary tumour and patient characteristics.

5. To compare the cost effectiveness of 3 years versus 6 years adjuvant anastrozole therapy, after subsequent 2 to 3 years of adjuvant tamoxifen treatment.

6. To assess patterns of care in The Netherlands in prevention, detection and treatment of osteoporosis in postmenopausal women with breast cancer treated with adjuvant anastrozole.

- To assess differences in management of bone health (DEXA scans, vitamin D / Calcium, bisphosphonates) in postmenopausal women with breast cancer treated with adjuvant anastrozole, between medical oncologists, surgeons, radiotherapists and nurse practitioners.

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- To relate the number of osteoporotic fractures during and following treatment with adjuvant anastrozole with the compliance to osteoporotic guidelines.

- To analyse the impact of prolonged anastrozole treatment on BMD and to analyse the impact of short versus prolonged treatment (6 versus 3 years anastrozole) on pattern of care.

- To analyse occurrence of distant (bone) metastases in relation to occurrence of osteopenia and osteoporosis, and in relation to use of supplements and therapy for reduced BMD.

3. STUDY PLAN AND PROCEDURES

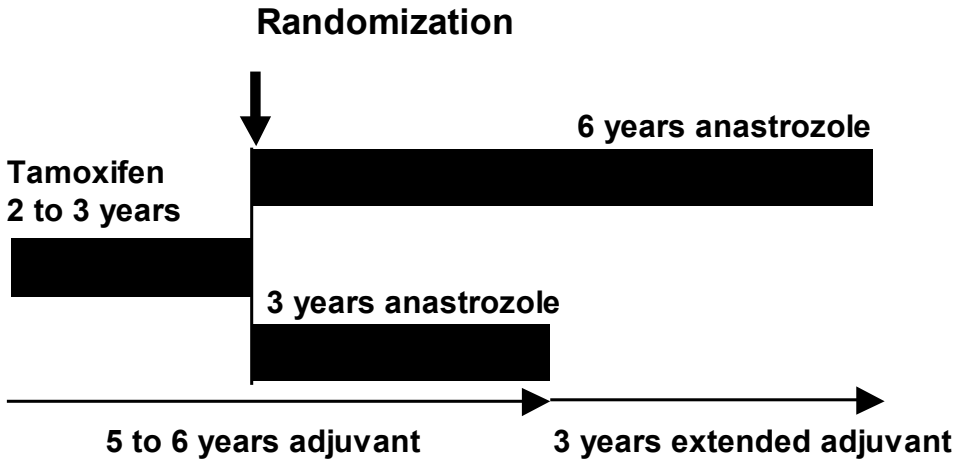
3.1 Overall study design and flow chart

This study is a prospective, randomised, open, parallel-group, multicentre, phase III study.

Patients are randomised between two arms:

A. Anastrozole 3 years, after 2 to 3 years adjuvant tamoxifen

B. Anastrozole 6 years, after 2 to 3 years adjuvant tamoxifen



Patients will be stratified for the following tumour characteristics:

- ER+PgR- versus ER+PgR+ versus ER-PgR+

- N+ versus N-

- Her2neu over expression versus no Her2neu over expression versus unknown Her2neu expression

- Duration of adjuvant tamoxifen (2.0 to 2.5 years versus 2.5 to 3.0 years) treatment

This study will be conducted in 1900 postmenopausal women in The Netherlands.

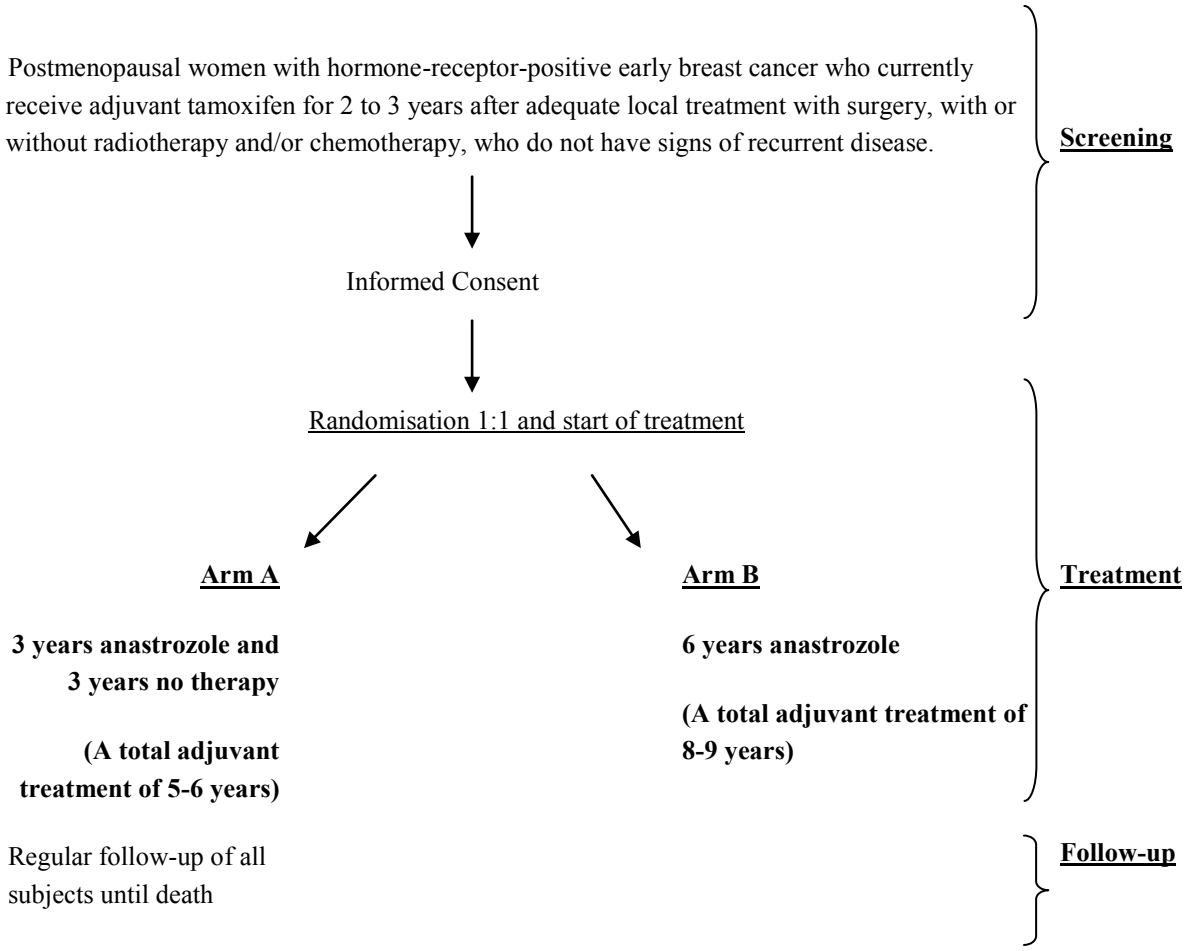
Postmenopausal female patients with hormone receptor positive breast cancer who have already received 2 to 3 years adjuvant tamoxifen, and who never had signs of loco-regional recurrence or distant metastasis. Chemotherapy and/or radiotherapy before or after local surgical treatment is allowed.

After randomisation and initiation of the patient in the study, the first two visits will be scheduled after 3 and 6 months. During the treatment period of 3 years anastrozole followed by three years nothing or 6 years anastrozole, patients are visiting the investigator every 6 months. Treatment discontinuation can be due to disease recurrence or death or patient unwillingness to continue to participate in the study. After the treatment period patients are followed for survival and disease recurrence once a year.

At each visit complaints will be recorded and a physical examination will be performed. A yearly X-mammography is performed. Furthermore, blood chemistry and haematology may be assessed according to local policy.

Additional secondary endpoints will be investigated in separate side-studies. Details of the side studies are described in the sub-protocols. Centres and investigators can decide to participate only in the main protocol or in the main protocol and in one or more of the side studies. Subjects participating in these side studies will be asked to give additional informed consent for each side study.

Figure 1 Study flow chart



3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

The control arm in this study (arm A) is in accordance with the Dutch EBRO multidisciplinary guidelines "Treatment of breast cancer" revised version 3.0 2005 (mammacarcinoom richtlijn 2005).

The dose regime of anastrozole is 1 mg oral a day. This dose is registered for the adjuvant treatment of hormone receptor positive breast cancer (IB1 text).

3.2.2 Risk/benefit and ethical assessment

According to the IB1 text anastrozole is not indicated for pre-menopausal breast cancer patients. In a recent publication by Smith et al. (2006) it is described that in a group of 45 women with chemotherapy-induced amenorrhoea, 12 women had a return of their ovarian function after using an aromatase inhibitor (AI). As a consequence, it is recommended to monitor more closely the ovarian function of patients with no amenorrhoea or bilateral oophorectomy who have been prescribed an AI. Anastrozole has not been investigated in patients with severe renal or hepatic impairment.

Drugs that lower the oestrogen blood levels, like anastrozole, can negatively influence the bone mineral density. The EBRO guidelines version 3.0 (mammacarcinoom richtlijn 2005) have included a section concerning osteoporosis prevention for therapy-induced osteoporosis. For postmenopausal women using aromatase inhibitors the following advice is given: Calcium intake (>1000 mg per day), sufficient physical exercise and adequate vitamin D status. To monitor osteoporosis for these high risk patients a baseline bone mineral density measurement can be performed. For treatment the investigator is also referred to these guidelines.

3.3 Selection of study population

3.3.1 Inclusion criteria

For inclusion in the study subjects must fulfil all of the following criteria:

1. Obtained written informed consent before entering the study

2. Histologically proven operable invasive breast cancer at the time of breast cancer diagnosis

3. Positive estrogen- and/or progesterone-receptor status (≥10% positive cells)

4. Postmenopausal at the time of randomization, according to one or more of the following:

    - aged 55 or more and natural amenorrhoea;
    - bilateral oophorectomy, irrespective of age;

- Aged 45-54 years and FSH and 17 beta oestradiol values within the postmenopausal range confirmed by local laboratory values within the last three months (including: patients who have had a hysterectomy).

5. No distant metastasis at the time of randomisation

6. No recurrences after the primary diagnosis and treatment of breast cancer

7. Patients currently using adjuvant tamoxifen for a duration of 2 to 3 years after surgery of the primary breast tumour

8. Prior (neo)adjuvant radiotherapy and/or chemotherapy is allowed

3.3.2 Exclusion criteria

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

1. Patients who have received previous hormonal therapy as adjuvant breast cancer treatment besides tamoxifen

2. Previous history of invasive breast cancer within the last 10 years, other then the breast cancer that is currently treated with adjuvant tamoxifen and diagnosed 2 to 3 years ago

3. Other invasive malignancy within the last 5 years, other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied.

4. Treatment with a non-approved or experimental drug during the 3 months before informed consent.

5. Performance status: Karnofski score 60% or less

6. Patients who, for whatever reason (e.g. confusion, infirmity, alcoholism), are unlikely to comply with trial requirements

7. Patients unwilling to stop taking any drug known to affect sex hormonal status (including HRT), or in whom it would be inappropriate to stop

8. Patients known to have one of the following hereditary illnesses; galactose-intolerance, Lapp lactase deficiency or glucose-galactose malabsorption

3.4 Treatments

3.4.1 Identity of investigational product and comparators

In this open label study commercially available Arimidex will be used. Each tablet of Arimidex contains 1 mg of anastrozole.

3.4.2 Doses and treatment regimens

One tablet (1 mg) has to be taken orally once a day. Subjects should be instructed to take their daily dose at approximately the same time each day. The patients will take anastrozole for 3 years or 6 years unless the patients receive a treatment end-point. No modification of the dose will be allowed. Temporary discontinuation (< 4 weeks) due to adverse events however is allowed.

3.4.3 Labelling

Commercially available Arimidex will be used and these treatment packs are marked according to the national requirements.

3.4.4 Storage

Arimidex must be kept in the original package and should not be stored above 30^{o}C.

3.5 Randomisation procedure

A total of 1900 patients will be entered in the study. After having properly checked all eligibility criteria, stratification parameters and having obtained patient's written informed consent, patients will be randomised by fax at the IKO trial office in Nijmegen (fax 024-3619080). Randomisation will be performed 1:1 for 3 years vs 6 years Anastrozole. Randomised treatment will be confirmed by fax or email within one (1) working day.

3.5.1 Method for assigning patients to treatment groups

Patients will be randomized based on stratification for the following tumour characteristics:

- ER+PgR- vs ER+PgR+ vs ER-PgR+
- N+ vs N-
- Her2neu over expression vs no Her2neu over expression vs unknown Her2neu expression
- Duration of Tamoxifen (2.0 to 2,5 years vs 2,5 to 3.0 years).

3.6 Blinding and procedures for unblinding the study

Not applicable

3.7 Pre-study, concomitant and post-study treatment(s)

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication that is given for treatment of a SAE or defined AE or for treatment of breast cancer (including investigational products) must be recorded in the appropriate sections of the case report form (CRF). Post-study medication (during the follow-up period) for the indication breast cancer is registered during the whole follow-up period.

3.8 Treatment compliance

Subject's compliance to treatment schedule should be monitored by the investigator by asking the patient every visit if trial therapy has been interrupted. This must be recorded in the patient files and the CRF.

3.9 Discontinuation of subjects from treatment or assessment

3.9.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or responsible physician
- Severe adverse events
- Incorrect enrolment (ie, the subject does not meet the required inclusion/exclusion criteria) of the subject
- Subject lost to follow-up

3.9.1.1 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). The reason for discontinuation should be recorded in the CRF. Adverse events should be followed up if possible. At the time of discontinuation of anastrozole therapy every attempt should be made to get information about the disease status of the patient to be able to determine the efficacy of the received treatment.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Screening and demographic measurements

The following information is collected at entry (screenings visit), within 4 weeks before randomisation and start of trial therapy, and recorded in the CRFs:

(a) Demography

Date of birth will be recorded.

(b) Medical history

Any relevant past medical history (including details of all previous bone fractures, cardiovascular disease and any lipid related disorders, e.g. hyperlipidaemia), any concurrent illness, familial history of osteoporosis, DEXA scans down to 1 year before randomisation and up to 7 years after randomisation and whether the subject has had a hysterectomy, smoking history or had previous HRT are recorded at entry. The Karnofski score is registered at entry.

(c) Concomitant medication

Concomitant medication/treatments are recorded at entry (cardiovascular, bisphosphonates, calcium supplements, vitamin D supplements, corticosteroids, etc). Concomitant medication/treatments concerning bisphosphonates, calcium supplements, vitamin D supplements and corticosteroids will be recorded down to 1 year before randomisation independent to whether they were stopped or were ongoing at the time of randomisation. Any changes in medication, medication present at entry or during study treatment prescribed for treatment of SAE or predefined AE are recorded until the subject stops study treatment. After stop of study treatment only new medication for treatment of breast cancer is recorded. Nevertheless, concomitant medication/treatments concerning bisphosphonates, calcium supplements, vitamin D supplements and corticosteroids will be recorded up to 7 years after randomisation to the study.

(d) Physical examination

Height and weight is measured at entry.

(e) Breast cancer history

Primary tumour size, ER and PgR status, Her2neu status, nodal status, histological grade, lymph vascular invasion if available, primary surgery procedure and date of surgery, radiation (date of start) if applicable, chemotherapy (date of start and regimen) if applicable, date of diagnosis and start date of tamoxifen are recorded at entry.

Retrospective histologic assessment, using paraffin blocks, of ER status, PgR status and other parameters may be carried out, in case of missing information.

Date of last X-mammography, must be performed within a year before screening, and outcome of the X-mammogram are recorded at entry.

(e) Haematology and biochemistry

The following routine laboratory assessments must be performed within three months before entry and repeated at visit 4, after 3 years and after 6 years:

- Haematology (Hb, WBC, platelets)
- Creatinine
- Calcium
- Alkaline phosphatase
- ALAT, ASAT
- LDL cholesterol
- HDL cholesterol
- Triglyceride

Patients between 45 and 54 with intact ovaries must have FSH and 17 beta oestradiol determined, and values within postmenopausal ranges, within three months before entering and during the study. These measurements must be repeated for this group of patients at visit 4 to 8.

These assessments are performed and analysed locally.

4.2 Primary variable

The primary outcome variable of this study is the DFS. This variable was used as the basis for the sample size calculation as described in section 6.

4.2.1 Disease Free Survival

Patients will be reviewed for recurrence of breast cancer at all visits during treatment and follow-up by history and physical examination. An X-mammography will be done once a year during treatment and follow-up, according to the Dutch EBRO guidelines.

For recurrence the following criteria, which are based on British Breast Group recommendations, are used:

SITE OF RECURRENCE	METHOD OF CONFIRMATION
LOCO-REGIONAL	
1. Ipsilateral breast (including DCIS)[1]	Histology or cytology
2. Chest wall	Histology or cytology
3. Axillary lymph nodes	Histology or cytology
4. Other regional nodes (supraclavicular and internal mammary)	Histology or cytology
DISTANT	
5. Skeletal	CT[2] scan, or bone scan with confirmatory x-ray evaluation of hot spots. Biopsy may be necessary in the case of a single lesion.
6. Pulmonary	Chest x-ray, CT-scan, and preferably histology or cytology in case of a single lesion
7. Hepatic	CT scan or ultrasound, and preferably histology or cytology in case of a single lesion
8. Other distant	Imaging and/or biopsy. (Rising tumour markers alone , eg CA15.3, are unacceptable)

[1] Ductal Carcinoma In Situ [2] Computed Tomography

The site and date of confirmed first loco-regional and first distant recurrence will be recorded in the CRF. After loco-regional and distant recurrence patient will be in follow-up for survival only.

After second primaries patient who is treated with curative intent should be treated according to study. After second primaries patient who is treated with palliative intent will be in follow-up for survival only.

New breast primaries (either contralateral or ipsilateral) will be regarded as disease recurrence events in the statistical analysis of DFS, as will intercurrent deaths without recurrence.

4.2.2 Overall survival

All patients are followed for survival until death or end of the study. When a subject has died, the date of death and the reason are registered.

4.3 Safety measurements and variables

The methods for collecting safety data are described below.

4.3.1 Adverse events

4.3.1.1 Definitions

The definitions of adverse events (AEs), other significant adverse events (OAEs) and serious adverse events (SAEs) and are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The local investigator is responsible for ensuring this.

Adverse event

An adverse event 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). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

In this study the following AE's must be registered in the CRF:

- AEs leading to discontinuation of study medication
- AEs concerning osteoporosis
- AEs concerning fractures
- AEs concerning arthralgia
- AEs concerning cardiovascular events

Other Significant Adverse Events (OAE) will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those Aes leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than

those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, and washout, follow-up), and at any dose of the investigational product, comparator or placebo, 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 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.

4.3.1.2 Recording of adverse events

AEs and all SAEs, as described in section 4.3.1.1, occurring from informed consent, and up to 30 days after end of study, should be recorded. Thus SAEs need to be reported during the total duration fo the study – 6 years – for both treatment arms.

The following definitions are used to assign intensity:

- 1- mild (awareness of sign or symptom, but easily tolerated)
- 2- moderate (discomfort sufficient to cause interference with normal activities)
- 3- severe (incapacitating, with inability to perform normal activities)
- 4- life-threatening

It is important to distinguish between serious and severe Aes. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.3.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.2, Procedures in case of overdose, regardless of whether the

overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as Aes.

The causality of (S)Aes

The causality of (S)AE's (ie, their relationship to study treatment) will be assessed by the investigator(s). The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in

cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Any conditions or hospitalisations that are unequivocally due to recurrence of breast cancer must not be recorded as an AE or SAE.

4.3.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that become serious but which is not fatal or life-threatening a report should be received within 5 days.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). AstraZeneca is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

4.3.2 Laboratory safety measurements and variables

4.3.2.1 Methods of assessment

No laboratory safety measures are scheduled. Additional laboratory safety measurements are made at the investigators discretion.

4.3.3 Vital signs, ECG and physical examination

Not applicable

Table 1 Visit schedule

Visit	**1**	**2**	**3**	**4**	**5 to 15**	**16 etc..**
Visit Description	Screening	Randomisation, Start Treatment	Treatment	Treatment	First 6 years after randomization, both arms	Follow-up, starting 6 years after randomization
Visit Window		**0-28 days After V 1**	**at 3 months**	**at 6 months**	**Every 6 month**	**Every year**
Informed consent	X					
Medical history	X					
In-/exclusion criteria	X					
Tumour characteristics	X					
Physical examination, weight	X		X	X	X	
Clinical chemistry and haematology, Hb, PLT, WBC, creatinine, calcium, ALAT, ASAT, AF, LDL, HDL and TG	X			X	X (only after 3 years and after 6 years)	
FSH and 17 beta oestradiol**	X			X	X (only at visits 5 to 8)	
Co-medication	X***		X	X	X	X*** (only for indication breast cancer)
Interruption trial medication			X	X	X	
Defined Adverse events			X	X	X	
X-mammography	X				X (once a year, unless distant metastases)	
Recurrence/Survival status					X	X
Fresh frozen blood sample (only when patient participates in side study)	X					
Side study : neuropsychology*	X				X (only after 3 years and after 6 years)	

* a side study, in due time

** Patients between 45 and 54 with intact ovaries must have FSH and 17 beta oestradiol determined, and values within postmenopausal ranges.

***Concomitant medication/treatments concerning bisphosphonates, calcium supplements, vitamin D supplements and corticosteroids will be recorded down to a year before randomisation and up to 7 years after randomisation independent to whether they were stopped or were ongoing at the time of randomisation.

5. DATAMANAGEMENT

The trial office of the IKO will be the Central Data Centre for this trial. The Central Data Centre will be responsible for randomisation of patients, check of receipt of CRF pages and generation of edits/queries. AstraZeneca will be responsible for the initiation of the study in the participating centres and will perform source data verification.

CRF's are used to record data. Data should be recorded legibly onto the CRF's in black or blue ballpoint pen. Correction fluid or covering labels must not be used. At the participating centres the data will be recorded in the CRF's by the data managers working for the local IK's. Any missing, impossible or inconsistent recordings in the CRF's are referred back to the investigator using a data query sheet (DQS), and is documented for each individual subject before clean file status is declared.

The CRF's must be completed and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available. The time between the patient's visit and completion/shipment of CRF pages should be kept to a reasonable minimum. It remains the responsibility of the investigator to verify that original CRF's are completed and filled out correctly.

After completion (within 1 month after the visit) of the CRF's, the pages must be sent by mail to the Central Data Centre. Copies of the CRF pages are kept with the investigator and AstraZeneca (up to the sponsorship transfer). If information is not known, this must be clearly indicated.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before database lock.

All main analyses will be according to the intention to treat principle. The data analysis will be performed by the department of Epidemiology and Biostatistics of the UMCN St Radboud Nijmegen.

6.2 Description of outcome variables in relation to objectives and hypotheses

The primary efficacy variable is an adaptation of the disease-free survival (DFS), where DFS is defined as: the interval between randomisation and occurrence of one of the following events:

- Local recurrence
- Regional recurrence

- Distant recurrence (soft tissue, bone, viscera)
- Occurrence of a secondary breast carcinoma (including contralateral breast cancer)
- Second, nonbreast cancer other than basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix
- Death without prior cancer event

Because after randomisation all patients receive the same therapy for 3 years, differences between both treatment groups are only to be expected starting 3 years after randomisation. Consequently, the parameter to be used in the statistical analyses will be the adapted disease-free survival (ADFS), defined as the DFS, but with starting point the date 3 years after randomisation instead of the randomisation date itself.

Analogously, adapted overall survival (AOS), defined as the OS, is defined as interval between the date 3 years after randomisation and death from any cause.

6.3 Description of analysis sets

The intention to treat (ITT) population comprises all randomised patients excluding ineligible patients. The primary objective and the secondary objectives contralateral breast cancer and OS will be analysed using the ITT population.

6.4 Method of statistical analysis

Demography and baseline data will be listed for each patient and summarised by randomised treatment group.

At randomisation, patients are stratified for nodal status, ER+/PgR- versus ER-/PgR+ versus ER+/PgR+, her2neu status and duration of tamoxifen treatment 2,0 to 2,5 years versus 2,5 to 3,0 years.

Kaplan-Meier survival curves will be used for the graphical representation of the therapy's effect on parameters of primary and secondary survival objectives (ADFS and AOS). Differences between the two treatment groups will be tested with the log-rank test (for ADFS and AOS) combined over the non-empty strata and logistic regression (for occurrence of contralateral breast cancer) adjusted for the stratification factors.

Hazard ratios and corresponding 95% confidence intervals (CIs) will be estimated with the Cox proportional-hazard model adjusted for stratification factors.

6.5 Determination of sample size

Patients included in this study are by good prognosis selected considering the fact that they are still disease-free two to three years after the primary diagnosis of breast cancer. Because after randomisation all patients receive the same therapy for 3 years, differences between both treatment groups will appear starting 3 years after randomisation. At that time, in both groups 91% of all subjects are expected to be disease-free (Coombes R.C. et al 2004). It is assumed

that 3 years later this rate has decreased to 80% in the control group, implying a 3-years ADFS (see section 6.2) rate of 90%.

This study is designed to detect an increase to 94% of the 3-years ADFS in the anastrozole group, corresponding with a hazard ratio of 0.60. With a statistical power of 80 percent and a two-sided alpha level of 0.04 (correcting for one interim analysis), 770 disease-free subjects in each group will have to start the treatment/control part of the trial, implying 850 evaluable subjects to be randomised. Accounting for approximately 10% drop-out, 950 subjects per group will be included in this study. The hazard ratio of 0.60 is based on prior studies using an aromatase inhibitor after shorter or longer treatment with tamoxifen, and compared with no treatment or placebo. Three studies showed that switching to an aromatase inhibitor after 2 to 3 years tamoxifen, for a total adjuvant treatment of 5 years, gave a better RFS HR (ranges from 0.70 (Coombes R.C. et al 2004), to 0.60 and 0.42 (Jakesz R. et al 2005, Boccardo F. et al 2005) then 5 years tamoxifen. There were two studies showing that switching patients to an aromatase inhibitor after 5 years tamoxifen gave a RFS HR advantage with an hazard ratio of 0.57 and 0.64 (Goss P. et al 2004, Jakesz R. et al 2005 6a).
We will not perform an interim analysis of DFS and OS for the ITT population, as we do not expect relevant difference at this early time point because of the recent results from ATLAS and aTTOM trials. Therefore, the final analysis will be evaluated at a significance level of 0.05, increasing the power to 82 percent.

Interim analysis
No interim analysis of ADFS and AOS for the ITT population will be performed. For monitoring the quality of the study an interim report will be made.

Final analysis
Final analyses will be performed after the last patient has reached a minimum follow-up of 6 years after randomisation.

Follow-up analysis
In order to detect long term effect, a follow-up analyses will be performed after the last patient has reached a minimum follow-up of 12 years after randomisation.

6.6 Data and safety monitoring board

An Independent Data Monitoring Committee (IDMC) will be established, which will be independent of the trial organisers, in case of and at the time of the planned and any unplanned interim-analysis for whatever reasons.

For monitoring the quality of the study an interim report will be made. A DSMB will evaluate this report according to instructions provided in the DSMB charter.

7. STUDYMANAGEMENT

7.1 Monitoring

Before inclusion of the first subject into the study, a representative of AstraZeneca will visit the investigational study site to:

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.
- discuss where the identification of the data will be recorded, e.g. medical records, CRF and other associated documents. This is documented in the clinical study agreement.

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs.
- perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre need information and advice.

7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the centre to perform audits or inspections, including source data verification for this study. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and

data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre considering this study.

7.3 Training of staff

The local responsible physician will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Principal Investigator, the Steering Committee and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be notified to or approved by each IRB or IEC, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB or IEC must be notified. Approval of the revised Informed Consent Form by AstraZeneca (up to the sponsorship transfer) and by the IRB or IEC is required before the revised form is used.

AstraZeneca will up to the sponsorship transfer distribute amendments and new versions of the protocol to each local responsible physician, who is in turn responsible for the distribution of these documents to his or her IRB or IEC, and to the staff at his or her centre. Thereafter, it is the responsibility of Maastricht UMC+.

7.5 Study agreements

The responsible physician at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

7.6 Study timetable and end of study

Before a subject's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.

- approval of the study by the IRB/IEC

The first subject is to be recruited by approximately March 2006. Recruitment is expected to be completed by December 2007. The last subject is expected to have completed the study by December 2013.

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

8.3 Informed consent

The principal investigator(s) at each centre will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

When the subject has agreed to participate in one of the sub-protocols an additional informed consent must be obtained.

The principal investigator(s) must store the original, signed Informed Consent Form in the investigator study file. A copy of the signed Informed Consent Form must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Subject data protection

The written Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.3.1.1.**

9.2 Procedures in case of overdose

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRFs as an AE of 'Overdose' unless there are associated symptoms or signs.
- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRFs.
- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRFs. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."
- An overdose without associated symptoms should not be recorded as an AE in the CRFs. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

9.3 Procedures in case of pregnancy

Not applicable

10. PUBLICATION RULES

The publication guidelines of the Dutch CCMO (Central Committee for Research in Humans, www.ccmo.nl, will be adhered to in full. These guidelines consist of a number of basic principles. First of all the results of scientific research involving human subjects must be disclosed unreservedly. All parties concerned must justify their actions in this regard. Both positive and negative research results will be disclosed, and submitted to peer-reviewed scientific journals. The principal investigator and steering committee will prepare the manuscripts together with the statistician, and other active writing committee members, in co-operation with the Sponsor of the study, Maastricht UMC+. Co-authorship is reserved for those investigators (one per centre) that enter more than 5% of the patients, in addition to those who constructively contributed to the study at the discretion of the project leader and steering committee (i.e. datamanager, etc); all other participating centers/physicians will be acknowledged. And finally, disputes on the interpretation of the results may not lead to an unnecessary delay in publication.

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APPENDIX A: SIGNATURES

SIGNATURE(S)

A prospective randomised, open, multicentre, phase III study to assess different Durations of Anastrozole therapy after 2 to 3 years Tamoxifen as Adjuvant therapy in postmenopausal women with breast cancer.

I agree to the terms of this study protocol

Maastricht UMC+ representative

Prof. dr. V.C.G. Tjan-Heijnen Principal Investigator Tel.: +31 43 3877025	Date (Day Month Year)

SIGNATURE PRINCIPAL INVESTIGATOR

A prospective randomised, open, multicentre, phase III study to assess different Durations of Anastrozole therapy after 2 to 3 years Tamoxifen as Adjuvant therapy in postmenopausal women with breast cancer.

I agree to the terms of this study protocol

Dr V.G.C. Tjan-Heijnen	Date (Day Month Year)

SIGNATURE OF INVESTIGATOR

A prospective randomised, open, multicentre, phase III study to assess different Durations of Anastrozole therapy after 2 to 3 years Tamoxifen as Adjuvant therapy in postmenopausal women with breast cancer.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.:

Signature:

_____ _____

Date
(Day Month Year)

APPENDIX B: SIDE STUDIES

1. BLOOD SAMPLING

An extra blood samples of 10 ml will be taken only from subjects that are included in this sub-protocol considering the retrospective analysis of biological markers in the blood to determine which patients benefit most from extended adjuvant anastrozole.

Patients included in this sub-protocol will be asked an additional informed consent concerning taking of the blood sample, storage of the blood sample and the future use.

The whole blood sample will be collected and fresh frozen. In due time, the blood will be analysed by micro-array analysis and other techniques to determine whether predictive factors can be identified, predicting an improved ADFS by prolonged treatment with adjuvant anastrozole.

2. NEUROPSYCHOLOGY

An addendum will be written in due time on this topic.

APPENDIX C: PATHOLOGY

Guidelines for the determination of oestrogen receptors (ER) and progesterone receptors (PR)

The formaline-fixed paraffin preparation will be used for immunohistochemistry

Method for immunohistochemistry
- Use the paraffin preparation
- Antigen retrieval (standardize method in own laboratory)

- The standard immunohistochemistry protocol can be used with antibodies against ER or PR

Scoring method
- The intensity of colouring is not included in this scoring method

- The percentage positive tumour cells should be reported. The tumour is ER or PR positive when the percentage positive cells is $\geq$ 10%

- Tumours that have a negative ER or PR status should be investigated for colouring of the normal epithelium adjacent to the tumour. The result is ER or PR negative if some of the normal cells are positive. If some of the normal cells showed no positive colouring, the test should be repeated. Another tumour paraffin preparation can be used. In the report it should be noted if the internal control was positive or negative (if the result of the repeated test is also negative, it should be noted that this result is probably not reliable)

Guidelines for the determination of HER2

Method of immunohistochemistry
- Use the paraffin preparation
- Antigen retrieval (standardize method in own laboratory)
- The standard immunohistochemistry protocol can be used with antibodies against HER2/neu
- The determination of HER2/neu positive tumour cells should be performed within 2 months after the preparation of the formaline-fixed paraffin coupe. The intensity of the colouring is deteriorated if the determination is performed later.

Scoring method
- Only the colouring of the membranes of invasive proliferating tumour cells should be reported as positive (colouring of the cytoplasm should not be reported)
- The following guideline should be used:

0: less than 10% of the tumour cells is positive

1+: more than 10% of the tumour cells is positive, but not the total membrane is coloured and the intensity is very weak

2+: more than 10% of the tumour cells show total colouring of the membranes but the intensity is not more than moderate

3+: more than 10% of the tumour cells show total colouring of the membranes and the intensity is strong

- The part of the tumour with the strongest colouring determines the score

- If normal tissue shows colouring of the membranes, the intensity of the whole colouring is too strong and the result is not reliable

A test of 3+ is considered positive, a test result of 0 or 1 is considered negative and a test result of 2+ is considered uncertain for HER2.

FISH testing

FISH testing is performed when the score is 2+. FISH testing should be performed in a refererence laboratory. In the near future PCR based amplification techniques should be validated.