PRAGMATIC CLINICAL TRIAL PROTOCOL

A PROSPECTIVE PRAGMATIC CLINICAL TRIAL OF CHINA EARLY INVASIVE BREAST CANCER PATIENTS RECEIVING ADJUVANT THERAPY WITH AROMASIN

Protocol Number:	A5991093
Medicinal product:	Aromasin® (Exemestane)
United States (US) Investigational New Drug (IND) Number:	Not applicable (N/A)
European Clinical Trial Database (EudraCT) Number:	N/A
Universal Trial Number:	N/A
Phase:	4

[redacted]

[redacted]

Document History

Document	Version Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of Changes	Reason
Amendment 4	29 June 2016	Substantial	Study type change	Requisite changes were made to the protocol in light of the change from a non-interventional study to an interventional study (CT-45); no other substantial changes were introduced	Non-interventional study transfer to pragmatic study type
Amendment 3	20 March 2015	Administrative Amendment		The protocol template update	The protocol template update
		Administrative Amendment	4 Milestones	Amend to "End of data collection: 31/12/2016"	Modified the study timeline
		Administrative Amendment	7.1 Study design	Amend End of data collection to 31/12/2016 and delete "If accrual is less than 550 cases by Dec.31, 2014, the analysis will be based on the actually recruited patients."	Modified the study timeline
		Administrative Amendment	7.3 Variables	Amend End of data collection to 31/12/2016 and delete "If accrual is less than 550 cases by Dec.31, 2014, the analysis will be based on the actually recruited patients."	Modified the study timeline
		Administrative Amendment	9 Management and reporting of adverse events/adverse reactions	Update the safety reporting language	Update the safety reporting language
Amendment 2	06 Jun 2013	Administrative Amendment		The protocol template update	The protocol template update
		Administrative Amendment	7.2.1 Inclusion criteria	Amend Inclusion Criteria to before or had received Aromasin® treatment no more than one week from before received Aromasin® treatment	Increase population who had received Aromasin® no more than one week

		Administrative Amendment	7.3.1 screening	Add "(Due to non-interventional study, permit to collect the screening procedures prior to ICD no more than 2 years)" into screening procedures	Don't limit the time of screening data collection due to Non-interventional study nature
		Administrative Amendment	7.8 Data analysis	Amend to "The first interim analysis data cut-off date is Dec 31, 2013. The second interim analysis data cut- off date is Dec 31, 2015." From "The first is to occur when approximately 50% of subjects completed their 1st year of follow up. The second is to occur when approximately 50% of subjects completed the study drug treatment or withdrawal from the study."	Meet the timeline of the license renewal submission
Amendment 1	24 Aug 2010	Administrative Amendment	Section 4.1	To update inclusion criterion 1	Modify postmenopausal criteria
Original protocol	12 May 2010			N/A	

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Abbreviations

This is a list of abbreviations used in the protocol template. All of these abbreviations may or may not be used in the protocol.	
Abbreviation	**Definition**
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFDA	China Food and Drug Administration
CRF	Case Report Form
CSA	Clinical Study Agreement
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal Carcinoma In Situ
E2	Estradiol
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure during pregnancy
ER	Estrogen Receptor
FSFV	First Subject First Visit
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transpeptidase
GPP	Good Pharmacoepidemiology Practices
Her2	Human Epidermal Growth Factor Receptor 2
HDL-C	High-density lipoprotein cholesterol
ICD	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IES	Intergroup Exemestane Study
IRB	Institutional Review Board
LDL-C	Low density lipoprotein-cholesterol
LH-RH	Luteinizing-Hormone-Releasing Hormone
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
PCD	Primary completion date
PR	Progesterone Receptor
PVC	Polyvinyl chloride polymer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRSD	Single Reference Safety Document
TNM	Tumor, Lymph Node and Metastasis

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Visit Identifier	Prior to Enrollment/Day 1	Enrollment/ Day 1	Between Day 1 and End of Treatment/ Early Termination
Screening	X		
Demographic data	X		
Performance status at diagnosis	X		
Histopathological diagnosis	X		
TNM current stage (as per AJCC, 2002)	X		
Hormone receptor status (ER/PR status)	X		
HER-2 receptor status	X		
Treatment history related to primary diagnosis	X		
Chemotherapy (CT)	X		
Radiotherapy	X		
History of hormonal therapy received before Aromasin®	X		
	X		
Laboratory	X		X
Hematology	X		X
Blood Chemistry	X		X
Serum FSH and E2	X		X
Lipid Profile	X		X
Bone mineral density estimations	X		X
Abdominal/transvaginal ultrasonography	X		X
Breast ultrasonography	X		X
Breast mammogram	X		X
Informed consent	X		
Registration/Enrollment		X	
Confirm eligibility.		X	
Aromasin treatment		X	X
Assessments			X
Symptoms			X
Details of Aromasin® treatment			X
Efficacy			X
Safety			X
HRQL			
HRU			
Concomitant Treatments		X	X
Adverse Events		X	X

Abbreviations: E2 = estradiol; FSH = follicle-stimulating hormone HRQL = health-related quality of life; HRU = healthcare resource utilization

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APPENDICES

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Aromasin® (Exemestane) is an irreversible, steroidal aromatase inhibitor that has been developed for adjuvant treatment of postmenopausal women with estrogen receptor (ER) positive early invasive breast cancer who have received 2-3 years of tamoxifen and are switched to Aromasin® for completion of a total of 5 consecutive years of adjuvant hormonal therapy .

1.2. Background and Rationale

Aromasin® (Exemestane) is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In the year 2002, Aromasin® (Exemestane) was approved in China for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following tamoxifen therapy.

Aromasin® (Exemestane) was approved in China for adjuvant treatment of postmenopausal women with estrogen receptor (ER) positive early invasive breast cancer who have received 2-3 years of tamoxifen & are switched to Aromasin® for completion of a total of 5 consecutive years of adjuvant hormonal therapy by China Food and Drug Administration (CFDA) with clinical trial waiver in May. 2008.[1] The approval was granted in view of the significant efficacy and tolerant safety from the Intergroup Exemestane Study (IES), which was a phase III randomized controlled trial conducted primarily in Caucasian patients.[2,3] While Aromasin® has been used in China for adjuvant therapy of breast cancer since then, there is currently a lack of systematic collection and analysis of the efficacy and safety data for Aromasin® in the adjuvant setting in Chinese population. The Aromasin® pragmatic clinical trial is being proposed to collect data systematically and to assess the efficacy and safety of Aromasin® in the adjuvant setting in Chinese population. Generation of such information is expected to provide evidence for Chinese physicians to manage clinical practice of Aromasin® in the adjuvant setting. The single reference safety document to be used in this study and complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the China Aromasin® Package Insert.

The ex-study number is NRA5990043.

This study was conceived and initiated as a prospective observational study and all subjects were enrolled under that paradigm. After all subjects had been enrolled, the original design was modified to an interventional pragmatic study, primarily for the purpose of allowing the study to provide study drug to the subjects, at no cost to the subject.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

This is a Post-Approval Safety Study (PASS) intended to generate efficacy and safety data from patients with early invasive breast cancer treated with Aromasin® in the adjuvant setting in China.

Primary objective: Efficacy of the treatment with Aromasin® in postmenopausal women with estrogen receptor positive early invasive breast cancer who have received adjuvant Tamoxifen therapy for up to 2-3 years

Secondary objective: Safety of treatment with Aromasin® in women with postmenopausal estrogen receptor positive early invasive breast cancer who have received adjuvant Tamoxifen therapy for up to 2-3 years

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoint will be time-to-event, where event is defined as the earliest occurrence any of the following:

- Loco-regional/distant recurrence of the primary breast cancer;
- Appearance of a second primary or contralateral breast cancer;
- Death due to any cause.

Loco-regional recurrence is defined as any recurrence in the ipsilateral breast, chest wall or axillary lymph nodes.

2.2.2. Secondary Endpoints

The proportion of subjects experiencing the events.

The incidence rate (per annum) is defined as a ratio of the number of events and the total exposure times (in years) to Aromasin® therapy.

The relationship between Human Epidermal Growth Factor Receptor 2 (Her2) overexpression level and efficacy endpoint will be analyzed.

The events define as below:

Patients who used Aromasin® met the occurrence of any of the following events, whichever occurs earliest:

- Loco-regional/distant recurrence of the primary breast cancer;
- Appearance of 2nd primary or contralateral breast cancer;
- Death due to any cause.

The incidence of adverse events and discontinuation of Aromasin® due to adverse event will be summarized.

3. STUDY DESIGN

This is a multicenter, single-arm, and prospective clinical study. This study is transitioned from a non-interventional (observational) study to an interventional, pragmatic clinical study. The study will collect and analyze efficacy and safety data from approximately 550 consecutive eligible patients from study beginning to last subject last visit.

The endpoints of the study include efficacy endpoints and safety endpoints.

All subjects enrolled must meet all inclusion criteria and none of the exclusion criteria.

The dose of Aromasin to be used in this study will be as specified in the protocol, which is intended to be in accord with the approved dose for this indication in China.

The subjects will receive 2-3 years of Aromasin® for completion of a total 5 years of adjuvant hormonal therapy or until the occurrence of any of the following events that would signify the need for treatment termination, whichever occurs earlier:

- Loco-regional/distant recurrence of the primary breast cancer;
- Appearance of a second primary breast cancer or contralateral breast cancer;
- Unacceptable toxicity, protocol deviation, withdrawal of subject consent or other reason for termination of treatment;
- Death due to any cause;
- Administration of another aromatase inhibitors (ie, not Aromasin®).

4. SUBJECT SELECTION

Under Amendment 4, this study transitioned from a non-interventional (observational) study to an interventional, pragmatic clinical study. Approximately 550 patients were planned to enroll by or before Dec. 31, 2016. At the time of the transition to a pragmatic study (May 2016), enrollment of the study had already completed in December 2015. The inclusion criteria and exclusion criteria applicable to all enrolled subjects were based on the previous non-interventional version of the study protocol. No additional subjects will be enrolled in the study following the transition to an interventional pragmatic clinical study design.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom the protocol intervention is considered appropriate by their health care provider.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Early invasive breast cancer (T1-4N0-3M0) confirmed by histology or cytology.

2. ER positive.

3. The patient must be postmenopausal woman. Post-menopause is defined as follows:

   a. Prior bilateral oophorectomy;

   b. Age ≥60 years;

   c. Age <60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and plasma Follicle-Stimulating Hormone (FSH) and estradiol in the postmenopausal range; if taking tamoxifen or toremifene, and age <60 years, then serial measurement of plasma FSH and estradiol are need to ensure in the postmenopausal ranges.

   d. In addition, following situations should be considered:

      - It is not possible to assign menopausal status to women who are receiving an Luteinizing-Hormone-Releasing Hormone (LH-RH) agonist or antagonist

      - In women premenopausal at the beginning of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status, because ovarian function may still be intact or resume despite anovulation/amenorrhea after chemotherapy.

      - For these women with chemotherapy-induced amenorrhea, ovarian suppression (oophorectomy or drug suppression) or serial measurement of FSH and/or estradiol are needed to ensure postmenopausal status if the use of aromatase inhibitors is considered as a component of endocrine therapy.

4. The patient has received adjuvant Tamoxifen therapy for up to 2-3 years and will switch to receive Aromasin® treatment or had received Aromasin® treatment no more than one week (The decision to prescribe Aromasin® will necessarily precede and will be independent of the decision to enroll patients in the study).

5. Evidence of a personally signed and dated informed consent document indicating that the patient (or legally acceptable representative, parent(s)/legal guardian) has been informed of all pertinent aspects of the study.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

2. Following the adjuvant Tamoxifen therapy for 2-3 years and prior to receiving Aromasin® treatment, there is evidence of a local relapse or distant metastasis of breast cancer, or a second primary cancer.

3. Following the adjuvant Tamoxifen therapy for 2-3 years and received other aromatase inhibitors (not Aromasin®)

4.3. Randomization Criteria

Not applicable as this is a single arm, non-randomized study.

4.4. Life Style Guidelines

Not applicable

5. STUDY INTERVENTION

5.1. Allocation to Intervention/Treatment

The investigator will assign subject identification numbers sequentially to the subjects as they are screened for the study. This identifying number will be retained throughout the study. A subject number must never be reassigned or reused for any reason. The investigator must maintain a log linking the subject number to the subject's name.

5.2. Drug Supplies

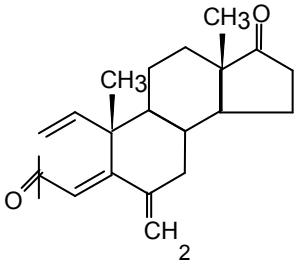
5.2.1. Dosage Form(s) and Packaging

Aromasin® (study drug) will be provided by Pfizer as round, biconvex, off-white sugar coated tablets with a white core for oral administration. The recommended dose of Aromasin® in early and advanced breast cancer is one 25 mg tablet once daily after a meal.

The label attached to each Aromasin® states the product name and amount, potency (drug only), lot number, directions for storage, and name of manufacturer. Labels may contain other information, such as expiry date, as required by local regulatory guidelines.

The active ingredient is: 6-methylenandrosta-l,4-diene-3,17-dione.

Structural formula:



Molecular formula: $C_{20}H_{24}O_2$

Molecular weight: 296.41

TABLET STRENGTH: 25 mg.

PACKAGING:

30 tablets in blister packs (Polyvinyl chloride polymer (PVC) /Aluminium foil).

5.2.2. Preparation and Dispensing

Pfizer will provide the investigators with a sufficient quantity of study drug. Once study drug is dispensed to a subject it must not be re-dispensed to another subject. The product should be used in accordance with the China Aromasin® Package Insert. At each visit before the End of Treatment/ Early Termination visit, the subject should receive a sufficient quantity of study drug in order to last until the next visit.

5.3. Administration

The product will be administered in accordance with the China Aromasin® Package Insert.

5.4. Drug Storage

The investigator, or an approved representative, eg, a pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label. See the China Aromasin® Package Insert for storage conditions of the product.

Storage conditions stated in the China Aromasin® Package Insert should be followed. The package that contains the study drug must be stored below 30°C.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study, on all business days. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the storage requirements for take-home medications including how to report temperature excursions.

5.5. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. When investigational product is taken home by the subject, any unused products must be returned to the investigator by the subject at the End of Treatment/ Early Termination visit.

The monitor will review drug accountability during routine monitoring visits. Drug accountability will be done at all study visits after Day 1 until End of Treatment/ Early Termination visit. Any discrepancies must be investigated and their resolution documented. At the completion or termination of the study, a final drug accountability review and reconciliation must be performed. Any discrepancies that cannot be reconciled must be documented in writing in the study file.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.6. Concomitant Treatment(s)

The use of permitted concomitant medication must be in accordance with the study drug label.

6. STUDY PROCEDURES

6.1. Screening (within 2 years prior to Day 1)

Due to the non-interventional- study design at the time subjects were enrolled, the Informed consent form (ICD) permitted the collection of data related to screening procedures up to 2 years prior to Informed Consent being given. After the transition from a non-interventional study to an interventional, pragmatic study, the ongoing subjects must re-sign the ICD.

The following screening procedures (to the extent that they are available) must be performed prior to the start of treatment on study unless otherwise stated.

Patient signature on current Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent document.

Demographic data;

- Subject date of birth, gender, race.

Physical examination including examination of major body systems (General, Lungs, Heart, Musculoskeletal, Genitourinary, Neurological, Lymph nodes, Skin, Abdomen and Other), Easter Cooperative Oncology Group (ECOG) performance status, body weight, height (screening only), and vital signs (temperature, blood pressure, heart rate, respiratory rate).

Breast cancer history:

- Date of initial diagnosis of breast cancer;
- Tumor location: Left/right breast.

Performance status at diagnosis (Easter Cooperative Oncology Group Performance Status).

Histopathological diagnosis:

- Tumor, Lymph Node and Metastasis (TNM) current stage (as per AJCC, 2002);
- Hormone receptor status (ER/PR status);
- HER-2 receptor status (as per Breast Cancer National Comprehensive Cancer Network (NCCN) clinical practice guideline Chinese version v.1.2009).

Medical history:

- Concomitant illnesses;
- Concomitant drug and non-drug treatment (within 21 days prior to the start of treatment on study) including supportive therapy (calcium, bisphosphonates, etc).

Treatment history related to primary diagnosis:

- Surgery related to primary diagnosis:
  - Date of surgery;
  - Type of surgery;
  - Outcome of surgery.

- Chemotherapy (CT):
  - Adjuvant CT: Agent name, date of starting, stop date, number of cycles.
- Radiotherapy:
  - Site of radiotherapy;
  - Dates started and stopped;
  - Total dose.
- History of hormonal therapy received before Aromasin®:
  - Agent used;
  - Dosage and duration.

Baseline investigations (the updated investigation result prior to the start of the treatment on study)

- Hematology: hemoglobin, platelet count, white blood cell count, and differential count (percent);
- Serum Chemistry: total bilirubin, ALT (Alanine Transaminase), AST (Aspartate Transaminase), alkaline phosphatase, GGT (Gamma-Glutamyl Transferase), total protein, albumin, BUN (Blood Urea Nitrogen), creatinine, uric acid, glucose;
- Serum FSH (follicle stimulating hormone) and E2 (estradiol);
- Lipid Profile: Serum HDL-C (high-density lipoprotein cholesterol), LDL-C (low density lipoprotein-cholesterol), total cholesterol, triglycerides;
- Bone mineral density estimations;
- Abdominal/transvaginal ultrasonography: Uterine hyperplasia, polyps, fibroids;
- Breast ultrasonography;
- Breast mammogram.

Assessment of ongoing symptoms/events (serious adverse events must be recorded from time of signed consent).

6.2. Day 1 (Enrollment and First Dose of Study Drug)

After the Screening Visit laboratory results are available, the investigator will confirm eligibility by ensuring that the laboratory related entry criteria have been fulfilled. This should occur before the date of Day 1.

The following procedure will be performed:

- Confirm eligibility.

Once baseline data has been collected and eligibility has been confirmed, study drug will first be dispensed to the subject at this visit.

Investigator (or designee) will provide the subject with instructions regarding Aromasin® dosing, administration and storage.

The subject may now commence treatment with study drug. Subjects will be treated with study drug at a dose and frequency prescribed by the subject's treating physician in accordance with the China Aromasin® Package Insert.

6.3. Study Period

6.3.1. Interim Visits between Day 1 and End of Treatment

Patients will receive the study drug (Aromasin®) as outpatients and are generally expected to return to the clinic for interim visits at approximately 6 month intervals. Since this study was originally configured as an observational study, patient visits during the course of the study may occur at the discretion of the Investigators according to local clinical practice guideline and/or the Investigator's clinical judgment.

A final End-of-Treatment/Early Termination Visit is required for all study subjects.

The following data will be collected at each study period visit:

- Symptoms;
- Physical examination including major body systems, ECOG performance status, body weight, and vital signs.
- Investigations (as available)**:**
  - Serum Chemistry: total bilirubin, ALT, AST, alkaline phosphatase, GGT, total protein, albumin, BUN, creatinine, uric acid, glucose;
  - Serum FSH and E2;
  - Lipid Profile: Serum HDL-C, LDL-C, total cholesterol, triglycerides;
  - Bone mineral density estimations;
  - Abdominal/transvaginal ultrasonography:Uterine hyperplasia, polyps, fibroids;
  - Breast ultrasonography;
  - Breast mammogram.

- Details of Aromasin® treatment:
  - Dose and duration;
  - Reason for dose change or an missed medication.

- Adverse events/ Serious adverse events.

- Concomitant drug and non-drug treatment (study period):
  - Change in concomitant drug and non-drug treatment including any change in supportive therapy (calcium, bisphosphonates, etc).

6.3.2. Final Visit

For each subject, the final visits will occur at completion the study drug or at the occurrence of any of the events signifying treatment termination (refer Section 7.2).

Observational Parameters collected at the Final Visit are identical to the Study Period Visits; with the addition of recurrence time and location, if the subject has recurrence.

6.4. Subject Withdrawal

When subjects are permanently withdrawn from treatment, the primary reason for discontinuation must be provided. Reasons for discontinuation include:

- Death due to any cause;
- Unacceptable toxicity;
- Disease recurrence/ metastases;
- Appearance of a second primary or contralateral breast cancer;
- Protocol deviation (eg, subject noncompliance, including the study drug accumulated dosage subject taken is less than 70% or more than 130% of the total study drug dosage);
- Receive other aromatase inhibitors (not Aromasin®);
- Withdrawal of subject consent;
- Study terminated by sponsor;
- Other reason.

- Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator.
    - Withdrawal of Consent: Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator, in writing, of their decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
    - If the patient withdraws consent, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

- Lost to Follow-Up:

    - If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In *all* circumstance*s*, every effort should be made to document subject outcome. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

    - All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

Data to be collected on the case report forms must be documented in patient records.

7.1. Efficacy Endpoint

The first occurrence of any of the following events constitutes an efficacy endpoint for the subject:

- Loco-regional/distant recurrence of the primary breast cancer;

- Appearance of a second primary or contralateral breast cancer;

- Death due to any cause.

Loco-regional recurrence is defined as any recurrence in the ipsilateral breast, chest wall or axillary lymph nodes.

7.2. Safety Parameters

The safety of treatment with Aromasin® will be assessed by Adverse Event reporting in the study. Every adverse event that is observed must be recorded as an adverse event in the CRF, whether or not the Investigator suspects a causal relationship with study drug.

Adverse events of particular interest in this study:

- Gynaecological: Bleeding ,discharge, uterine dilatation and curettage;
- Cardiac: myocardial infarction, hypertension;
- Venous thromboembolic events;
- Musculoskeletal: Joint stiffness, arthralgia, muscle cramps, fractures;
- Menopausal symptoms: Hot flushes, anxiety, depression, headaches;
- Changes in lipids;
- Changes in bone mineral density.

Severity of the adverse events reported while on Aromasin® will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 3.0.

Please refer to the Section 8 for additional details on recording and reporting of adverse events.

7.3. Pregnancy Testing

Not applicable for this Aromasin® pragmatic clinical trial because the use of Aromasin® for this indication is for post-menopausal women.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered Adverse Event (AEs) regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.

AEs (serious and nonserious) should be recorded on the Case Report Form (CRF) from the time the subject has taken at least 1 dose of study treatment through the last subject visit.

- If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the case report forms (CRFs) and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated AE(s) are captured on an AE CRF page (refer to the ADVERSE EVENT REPORTING section for further details).

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria (CTC) Grade 5 (see section on Severity Assessment).
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. The important medical event should be reported as serious, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased by 1 X ULN **or** ≥3 X ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute an hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.0 CTC document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious). The investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male subject has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE

has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent/legally acceptable representative. In addition, each study subject /parent/legally acceptable representative will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.15. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.16. Sponsor Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

No inferential statistical analyses for primary and secondary endpoints are planned. Analyses will consist of descriptive statistics and corresponding 95% 2-sided confidence intervals when appropriate.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.1. Sample Size Determination

Analyses will be primarily descriptive in nature, and therefore no statistical sample size estimation was performed.

9.2. Data Sources

This study data will be recorded by a physician/nurse in the medical records, through subject interview, and in the Case Report Form (CRF).

This study will collect and analyze the efficacy and safety data from approximately 550 eligible consecutive patients. All recruited 550 patients or actually recruited patients will be observed until the end of Aromasin® therapy.

9.3. Effectiveness Analysis

All summaries of efficacy parameters will be reported within the Full Analysis Set (FAS). This is defined as all patients who receive at least one dose of Aromasin® during the observation period.

9.3.1. Analysis of Primary Endpoint

The primary efficacy variable will be time-to-event, where event is defined as the earliest occurrence any of the following:

- Loco-regional/distant recurrence of the primary breast cancer;
- Appearance of a second primary or contralateral breast cancer;
- Death due to any cause.

Time-to-event will be calculated as the time from date of enrollment to first objective documentation of the event defined above. In the analysis of time to event, subjects lost to follow-up and subjects who are still being followed at the time of analysis with no documented event will be censored at the last date the subject was known to be event-free.

The Kaplan Meier non-parametric estimate will be used to summarize the survival distribution and median for time-to-event. Ninety-five percent confidence intervals for the survival distribution will be computed.

9.3.2. Analysis of Secondary Endpoints

Loco-regional/distant recurrence, appearance of a second primary or contralateral breast cancer, and death will also be summarized as follows:

- Time to each event;
- The proportion of subjects experiencing the event;
- The incidence rate (per annum) is defined as a ratio of the number of events and the total exposure time (in years) to Aromasin® therapy;
- The relationship between Her2 overexpression level and time-to-event.

Categorical data will be presented using counts, percentages and 95% confidence intervals for percentages. Continuous data will be reported using n, mean, standard deviation, median and range, 95% confidence interval may also be presented where specified. The Kaplan Meier non-parametric estimate will be used to summarize the survival distribution and median for time-to-event, 95% confidence intervals for the survival distribution will be computed.

CCI [redacted]

9.4. Safety Analysis

All safety analyses will be performed on all enrolled subjects who receive at least one dose of Aromasin®.

Severity of the adverse events reported while on Aromasin® will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 3.0.The reasons for discontinuation of Aromasin® therapy will be described.

Safety data will be tabulated and listed according to Pfizer's standard reporting algorithms.

9.5. Interim analysis

Up to 2 early analyses of the data will be performed. The first interim analysis data cut-off date is Dec 31, 2013. The second interim analysis data cut-off date is to occur when the study has enrolled 550 subjects. The final analysis will be done at the end of treatment.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the subject’s chart in the hospital or the physician's office. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must be re-consented as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF STUDY

13.1. End of Study in all Participating Countries

End of Study in all participating countries (only one country of China for this study) is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a time period set by Pfizer. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

15.2. Publications by Investigators

Pfizer has no objection to publication by investigator of any information collected or generated by investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the Study results themselves) before disclosure.

If the study is part of a multicenterr study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Aromasin® Locally Approved Prescribing Information. Pfizer China. 2008.

2. Coombes C, Hall E, Gibson L, et al. A randomized trial of Exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 350: 1081

3. Coombes C, Kilburn L, Snowdon C, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): A randomised controlled trial. Lancet 2007; 369: 559.

APPENDICES

Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 2. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 3.0, dated 09 August 2006) can be reviewed online at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html