Clinical Study Protocol

Drug Substance	ZD9393
Study Code	D8666C00001
Edition Number	1

An Open Label, Randomised, Parallel Group, Multicentre Study to Compare ZOLADEX™ 10.8 mg Given Every 12 Weeks with ZOLADEX 3.6 mg Given Every 4 Weeks in Pre-menopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer

Sponsor:

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

An Open Label, Randomised, Parallel Group, Multicentre Study to Compare ZOLADEX™ 10.8 mg Given Every 12 Weeks with ZOLADEX 3.6 mg Given Every 4 Weeks in Pre-menopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer

International Co-ordinating Investigator

Principal Investigators

Study centre(s) and number of subjects planned

This study will be conducted in approximately 216 randomised patients in Asian countries. The planned countries to be included in this study are: China, Thailand, India, Japan, Korea, and Philippines etc..

Study period	Phase of development
Estimated date of first subject enrolled	III
Estimated date of last subject completed	

The end of study is defined as the last visit of the last patient undergoing the study.

Objectives

The primary objective of this study is to evaluate whether ZOLADEX 10.8 mg is non-inferior to ZOLADEX 3.6 mg in pre-menopausal women with oestrogen receptor (ER) positive advanced breast cancer by assessment of progression-free survival (PFS) at 24 weeks.

The secondary objectives are:

- To provide supportive data confirming that ZOLADEX 10.8 mg is non-inferior to ZOLADEX 3.6 mg by assessment of:

  - Objective response rate (ORR) at 24 weeks, determined by Response Evaluation Criteria In Solid Tumours (RECIST) criteria (Ver.1.1)

  - Oestradiol (E_2) serum concentrations at 24 weeks

- To compare the safety and tolerability profile of ZOLADEX 10.8 mg and ZOLADEX 3.6 mg by assessment of adverse events (AEs)

- To assess the pharmacokinetics of goserelin in Japanese and Non Japanese patients except for patients in China in the PK sub-group following administration of ZOLADEX 10.8 mg by measurement of plasma concentrations of goserelin. And to assess the E_2 serum concentration profiles in the PK sub-group.

Study design

This is a multicentre, open label, randomised, parallel group study to compare ZOLADEX 10.8 mg given every 12 weeks with ZOLADEX 3.6 mg given every 4 weeks.

Target subject population

Pre-menopausal female patients with locally advanced or metastatic ER positive breast cancer who are candidates to receive hormonal therapy.

Investigational product (ZOLADEX 10.8 mg)

- ZOLADEX 10.8 mg (goserelin acetate): one subcutaneous depot injection once every 12 weeks (± 7 days).

- One oral tamoxifen 20 mg tablet daily.

Comparator (ZOLADEX 3.6 mg), dosage and mode of administration

- ZOLADEX 3.6 mg (goserelin acetate): one subcutaneous depot injection once every 4 weeks (± 7 days).

- One oral tamoxifen 20 mg tablet daily.

Duration of treatment

Study medication will be administered from Day 1 until completion of 24 weeks of study treatment or any other criterion for treatment discontinuation are met whichever is sooner.

Outcome variables

Primary outcome variable

- Efficacy

  - The primary outcome variable is PFS at 24 weeks. A progression-free patient is defined as a patient for whom neither objective disease progression nor death (due to any cause) has been observed

Secondary outcome variables

- Efficacy/PD
  - ORR at 24 weeks: with response defined as either a complete or partial response based on the RECIST criteria (Ver. 1.1)
  - E_2 serum concentrations at 24 weeks
  - E_2 serum concentration profiles (PK sub-group only)
- Safety
  - AE profile
- PK analysis
  - Plasma concentration–time profile and related PK parameters of goserelin

Statistical methods

The non-inferiority of ZOLADEX 10.8 mg to ZOLADEX 3.6 mg will be tested using 95% confidence intervals (CI) of the difference (ZOLADEX 10.8 mg – ZOLADEX 3.6 mg) of proportions of patients with progression-free at 24 weeks. The non-inferiority will be concluded when the lower limit of the CI is greater than or equal to –17.5%. The choice of this limit is based on a 75% relative efficacy of ZOLADEX 10.8 mg to ZOLADEX 3.6 mg, for which a 24-week progression-free proportion of 70% is anticipated.

Assuming the proportion of patients who are progression-free at 24 weeks is 70% in both treatment groups in this study, and define the limit of non-inferiority as an absolute difference of 17.5% between these two proportions, a sample size of 216 patients (108 per group) ensures that 80% power is achieved to conclude non-inferiority with a two-sided 95% CI.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (serum glutamic pyruvic transaminase [SGPT])
AUC	Area under the curve
$AUC_{(0\text{-}t)}$	Area under the curve - time curve from 0 to time t
$AUC_{(0\text{-}12\ weeks)}$	Area under the curve- time curve from 0 to Week 12
CI	Confidence interval
C_{max}	Maximum plasma concentration
conc.	Concentration
CPD	AstraZeneca Clinical Pharmacology & DMPK (CPD)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE v3.0	Common Terminology Criteria for Adverse Events v3.0
DAE	Discontinuation of Investigational Product due to Adverse Event
D/d	Day or day
DMPK	Drug Metabolism and Pharmacokinetics
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	electronic Case Report Form
ER	Oestrogen receptor
E_2	Oestradiol
FAS	Full analysis set
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH(a)	Gonadotrophin-releasing hormone (analogue)

Abbreviation or special term	Explanation
h	hour
HER2	Human Epidermal Growth Factor Receptor 2
HRT	Hormone replacement therapy
IB	Investigators Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LH	Luteinising hormone
LHRH(a)	Luteinising hormone-releasing hormone (analogue)
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
min	minimum
MRI	Magnetic resonance imaging
NE	Not Evaluable
NCI	National Cancer Institute
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
ORR	Objective Response Rate
PD	Progression Disease
PFS	Progression Free Survival
PgR	Progesterone Receptor
PI	Principal Investigator
PK	Pharmacokinetic
PPS	Per protocol set
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event (see definition in Section 6.4.2).
SAP	Statistical Analysis plan
SD	Standard Deviation

Abbreviation or special term	Explanation
SDV	Source Data Verification
T_{max}	Time to maximum plasma concentration
TNM	Tumour, node, metastases
ULRR	Upper limit of Reference Range
WBDC	Web Based Data Capture
WHO	World Health Organization
Wk	Week
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
Investigator(s)	Principal investigator and sub investigator

1. INTRODUCTION

Breast cancer is the most common cancer in women, and is second only to lung cancer as a cause of cancer death in women (Dumitrescu et al 2005). Approximately 10% of newly diagnosed patients have locally advanced or metastatic disease, and approximately 20% to 85% of patients who are diagnosed with early breast cancer will later develop recurrent and/or metastatic disease (Bernard-Marty et al 2004). The median survival time after diagnosis of metastasis is approximately 2 years (Bernard-Marty et al 2004).

17β-Oestradiol (E_2) has a growth-promoting role in the pathogenesis of E_2-dependent breast cancer (Klijn et al 2000). Disease management strategies therefore include E_2 deprivation/antagonism by either medical or surgical means (Klijn et al 2000). In pre-menopausal women, the ovaries are the primary source of oestrogen and surgical ovarian ablation is the traditional option (Klijn et al 2000). However, oophorectomy is irreversible. An alternative is the use of reversible endocrine therapies such as gonadotrophin-releasing hormone/luteinising hormone-releasing hormone analogues (GnRHa/LHRHa).

AstraZeneca ZD9393 (goserelin acetate, ZOLADEX™[1]) is a synthetic GnRHa. GnRH stimulates the release of luteinising hormone (LH) and follicle stimulating hormone (FSH), which in pre-menopausal women regulate the cyclical synthesis and release of oestrogen and progesterone from the ovaries. On chronic administration in women, goserelin causes potentially reversible ovarian ablation resulting in oestrogen suppression and amenorrhoea in the majority of patients, rendering the patient menopausal.

Relevant pre-clinical data for ZOLADEX 10.8 mg and ZOLADEX 3.6 mg are presented in the latest Investigator's Brochure (IB).

1.1 Background

The efficacy, safety and endocrine effects of ZOLADEX 3.6 mg, administered every 4 weeks, in pre- and peri-menopausal women with advanced breast cancer are well documented (Dalton et al 1987, Boccardo et al 1994, Jonat et al 1995, Taylor et al 1998; see the latest ZOLADEX IB), and ZOLADEX 3.6 mg is approved in this indication in many countries.

ZOLADEX 10.8 mg given every 12 weeks is approved in many countries for use in prostate cancer, endometriosis and uterine fibroids and has been shown to be as effective as 4-weekly injections of ZOLADEX 3.6 mg in the management of prostate cancer in patients of both European and Japanese origin (studies 118630/1805, 9393HQ/0001, and ZD-55-11, see the latest ZOLADEX IB). This formulation is potentially more convenient than ZOLADEX 3.6 mg due to its less frequent administration.

[1] ZOLADEX is a trademark of the AstraZeneca group of companies.

ZOLADEX 10.8 mg was investigated in 1991 in an open, uncontrolled study of 21 pre- and peri-menopausal women with advanced breast cancer (study 9393HQ/0002, see the latest ZOLADEX IB). E_2 suppression was measured as a marker of clinical efficacy and successful E_2 suppression was defined as all on-dose E_2 measurements less than 92 pmol/L. The E_2 suppression was assessed in the total 19 patients, and there were 9 patients (47 %) of failures seen in this study, but in the majority of cases failure was due to a transient increase of E_2 levels above the 92 pmol/L threshold and there was no consistent time of failure. Further investigation showed that there was no consistent relationship between the transient increase in E_2 level and clinical outcome in these patients: 1 patient with a partial objective tumour response had a transient increase in E_2 while 3 patients had disease progression but their E_2 levels were consistently below the post-menopausal threshold. When the threshold was revised to 140 pmol/L, in line with results published in 1995, E_2 suppression was successfully maintained for up to 84 days (3 menstrual cycles) after administration of ZOLADEX 10.8 mg in 15 of 17 evaluable patients receiving the first depot and 12 out of 13 patients receiving the second depot.

Initial 12-week data in female patients with endometriosis indicated that ZOLADEX 10.8 mg was less effective in suppressing E_2 than ZOLADEX 3.6 mg, although the differences between the products were relatively small and of uncertain clinical relevance (study 9393IL/0026, see the latest ZOLADEX IB). However, longer follow-up data in women with benign gynaecological conditions indicated that, after 24 weeks of therapy, the differences between ZOLADEX 10.8 mg and ZOLADEX 3.6 mg are very small in terms of E_2 suppression (6% difference in E_2 area under the plasma concentration–time curve over a 24-week period) with no difference in clinical outcomes over a 24 to 96 weeks (6 to 24 months) period (studies 9393IL/0026 and 9393IL/0027, data on file).

In Japan, trial 0004 was started in 2005 to compare the effect in suppressing E_2 between ZOLADEX 10.8 mg and ZOLADEX 3.6 mg in adjuvant therapy and the result showed ZOLADEX 10.8 mg was non-inferior to ZOLADEX 3.6 mg in terms of E_2 suppression in pre-menopausal patients with ER positive breast cancer. Furthermore, in east Europe and Japan, international trial (trial 0008) was started in 2006 to verify the non-inferiority of ZOLADEX 10.8 mg to ZOLADEX 3.6 mg in pre-menopausal patients with locally advanced or metastatic breast cancer but the recruitment was halted in December 2007 due to lower rate of recruitment in east Europe than expectation.

1.2 Research hypothesis

The primary objective of this study is to evaluate whether ZOLADEX 10.8 mg is non-inferior to ZOLADEX 3.6 mg in pre-menopausal women with ER positive advanced breast cancer by assessment of PFS at 24 weeks.

1.3 Rationale for conducting this study

As described in Section 1.1, as a result of trial 0004, ZOLADEX 10.8 mg was non-inferior to ZOLADEX 3.6 mg in terms of E_2 suppression in pre-menopausal patients with ER positive breast cancer. On the other hand, trial 0008 conducted in east Europe and Japan was halted

due to poor recruitment. However, the data of 98 patients who were randomised until December 2007 was analysed and the result showed that PFS at week 24 was around 70% in ZOLADEX 10.8 mg and in ZOLADEX 3.6 mg and the efficacy of ZOLADEX 10.8 mg seemed to be similar to that of ZOLADEX 3.6 mg. There were no issue of efficacy and safety, which required to discontinue the trial as of data cut off in June 2008.

Therefore it was considered to be possible to verify the non-inferiority of ZOLADEX 10.8 mg to ZOLADEX 3.6 mg statistically, by conducting and completing a similar study to the trial 0008. ZOLADEX 10.8 mg could offer a more convenient therapy to patients with breast cancer than ZOLADEX 3.6 mg due to its less frequent administration schedule. This study will be conducted in Asia including Japan.

This study will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

1.4 Benefit/risk and ethical assessment

In women, ZOLADEX suppresses serum E_2 concentrations, which for 4-weekly ZOLADEX 3.6 mg administration is associated with a response in hormone-dependent breast cancer. The 12-weekly ZOLADEX 10.8 mg offers a potentially more convenient (less frequent) therapy to patients with breast cancer. Current data indicate little clinical difference of serum E_2 suppression between the 2 formulations in pre-menopausal breast cancer in trial 0004.

Generally, ZOLADEX 3.6 mg is well-tolerated in patients with breast cancer with the most frequent AEs being those commonly associated with serum E_2 suppression. Initially, breast cancer patients given ZOLADEX 3.6 mg may experience a temporary increase of serum E_2, signs and symptoms, which can be managed symptomatically. The most frequent AEs caused by ZOLADEX 10.8 mg is commonly associated with serum E_2 suppression and they can be managed symptomatically .

This study has a favourable risk/benefit assessment.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate whether ZOLADEX 10.8 mg is non-inferior to ZOLADEX 3.6 mg in pre-menopausal women with oestrogen receptor (ER) positive advanced breast cancer by assessment of progression-free survival (PFS) at 24 weeks.

2.2 Secondary objectives

The secondary objectives are

- To provide supportive data confirming that ZOLADEX 10.8 mg is non-inferior to ZOLADEX 3.6 mg by assessment of:

  - Objective response rate (ORR) at 24 weeks, determined by Response Evaluation Criteria In Solid Tumours (RECIST) criteria (Ver.1.1)

  - Oestradiol (E_2) serum concentrations at 24 weeks

- To compare the safety and tolerability profile of ZOLADEX 10.8 mg and ZOLADEX 3.6 mg by assessment of adverse events (AEs)

- To assess the pharmacokinetics of goserelin in Japanese and Non Japanese patients except for patients in China in the PK sub-group following administration of ZOLADEX 10.8 mg by measurement of plasma concentrations of goserelin. And to assess the E_2 serum concentration profiles in the PK sub-group.

2.3 Safety objective

See Section 2.2

2.4 Exploratory objectives - NA

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a multicentre, open label, randomised, parallel group study to compare ZOLADEX 10.8 mg given every 12 weeks with ZOLADEX 3.6 mg given every 4 weeks.

Target subject population

Pre-menopausal female patients with locally advanced or metastatic ER positive breast cancer. (See Section 4.1 and 4.2 for inclusion and exclusion criteria)

Study medication

'Study medication' is a combination of investigational product 'ZOLADEX 10.8 mg' or comparator 'ZOLADEX 3.6 mg' and study concomitant medication 'tamoxifen'.

Study period

This study period is composed of screening period and study treatment /assessment period.

Screening period (Visit 1, Day – 21 to Day 0)

- Only eligible patients should be randomised by assessment based on the inclusion criteria and exclusion criteria (See Section 4.1 and 4.2).

- Eligible patients will be randomised 1:1 to receive ZOLADEX 10.8 mg or ZOLADEX 3.6 mg at visit 2.

Treatment/Assessment period

Administration of Investigational product (ZOLADEX 10.8 mg) or comparator (ZOLADEX 3.6 mg) should be started within 1 day after randomisation. Study concomitant medication (Tamoxifen 20 mg) should be started on the same day of or one day after starting the administration of ZOLADEX.

Study medication will be administered from Day 1 until completion of 24 weeks of study treatment or any other criterion for treatment discontinuation are met whichever is sooner. In other words, administration of ZOLADEX 10.8 mg will be continued until Week 12 or any other criterion for treatment discontinuation are met whichever is sooner. Administration of ZOLADEX 3.6 mg will be continued until Week 20 or any other criterion for treatment discontinuation are met whichever is sooner. Administration of tamoxifen will be continued until Week 24 or any other criterion for treatment discontinuation are met whichever is sooner.

Assessment schedule

Study visits to assess efficacy and safety are scheduled at Day 1(Visit 2), Week 12(Visit 3), and Week 24 (see Table 2 for study visit windows).

Assessments to identify disease progression will be conducted at each scheduled visit, Week 12 and Week 24. Assessments for progressive disease will also be done between scheduled visits as clinically indicated.

Final assessment of efficacy will be done at the time of disease progression or at Week 24 (Study completion visit) whichever is sooner.

Final assessment of safety will be done at Week 24 (Study completion visit) but if criterion for treatment discontinuation is met before Week 24, the assessment will be done 12 weeks after the final administration of ZOLADEX 10.8 mg or 4 weeks after the final administration of ZOLADEX 3.6 mg respectively or at Week 24 whichever is sooner.

The principal investigator/sub-investigator is responsible for following the schedule of study procedures as defined in the study protocol.

3.1.1 PK subgroup and schedule

Additional blood samples will be collected from at least 20 evaluable patients (PK subgroup) randomised to ZOLADEX 10.8 mg for assessment of goserelin plasma concentrations. Additional E_2 serum concentration assessments will also be made in these patients.

At least 10 Japanese patients will be recruited from Japan and at least 10 Non Japanese patients will be recruited from non-Japanese countries except for China.

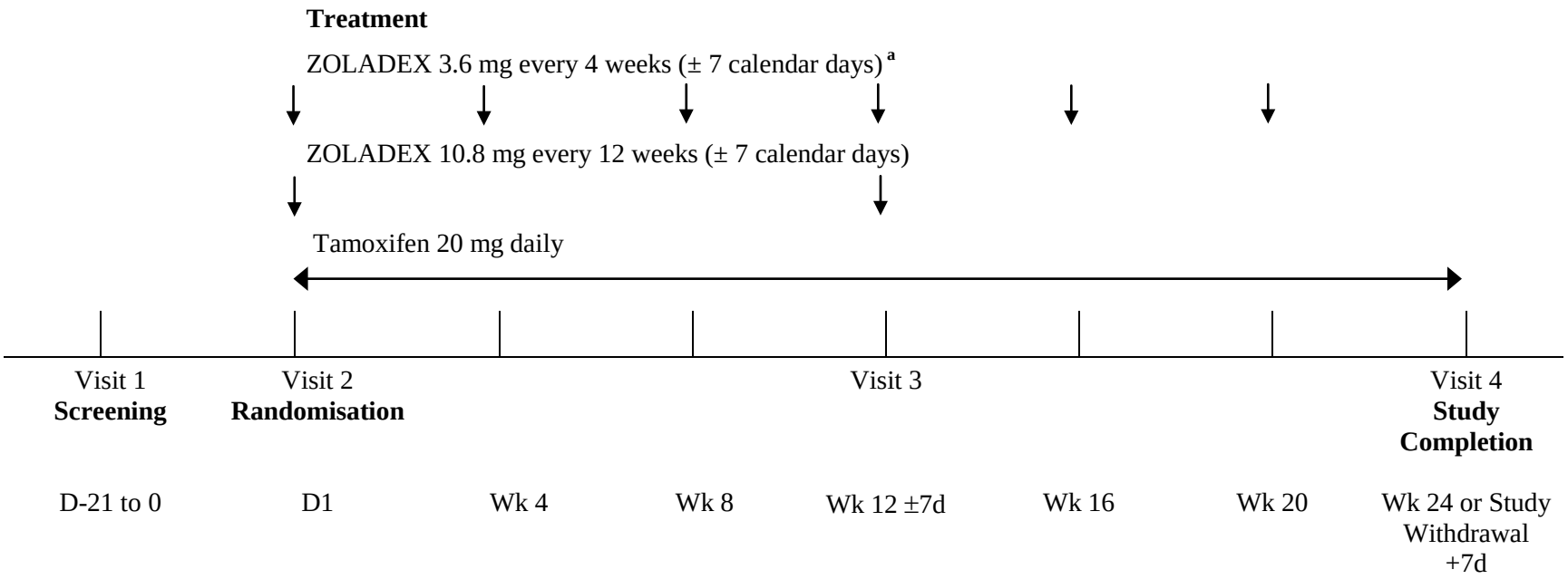
Patients will attend all main study visits (see Table 2) and will have additional visits for collection of blood samples at the schedule shown in Table 1.

Table 1 Study schedule for pharmacokinetic subgroup

Blood sample for:	**Time point for sampling**							
	Day 1	**Day 1**	**Day 1**	**Day 2**	**Day 3**	**Wk 4**	**Wk 12[b]**	**Wk 24**
	Pre-dose	**1 h ±5 min**	**2 h ±5 min**	**24 h ±2 h**	**48 h ±2 h**	**±7d**	**±7d[b]**	**±7d**
Goserelin plasma conc.	X	X	X	X	X	X	X	X
E_2 serum conc.[a]		X	X	X	X	X		

a) Only samples in addition to those scheduled for the main study (see Table 2) are included.
b) The sample should be taken prior to ZOLADEX 10.8 mg administration.

Figure 1 Study flow chart



a) Make sure that interval of the administration should not meet the criteria of Overdose (see Section 13.2)

Table 2 Study plan

Randomization ↓

Visit	**1**	**2**	**3**	**4**
Visit Description	**Screening**	**Treatment**		**Study Completion**
Time of Visit (Visit Window)	**Day -21 to Day 0**	**Day 1**	**Week 12 (±7d)**	**Week 24 or Study withdrawal (+7d)**
Informed consent (before study-related procedures)	X			
Medical history and demography	X			
Urine pregnancy test (repeated after amenorrhoea)	X	X[a]		
Physical examination	X			
Bone scan and chest assessment [b]	X			
Tumor assessment [c]	X		X	X [k]
Confirmation of ER, PgR and HER2 status	X			
Confirmation of patient eligibility	X			
Standard laboratory assessments [d]	X	X [i]	X	X
Sex hormones (E_2 and FSH)[e]	X	X [i]	X	X
Body weight, Vital signs (Blood pressure at rest, Heart rate, Body temperature)		X [i]	X	X
Height		X [i]		
PK Sampling [f]		X [f]	X [f]	X [f]
AEs [g]	←	—	—	→
Concomitant medications [g]	←	—	—	→

Table 2 Study plan

Randomization ↓

Visit	1	2	3	4
Visit Description	**Screening**	**Treatment**		**Study Completion**
Time of Visit (Visit Window)	**Day -21 to Day 0**	**Day 1**	**Week 12 (±7d)**	**Week 24 or Study withdrawal (+7d)**
ZOLADEX 3.6 mg or ZOLADEX 10.8 mg		X [j]	X [j]	
Tamoxifen 20 mg		←	—	→
Tamoxifen prescription [h]		X		

a) The pregnancy test is performed to confirm amenorrhoea due to the investigational product administration. It should be performed as soon as amenorrhoea is diagnosed according to the local standard. (See Section 6.4.6.1)

b) A chest assessment and bone scan are mandatory. Chest assessment must be done by chest X ray or chest CT or chest MRI. If there are any hotspots detected by bone scan, then they should be evaluated as appropriate according to local practice (eg, by x ray, computed tomography scan, or MRI). Tests already performed prior to screening (within 6 weeks before randomisation) may be used as screening assessments at the discretion of the investigator(s) (within 3 weeks before randomisation). For patients with prior chemotherapy, the screening imaging tests must have been performed at least 4 weeks after the last cycle of prior chemotherapy. See Section 6.3.1 for further details.

c) Tumor assessment should be done in the same manner as the baseline in accordance with RECIST Ver 1.1. For patients with prior chemotherapy, the screening imaging tests must have been performed at least 4 weeks after the last cycle of prior chemotherapy.

d) Standard laboratory tests will be done locally and actual blood values at screening will not be collected or entered into the database. The laboratory data at/after Day 1 will be collected and enterd. Screening tests will be used to assess suitability for entry into the study and confirmation of inclusion and/or exclusion criteria will be documented on the eCRF.

e) Screening tests will be analysed locally and are only used to assess suitability for entry into the study (see Section 6.2.1). Actual screening values will not be collected or databased but confirmation of eligibility will be documented on the eCRF. Tests on Day 1 and subsequent tests will be analysed using a central laboratory and will be databased. Samples will be taken pre-dosing on Day 1. From Week 12 onwards, blood samples will be drawn prior to ZOLADEX administration if dosing is due on the same day.

f) PK sub-group Only. For sampling schedule, see Table 1.

g) AEs and concomitant medication will be collected from the time of patient informed until 4 weeks after the final administration of ZOLADEX 3.6 mg or 12 weeks after the final administration of ZOLADEX 10.8 mg.

h) Tamoxifen will be prescribed at Visit2 for 24 weeks

i) The assessments will be performed before study dosing. Regarding the sampling schedule of E_2 for the PK sub-group, see Table 1.

j) Zoladex 3.6 mg will be administered every 4 weeks from Day 1 until Week 20. Zoladex 10.8 mg will be administered at Day 1 and Week 12.
k) Any patient who discontinues treatment for reasons other than disease progression (except for withdrawal of consent) should continue, where possible, to have objective tumour assessments until week 24 or until objective progression is confirmed according to RECIST (Ver1.1) which is sooner.

3.2 Rationale for study design, doses and control groups

Study design

This is a multicentre, open label, randomised, parallel group study to show that ZOLADEX 10.8 mg is non-inferior to ZOLADEX 3.6 mg, which has proven efficacy in ER positive breast cancer. This study will be open lable due to the different administration regimen of ZOLADEX 3.6 mg (every 4 weeks) and ZOLADEX 10.8 mg (every 12 weeks) but this is not expected to affect the results of the primary outcome variable, PFS, which will be measured by objective tumour assessment.

Doses and control groups

In this study, ZOLADEX 10.8 mg or ZOLADEX 3.6 mg will be taken in combination with selective estrogen receptor modulator, 'Tamoxifen (Nolvadex™[2])'. This is because the combination use of LHRH agonist and tamoxifen for pre-menopausal advanced breast cancer patients was shown to be more effective than alone in clinical trial (Klijn et al 2000, Klijn et al 2001). The reason why comparator treatment group is the combination of ZOLADEX 3.6 mg and tamoxifen 20 mg is that it is the standard treatment for pre-menopausal ER positive breast cancer patients. (Forward et al 2004). The two doses and associated regimens of ZOLADEX used in this study are the standard doses/regimens used in clinical practice.

Pharmacokinetic analysis

This study will collect PK and additional E_2 data from a subgroup of patients allocated to the ZOLADEX 10.8 mg treatment group in order to assess goserelin and E_2 serum concentrations in Japanese and Non Japanese (except for China) patients who have received ZOLADEX 10.8 mg. As this study requires additional blood samples to be taken, patients willing to participate in this subgroup will be required to provide additional informed consent (see Section 8.4.1). The PK profile of patients on ZOLADEX 3.6 mg is well characterised and so is not required in this study (see the latest ZOLADEX IB).

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

All patients eligible for the main study are potentially eligible for inclusion in the PK component of the study.

4.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

[2] Nolvadex is a trademark of the AstraZeneca group of companies.

1. Provision of written informed consent prior to any study specific procedures.
   - For the PK analyses in this study additional written informed consent will be required to confirm that they are willing to participate in this part of the study.

2. Female ≥20 years and pre-menopausal.
   - Pre-menopausal defined as 1) last menses within 1 year of randomisation, and 2) E_2 ≥10 pg/mL and FSH ≤ 30 mIU/mL within 4 weeks of randomisation. For patients who have had a hysterectomy, it is acceptable to meet only criterion 2.

3. Histological/cytological confirmation of breast cancer and are candidates to receive hormonal therapy as therapy for advanced breast cancer.
4. Hormone sensitivity (ER positive) of primary or secondary tumour tissue.
5. World Health Organization (WHO) Performance status of 0, 1 or 2 (see Appendix E).
6. At least one measurable lesion or assessable lesion according to RECIST(Ver1.1).

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled.

1. Patients who have received tamoxifen or other hormonal therapies as adjuvant therapy for breast cancer within 24 weeks before randomisation and/or who have received prior treatment with hormonal therapies for advanced breast cancer.
2. Patients who have received LHRHa as adjuvant therapy for breast cancer within 48 weeks before randomisation.
3. Patients who have received any radiotherapy as adjuvant therapy for breast cancer or for advanced breast cancer within 4 weeks before randomisation.
4. Patients who have received any chemotherapy within 4 weeks before randomisation.
5. Patients who have relapsed during adjuvant hormonal therapy or within 48 weeks after completion of adjuvant hormonal therapy and/or patients who have relapsed during adjuvant chemotherapy or within 24 weeks after completion of adjuvant chemotherapy.
6. Patients who have received chemotherapy for advanced breast cancer with the exception of first line chemotherapy providing that a) there is no evidence of progressive disease since the start of the chemotherapy and b) the patient has menses after starting chemotherapy.
7. Patients who have prior treatment with trastuzumab or lapatinib for early breast cancer as adjuvant therapy within 4 weeks before randomisation and/or who have prior treatment with trastuzumab or lapatinib for advanced breast cancer.
8. Presence of life-threatening metastatic visceral disease, defined as extensive hepatic involvement, or any degree (proven or suspected) of brain or leptomeningeal involvement (past or present) or symptomatic pulmonary lymhangitic spread. Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not compromised as a result of disease.
9. Estimated survival less than 24 weeks from the start of study therapy (Day 1) based on clinical judgment.

10. History (within previous 3 years before randomisation) of systemic malignancy other than breast cancer with the exception of basal cell/squamous cell carcinoma of the skin or cancer of the cervix that has been satisfactorily controlled.
11. Platelets $<100x10^9$/L; total bilirubin >1.5x upper limit of reference range (ULRR); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5xULRR if no demonstrable liver metastases or >5xULRR in presence of liver metastases.
12. Any other significantly abnormal laboratory test result at baseline that would place the patient at unusual risk or confound the results of the study as assessed by the investigator(s).
13. Treatment with a non-approved or experimental drug within the preceding 12 weeks before randomisation.
14. Patients with a relevant history of any severe concomitant disease that would place the patient at unusual risk or confound the results of the study (eg, a strong family history of osteoporosis or severe renal or hepatic impairment) as assessed by the investigator(s).
15. Patients who, for whatever reason (eg, confusion, infirmity, alcoholism) are unlikely to comply with study requirements as assessed by the investigator(s).
16. Patients considered by the investigator(s) to be at risk of transmitting any infection through blood or other body fluids including the agents for acquired immune deficiency syndrome (AIDS) or other sexually transmitted disease or hepatitis.
17. History of bleeding diathesis (ie, disseminated intravascular coagulation (DIC) or clotting factor deficiency) or long-term anticoagulant therapy (other than antiplatelet therapy and low dose warfarin) .
18. History of any hypersensitivity to active or inactive excipients of ZOLADEX or tamoxifen.
19. Pregnancy or breast feeding.
20. Patients unwilling to stop taking any drug known to affect sex hormonal status, or in whom it would be inappropriate to stop.
21. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study centre) .
22. Previous enrolment or randomisation of treatment in the present study.

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. anti-coagulant therapy
   - Patients receiving long-term anti-coagulant therapy with warfarin should be managed appropriately to reduce the risk of injection site reactions

   - Patients who need to begin anti-coagulant therapy while receiving study treatment may be treated at the discretion of the investigator(s). There is an

increased risk of haemorrhage in these patients and the investigator(s) should decide whether that risk is outweighed by the possible benefits of continued treatment

2. anti-platelet therapy (eg, acetylsalicylic acid, ticlopidine, clopidogrel)
   - Patients receiving anti-platelet may be at increased risk of bleeding from injection. The investigator(s) should decide whether the risk is outweighed by the possible benefits of continued treatment. It is advised to apply direct pressure to the injection site in these patients

3. Medication including over-the-counter medications which are known to affect sex hormone status (eg, hormone replacement therapy [HRT] or oral contraceptives)
   - They are not permitted since informed consent until final administration of study medication including study concomitant medication.

4. Anti-cancer chemotherapy, radiotherapy or trastuzumab or lapatinib
   - They must not be started after from entry to the study through to final administration of study medication including study concomitant medication; if needed due to disease progression (as confirmed by imaging) the patient should be withdrawn from the study

5. Contraception
   - Non-hormonal methods of contraception should be used from signing informed consent until study completion visit

6. Blood donation
   - Blood donation should be restricted since informed consent until study completion visit

5.2 Subject enrolment and randomisation

5.2.1 Procedures for randomisation

Patients will be assigned a unique identifying number. The patient number will be assigned on enrolment (ie, provision of written informed consent) in chronological order of screening and this number will be used throughout the study. If a patient is subsequently not randomised, her patient number will not be re-used. Patient identifiers will be 8-digit numbers, Exxyyzzz, where xx is a 2-digit country ID, yy is a 2-digit centre ID and zzz is a 3-digit patient identifier.

Randomisation will be done per centre, and a sequence of randomisation numbers will be assigned to each study centre. The size of randomisation blocks will not be disclosed to the study centres. The study drug will be randomly assigned to the randomisation numbers in advance according to the randomisation scheme.

After confirming a patient's eligibility to enter the study, the investigator(s) will fill in the Patient Enrolment Form and will send this to the Centralised Registration/Allocation Centre via the web site. The Centralised Registration/Allocation Centre, after confirming that the patient is eligible, will randomise the patient.

If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

5.2.2 Assignment to the pharmacokinetic subgroup

For patients allocated to ZOLADEX 10.8 mg, the investigator(s) will ask the patient whether or not she is willing to participate in the PK subgroup. If yes, the investigator(s) should ensure that the patient fills in the informed consent form for the PK subgroup (see Section 8.4.1). Once the required numbers for the PK subgroup are attained, all sites will be informed.

5.3 Procedures for handling subjects incorrectly enrolled or randomised

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomised. There can be no exceptions to this rule.

Where subjects that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where it was confirmed post initiation that subjects fail to meet the study criteria, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the subject should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study - NA

5.5 Treatments

5.5.1 Identity of investigational product(s)

Details of the investigational study medication and comparator are provided in Table 3.

Each depot is supplied sterile in a disposable syringe applicator which is sealed in a light and moisture-proof aluminium pouch.

Table 3 Investigational products and comparator

	Investigational product	Comparator
Drug substance	Goserelin acetate	Goserelin acetate

Table 3 Investigational products and comparator

	Investigational product	Comparator
Strength, dosage form	10.8 mg depot for injection (equivalent to 10.8 mg goserelin) homogeneously dispersed in co-polymer	3.6 mg depot[a] for injection (equivalent to 3.6 mg goserelin) homogeneously dispersed in co-polymer
Excipients	95/5 lactide/glycolide biodegradable copolymer	50/50 lactide/glycolide biodegradable copolymer
Manufacturer	AstraZeneca UK Limited	AstraZeneca UK Limited
Formulation number	F06054	F05589

Table 4 Study concomitant medication

	Study concomitant medication
Drug substance	Tamoxifen
Brand name	Nolvadex
Strength, dosage form	20 mg oral tablets (containing 30.4 mg tamoxifen citrate equivalent to 20 mg of tamoxifen)
Excipients	Lactose, Corn starch, Croscarmellose Sodium, Gelatin, Magnesium stearate, Hydroxypropylmethylcellulose, Macrogol 300, Titanium oxideCarboxymethylcellulose
Manufacturer	AstraZeneca UK Limited
Formulation number	F6293

5.5.2 Doses and treatment regimens

5.5.2.1 Treatment procedure of study medication

During the treatment period, patients will receive either ZOLADEX 3.6 mg or ZOLADEX 10.8 mg at dose visits:

Patients will be administered ZOLADEX at the study centre by the investigator(s) (or by designated medically qualified or nursing study centre personnel if local regulatory guidelines permits. It is highly recommended that patients attend the study centre for all dose visits. When dosing at the study centre is not possible, medically qualified or nursing study centre personnel may visit the patients for home study drug administration.

Arm of patients who will take Investigational product (ZOLADEX 10.8 mg)

- ZOLADEX 10.8 mg (goserelin acetate): one subcutaneous depot injection into interior abdominal wall once every 12 weeks(± 7 days).(i.e. Visit 2, Visit 3)

- One oral tamoxifen 20 mg tablet daily.

Arm of patients who will take Comparator (ZOLADEX 3.6 mg)

- ZOLADEX 3.6 mg (goserelin acetate): one subcutaneous depot injection into interior abdominal wall once every 4 weeks (±7 days)(i.e. Visit 2, Week 4, Week 8, Week 12:Visit 3, Week 16 and Week 20)

- One oral tamoxifen 20 mg tablet daily.

<<Japan Specific procedures>>

In Japan, the patients must visit the study centre and the patients will be administered ZOLADEX 3.6 mg or ZOLADEX 10.8 mg by investigator(s). (Ditto with Section 5.7 in the clinical study protocol).

The following contents in Section 5.5.2.1 of the clinical study protocol do not apply to the Japanese study.

"When dosing at the study centre is not possible, medically qualified or nursing study centre personnel may visit the patients for home study drug administration."

Patients will be given pack of tamoxifen containing sufficient tablets for 24 weeks supply at Visit2.

Patients will administer tamoxifen by themselves and will be instructed as follows:

- To swallow the tablet whole with water or another non-alcoholic drink at approximately the same time each day.

- In the case that a dose is missed, to take the missed tablet as soon as they remember and to take the next dose as scheduled, unless it is almost time for their next dose, or they remember at the next dose.

- To return a bottle of tamoxifen.

Administration of Investigational product (ZOLADEX 10.8 mg) or comparator (ZOLADEX 3.6 mg) should be started within 1 day after randomisation. Study concomitant medication (Tamoxifen 20 mg) should be started on the same day of or one day after starting the administration of ZOLADEX.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (Investigational products-GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

All primary containers (pouches or bottles) will have an investigational product label permanently affixed to the outside and will be clearly marked with country-specific local regulations, stating that the drug is for clinical study use only and should be kept out of reach of children. Details of labelling study drug will be described in a separate document, "Storage conditions of investigational products".

5.5.4 Storage

All study medication must be kept in a secure place under appropriate storage conditions in accordance with local regulatory guidelines. A description of the appropriate storage and shipment conditions for ZOLADEX 10.8 mg and ZOLADEX 3.6 mg are specified on the investigational product label and IB. For tamoxifen, a description of the appropriate storage and shipment conditions are specified on the respective labels.

All patients will be instructed to store tamoxifen according to the instructions on the product label.

A description of the appropriate storage and shipment conditions are specified on 'Procedure of storage conditions for investigational product'.

5.6 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) and recorded in the appropriate sections of the eCRF.

5.6.1 Pre-study medications

Restriction of pre-study medications are stated in the exclusion criteria. (See Section 4.2)

5.6.2 Concomitant medications

Bisphosphonates (Bone resorption inhibitor)

- Bisphosphonates (Bone resorption inhibitor) are permitted during the study without change of the dose and usage, only if started before randomisation.

For the restriction of anti-coagulant therapy and anti-platelet therapy, and prohibiting medication, see Section 5.1.

5.6.3 Medication after discontinuation of study drug

Medication after discontinuation of study drug is at the discretion of the investigator(s).

5.7 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of the eCRF.

The dates and doses of all ZOLADEX doses will be recorded on the eCRF.

Patients will be asked to return their unused tamoxifen medication at study completion visit. Compliance will be assessed by means of tablet counts of returned unused study medication at each clinic visit. Compliance will be calculated at the end of the study.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol. And study centres will be supplied with sufficient medication for a total of 24 weeks per patient.

The investigational product storage manager will account for all study drugs dispensed to and returned from the subject.

It is the study centre's responsibility to establish a system for handling study treatments, including investigational products, so as to ensure that:

- Deliveries of such products from the sponsor are correctly received by a responsible person
- Deliveries are recorded
- The study drugs are handled and stored safely and properly
- The study drugs are dispensed only to study patients in accordance with the protocol
- Patients return all unused study drug and empty containers to the investigator(s)
- Unused study medication and empty containers are destroyed at the centre. In Japan, unused study drugs and empty containers will be returned to the sponsor through the monitor.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the trial treatment was dispensed, the quantity and date of dispensing, and unused study treatment returned to the investigator(s). This record is in addition to any drug accountability information recorded on the eCRFs. Any discrepancies must be accounted for on the appropriate form. Certificates of delivery and return must be signed, preferably by the investigator(s) or a pharmacist, and copies retained in the investigator file.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents "Procedures for drug accountability" and "Procedures for drug storage" which describes the specific requirements. The investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

The principal investigator/sub-investigator is responsible for ensuring that the patient has returned all unused study drug. The patient must be asked to return unused study drug, empty cartons and packaging. Any study drug materials returned by the patient must be promptly passed to the Investigational Product Storage Manager to complete drug accountability.

5.8 Discontinuation of study treatment

Specific reasons for study completion are:

- Patient complete all treatment for 24 weeks and all assessments as scheduled
- Voluntary discontinuation by the patient who is, at any time, free to discontinue her participation in the study, without prejudice to further treatment
- Patient lost to follow-up
- Patients complete all of required assessment after meeting criterion of discontinuation

Specific reasons for discontinuing a patient from this study treatment are:

- Voluntary discontinuation by the patient who is, at any time, free to discontinue her participation in the study, without prejudice to further treatment
- Safety reasons, as judged by the investigator(s) and/or Study Delivery Team Physician
- Severe non-compliance to protocol, as judged by the investigator(s) and/or Study Delivery Team Physician
- Incorrect enrolment of the patient (ie, the patient does not meet the required inclusion/exclusion criteria) if this is considered to be a safety issue by the investigator(s) and Study Delivery Team Physician
- Pregnancy
- Observation of disease progression as defined by any one of the following:
  - Progression disease according to RECIST (Ver1.1) (See Appendix D.)
  - Death of the patient in the absence of progression

  Any clinical evidence of disease progression (eg, worsening of symptoms such as bone pain) must be confirmed by imaging. Study treatment should only be stopped if clinical evidence of disease progression is confirmed by imaging.

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The Principal Investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. Adverse events will be followed up and study drug should be returned by the subject.

Withdrawal from the study

On patient withdrawal of consent, the assessments required at Study Completion (Visit 4, see Table 2) should be performed where possible. Patient data will not be collected beyond the date of consent withdrawal.

Patients who withdraw their consent for study participation will no longer receive any protocol-mandated assessments (including assessments for the PK subgroup for those patients also enrolled in this subgroup).

Withdrawal from the PK subgroup

Patients who withdraw from the PK subgroup will not undergo further protocol-mandated assessments specific to the PK subgroup beyond the point of withdrawal. Patients who withdraw their consent for participation in the PK subgroup should be asked whether they also wish to withdraw their consent to participate in the main study. In this case, the above procedures should be followed for discontinuation from the study.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and study drug should be returned by the subject.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The Principal Investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the electronic CRFs (eCRFs) provided by AstraZeneca. The eCRF will be accompanied with ‘Instructions for the Investigator’, which should be followed. These instructions provide guidance for the recording of study data in the eCRF including how to change data incorrectly recorded.

The investigator(s) will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator(s) ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement with applicable information. The principal investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

6.2 Data collection and enrolment

6.2.1 Screening and demographic measurements

The following screening and demographic data will be collected in the eCRF (see Table 2 for the timing of these assessments). Tests performed before screening may be used as screening assessments with patient informed consent

- Provision of written informed consent
  - Provision of written informed consent must be obtained prior to screening for all patients.
- Date of birth, sex, and race
- Relevant medical and surgical history, including menstrual status and concurrent illness
- Urine pregnancy test
- Previous therapy, including surgery for early breast cancer (concomitant medications will be recorded from the informed consent day until the Study Completion Visit)
- Physical examination
- Bone scan and chest assessment
  - If there are any hotspots detected by bone scan, then they should be evaluated as appropriate according to local practice (eg, by x ray, computed tomography scan, or MRI).
  - Chest assessment must be done by chest X ray or chest CT or chest MRI.
  - See Section 6.3.1 for further details
- Tumour assessment according to RECIST criteria (Ver1.1)
- Haematology, clinical chemistry analysis and sex hormone assessment

- For assessment of patient eligibility for study entry, the blood samples will be collected according to standard local practice and analysed at the local laboratory of each study centre using standard procedures. Platelets, AST, ALT, total bilirubin, E_2, and FSH must be measured. The actual values will not be collected in the eCRF or entered into the study database but confirmation that the values meet the inclusion or exclusion criteria will be recorded in the eCRF.

- Note that the E_2 and FSH assays used by the local laboratories may be different from those used by the central laboratory (Covance Asia Pte. Ltd., see Section 6.3.3).

- Histological or cytological confirmation of breast cancer
- Confirmation of ER, PgR and HER2 status of primary or secondary tumour tissue
- Confirmation that Patients fulfil all inclusion and exclusion criteria before randomised to treatment.
- Confirmation of AEs and concomitant medications

6.3 Efficacy

6.3.1 Progression Free Survival

Screening assessments should be performed within 21 days prior to randomisation and do not need to be repeated unless the there is a reason to believe that there has been a change to tumour burden. However, tests performed before screening (within 6 weeks before randomisation) may be used as screening assessments at the discretion of the investigator(s) (with patient informed consent), although it is strongly recommended that tests are done within 3 weeks before randomisation where possible. For patients who have had prior first line chemotherapy for advanced breast cancer the screening imaging tests must have been performed at least 4 weeks after the last cycle of prior chemotherapy.

The screening assessment will be documented according to RECIST as the “baseline” assessment against which all subsequent tumour evaluations will be evaluated.

Tumour assessment will be done according to RECIST (Ver.1.1), which requires that the same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up. Any other sites at which new disease is suspected should be also be appropriately imaged. Imaging will be done by the investigator(s) or designee.

Any patient who discontinues treatment for reasons other than disease progression (except for withdrawal of consent) should continue, where possible, to have objective tumour assessments until week 24 or until objective progression is confirmed according to RECIST (Ver1.1) which is sooner.

6.3.2 Objective tumour response

Objective tumour response will be assessed at each tumour assessment until Week 24 in those patients with measurable disease at screening (see Table 2 for the timing of assessments).

Imaging methods for tumour assessment are provided in Section 6.3.1. Response will be evaluated using RECIST criteria (Ver.1.1), which are provided in Appendix D.

6.3.3 Oestradiol and follicle stimulating hormone serum concentration

Blood samples for measurement of E_2 and FSH serum concentrations will be collected from all patients at scheduled visits (see Table 2) by the investigator(s) or designee according to standard procedures. From Week 12 onwards, the blood samples will be drawn prior to ZOLADEX administration. See Section 6.2.1 for details of samples collected at screening.

All blood samples for E_2 and FSH serum concentrations analysis collected from Day 1 onwards will be analysed using a central laboratory according to the standard procedures described in the laboratory manual. The central laboratory will be required to provide up-to-date reference ranges.

See Section 7.1 for the total estimated volume of blood samples to be collected and the handling of blood samples. Evaluation of E_2 and FSH serum concentrations will be done by the central laboratory according to internal assay validation documentation.

Blood samples collection, transfer and storage for measurement of E_2 and FSH serum concentrations will be performed by .

PK subgroup

In addition, blood samples for measurement of additional E_2 samples will be collected from the patients in the PK subgroup, at the time points shown in Table 1, by the investigator(s) or designee according to standard procedures. On Day 1, blood samples are taken within 5 minutes of the protocol-specified time; on Days 2 and 3, sampling is done within 2 hours of the scheduled time; and from Week 4 onwards sampling is done within 7 calendar days of the scheduled time. From Week 12 onwards, the blood samples will be drawn before ZOLADEX 10.8 mg administration. The time that each blood sample is taken will be recorded in the eCRF.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.4.1 Definition of adverse events

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.

Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an adverse event as far as the deterioration can be anticipated.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), 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

Japan specific definition:
Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment

- 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.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant eCRF must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?”. For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as “yes”. Elective hospitalisations to facilitate treatment procedures should not be reported as SAEs.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Non serious AEs and SAEs will be collected from the time of patient informed until 4 weeks after the final administration of ZOLADEX 3.6 mg or 12 weeks after the final administration of ZOLADEX 10.8 mg (see Section 3.1).

Follow-up of unresolved adverse events

After the initial AE/SAE report the investigator(s) is required to follow up proactively each patient and provide further information to the sponsor on the patient's condition. During the study all AE/SAEs should be followed up to resolution or until the condition stabilises, unless the event is considered by the investigator(s) to be unlikely to resolve due to the patient's underlying disease (in these cases, the investigator(s) must record their opinions in the patient's medical records), or the patient is lost to follow-up.

AstraZeneca reserves the right to ask for further information on any AE which may be considered of interest.

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- Date when the AE started and stopped
- Maximum CTCAE grade (For CTCAE version 3.0, see Appendix F)
- Whether the AE is serious or not
- Investigator causality rating against the each Investigational Product (yes or no) : ZOLADEX 3.6 mg, ZOLADEX 10.8 mg and tamoxifen
- Causality assessment in relation to Other medication
- Action taken with regard to investigational product
- Subject received any treatments (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE

- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE

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 6.4.2. 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.

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "*Have you had any health problems since the previous visit/you were last asked?*", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator(s) uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Recurrence

Any events that are unequivocally due to recurrence of the breast cancer must not be reported as an AE (see Section 6.4.1).

Deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death that is clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as a SAE

- Where death is not due (or not clearly due) to progression of disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death

- Deaths with an unknown cause should always be reported as a SAE. A post mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post mortem results should be forwarded to the sponsor within the usual timeframes

A statement of death form should be submitted at any point during the study (to the sponsor) when a patient has died.

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE as they are considered to be disease progression.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 13.2 regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 13.3. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as “immediately but no later than the end of the next business day”) of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator should notify the serious adverse events in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s); study code, site number, Enrolment code, adverse event, seriousness, start date. The following detailed information should be sent to AstraZeneca as soon as it becomes available;

Severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of adverse event, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

In addition AstraZeneca will provide the information on the serious adverse drug reactions collected domestically and abroad regarding the investigational product to the Head of the study site, Principal Investigator and the regulatory agency as per local requirements. The Head of the study site must submit a written report to the IRB providing the information reported by AstraZeneca.

Reporting Procedure of Serious Adverse Events using Web-based Data Capture (WBDC) system.

The investigator(s) and other site personnel will access Web Based Data Capture (WBDC) system and report SAE information by entering it into the relevant eCRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative. If the system is unavailable, the investigator(s) should take other appropriate measures to provide SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator(s) is responsible for completing the eCRF as soon as the system becomes available again.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into eCRF via WBDC system by the investigator(s).

6.4.5 Laboratory safety assessment

All blood samples will be collected according to standard procedures.

At Day 1 (pre dose), Week 12 and Week 24, the laboratory tests in Table 5 are performed at each study sites according to the standard procedures described in the laboratory manual of each study sites.

Further laboratory tests in addition to those in Table 5 may be done locally at the discretion of the investigator(s) as clinically indicated. Clinical decisions may be based on locally obtained laboratory tests.

For blood volume see Section 7.1.

Table 5 Clinical chemistry and haematology parameters

Clinical chemistry	Haematology
ALT	Absolute neutrophil count
Albumin	Haematocrit
Alkaline phosphatase	Haemoglobin
AST	Mean cell volume
Calcium	Platelet count
Creatinine	White blood cell count (total)
High density lipoprotein cholesterol	
Inorganic phosphate	
Low density lipoprotein cholesterol	
Plasma glucose	
Potassium	
Lactate dehydrogenase	
Triglyceride	
Sodium	
Total bilirubin	
Total cholesterol	

All clinical chemistry parameters measured in serum unless stated otherwise

6.4.6 Other safety assessments

6.4.6.1 Pregnancy status

In order to confirm that the presence of amenorrhoea is due to the administration of study drug and not due to pregnancy in this potentially child-bearing patient population, a urine pregnancy test will be done as soon as amenorrhoea is diagnosed according to the local standard.

In the event of suspected pregnancy during the study, a urine test will be done.

See Section 13.3 for procedures in the case of pregnancy.

6.4.6.2 Vital Signs

Blood pressure, heart rate, body temperature and body weight will be assessed at all scheduled visit after Visit 2.

Height will be measured at Visit 2 (see Table 2).

6.5 Patient reported outcomes (PRO) - NA

6.6 Pharmacokinetics

The methods for collection of blood samples and derivation of PK variables are presented below in Sections 6.6.1 and 6.6.2. These samples will be collected in patients in the PK subgroup only. Note that additional samples for E_2 analysis will also be collected in these patients, and these are described in Section 6.7.

6.6.1 Collection of samples

Blood samples for measurement of plasma concentrations of goserelin will be collected from the patients in the PK subgroup at the time points shown in Table 1 by the investigator(s) or designee according to standard procedures. On Day 1, the blood samples are taken within 5 minutes of the protocol-specified time; on Days 2 and 3, the sampling is done within 2 hours of the scheduled time; and from Week 4 onwards, the sampling is done within 7 calendar days of the scheduled time. From Week 12 onwards, the blood samples will be drawn prior to ZOLADEX 10.8 mg administration to provide data on trough levels. The date and time that each blood sample is taken will be recorded in the eCRF.

See Section 7.1 for the total estimated volume of blood samples to be collected.

The obtained plasma samples will be transferred to the bioassay laboratory,

. For transfer to , plasma samples will be labelled, stored and shipped according to AstraZeneca standard operating procedures. Plasma samples will be sent from the study sites to or delegate, who will forward the samples to .

Plasma samples for measurement of plasma concentrations of goserelin will be collected by or delegate, stored appropriately for a while, and then or delegate will transfer the samples to .

6.6.2 Determination of plasma concentrations of goserelin

will determine the plasma concentrations of goserelin using the well validated bioanalytical method according to the standard procedures.

6.7 Pharmacodynamics

According to the schedule of Table 1 and Table 2, the blood sampling for E_2 and FSH will be performed.

6.8 Pharmacogenetics -NA

6.9 Health economics - NA

7. BLOOD SAMPLING PROCEDURES

7.1 Volume of blood

The estimated volume of blood that will be drawn from each patient in this study is indicated in Table 6. The maximum total volume of blood drawn from each patient will not exceed approximately 60 mL (or approximately 112.5 mL for patients in the PK subgroup).

Where blood samples for more than one analysis are to be collected at the same visit, these will be taken at the same time where possible.

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 6 Volume of blood to be drawn from each subject

Assessment		**Sample volume (mL)**	**No. of samples**		**Total volume (mL)**
			Screening	**Day 1 to Week 24**	
Pharmacodynamics (E_2 and FSH)		5[a]	1	3	20
Safety	Haematology	4[a]	1	3	16
	Clinical chemistry	6[a]	1	3	24
Total for main study					60
Additional samples for PK subgroup					
	Plasma concentration of goserelin	5	0	8	40
	Serum E_2 concentration	2.5[a]	0	5	12.5
Total for additional samples					52.5

a) Blood volumes may vary for those samples collected for analysis by local laboratories

7.2 Handling, storage and destruction of blood samples

7.2.1 Pharmacokinetic samples

Plasma samples must be stored at -20°C or below until they are used for analysis. If the samples will be transferred to the bioassay laboratory, , they must be kept at -20°C or below during transportation. These samples must be used for analysis within 22 months after collection. However, results from analyses of samples stored longer than the time period for which stability has been demonstrated should not be reported unless

complementary analyte(s) stability data is acquired and amended to the relevant method validation report.

7.2.2 Serum E_2 and FSH samples

Except for the screening measurement, E_2 level and FSH level must be measured by Covance Asia Pte. Ltd.. Each laboratory at the study centres can be measured them at screening.

Serum samples for E_2 and FSH measurement will be collected by or delegate and stored at -20°C or below until they are used for analysis.
will transfer the samples to according to the specified procedure.

The long-term stability of the analyte(s) should be documented in method validation produced by the assay laboratories. Results from analyses of samples stored longer than the time period for which stability has been demonstrated should not be reported unless complementary analyte(s) stability data is acquired and amended to the relevant method validation report.

7.2.3 Disposal of samples

The samples will be used up or disposed of after the clinical study report has been finalised.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

Blood samples that will be analysed at local laboratories will be labelled, stored and transported according to local procedures.

For transfer to the central laboratory, blood samples will be labelled, stored and shipped according to the procedures outlined in the central laboratory's study manual.

For transfer to the , blood samples for PK analysis will be labelled, stored and shipped according to AstraZeneca standard procedures. All samples to be sent to
will be initially sent to by the study sites;
will then forward the samples to

7.4 Chain of custody of blood samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected blood samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of collection.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

7.5 Withdrawal of informed consent for donated blood samples

If a subject withdraws consent to the use of donated blood samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

If a subject withdraws consent to the use of donated blood samples, then the subject may continue in the study.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that blood samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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 and Human Blood Samples.

<<Japan Specific requirement>>

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs , partially revised by MHLW Ordinance and their related notifications

8.2 Subject data protection

The Master ICF 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, patients will authorise the collection, use and disclosure of their study data by the investigator(s) and by those persons who need that information for the purposes of the study.

The Master ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data processed by AstraZeneca will be identified by enrolment number and study code.

The Master ICF will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB or IEC may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The investigator(s) will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator(s) should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

<<Japan Specific requirements>>

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form, eCRFs and any other written information and/or materials to be provided to the subjects. The Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

- Ensure each subject is notified that they are free to discontinue from the study at any time.

- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File.

- Ensure a copy of the signed Informed Consent Form is given to the subject.

- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

<<**Japan Specific procedures**>>

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) should inform the subject of such information immediately, record this in a written form, and confirm with the subject if he or she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 8.5). The investigator(s) should re-explain the subjects using updated Informed Consent Form even if although the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

8.4.1 Informed consent for the pharmacokinetic subgroup

The blood sampling in this study for the purposes of PK and additional E_2 analyses is optional to those patients randomised to ZOLADEX 10.8 mg and the patient may participate in other components of the study without agreeing to have additional blood samples taken. If a patient declines to participate in the PK subgroup, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they provide written informed consent for the main study.

For Participation in the PK subgroup, Patients will provide informed consent in addition to written informed consent for the main study. Consent may be provided by the patient's legally acceptable representative/impartial witness, as appropriate, according to the local regulatory and legal requirements. The principal investigator is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the PK component of the study at any time. If modifications to the ICF are made according to local requirements, the new version has to be approved by the sponsor.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

<<Japan Specific procedures>>

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an 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 stated in Section 8.1. The investigator(s) will contact

AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

<<Japan Specific additional procedures>>

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

9. STUDY MANAGEMENT

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- 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(s)

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative 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 and timely recorded in the eCRFs, that blood samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed.

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the subject's blood samples is reported and blood samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

<<Japan Specific additional requirements>>

1. Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records Original data recorded on the eCRFs and regarded as source data are as specified in the Clinical Study Agreement.

9.3.2 Direct access to source data in Japan

The Head of the institution and the Principal Investigator/sub-investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRFs against source data before collecting the eCRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator/sub-investigator has submitted the eCRFs to AstraZeneca. If the investigator(s) wishes to amend the collected eCRFs, the monitor will ensure that the Principal Investigator/sub-investigator has documented the amendment in writing (signed and dated) and provided this to AstraZeneca.

9.4 Study agreements

The Principal Investigator at each/the centre should 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 terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

The CSA will be between the AstraZeneca and the Principal Investigator.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

<<Japan Specific procedures>>

(i) **Study files.** AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.

(ii) **Period of record retention**. The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

<<Japan Specific procedures>>

9.4.2 Deviation from the clinical study protocol in Japan

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical trial (e.g. changes to the organisation/structure of the sponsor, the name/department name of the medical institution, the address or phone number of the medical institution or the sponsor, the job title of the investigator(s), and monitors).

The investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the investigator(s) should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca K.K. or the IRB approval, only in the event of a medical emergency, e.g. it is only way to avoid an immediate hazard to the patients. In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca K.K. and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca K.K. should be obtained via the head of the study site.

9.5 Study timetable and end of study

Before a patient'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
- Approval of the study by the head of study site **(Japan Only)**
- Approval of the study, if applicable, by the regulatory authority

Planned duration of the study

Study period:

Registration period:

The investigator(s) will be notified by representatives of the sponsor when recruitment is complete.

The end of study is defined as the last visit of the last patient undergoing the study, after which no patient will be exposed to study-related activities.

Discontinuation or suspension of the whole study programme

If AstraZeneca decides to prematurely terminate or suspend the study, the principal investigator, sub-investigator, head of the study site for Japan and regulatory authorities must receive written notification of the reasons for the premature termination or suspension.

The principal investigator/sub-investigator will immediately notify the decision to the patients, give appropriate medical treatment, take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study (Japan Only)

Upon terminating the study, the Principal Investigator/sub-investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution's rules. The head of the study site, who is informed of the termination by the investigator(s), will provide a written notification of the results to the IRB and AstraZeneca.

10. DATA MANAGEMENT

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. The principal investigator will then sign the eCRF electronically. Clean file occurs when all data have been declared clean and signed by the principal investigator. The data will be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database and/or the Investigational Site.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

The tumour assessment at screening is regarded as baseline.

11.1.1 Progression Free Survival

The primary outcome variable, PFS, is defined as the proportion of patients who remain progression-free at 24 weeks.

Observation of disease progression is defined by any one of the following:

– Enlargement of the existing lesion or development of a new lesion according to RECIST (Ver.1.1.) (see Appendix D)

– Death of the patient in the absence of progression

11.1.2 Objective tumour response

Responders are defined as those patients with a best objective tumour response of complete response or partial response during the first 24 weeks of therapy (see RECIST criteria in Appendix D). ORR is defined as the proportion of patients who are responders.

Overall response at Week 12 and Week 24 will be assessed according to the RECIST (Ver. 1.1). The response will not need to be confirmed.

Patients without measurable disease at baseline according to RECIST (Ver1.1) will not be evaluated for objective tumour response but will be assessed for disease progression only (see Section 6.3.1).

11.2 Calculation or derivation of safety variable(s)

The laboratory results and vital signs at Visit 2 pre-dose are regarded as baseline.

11.2.1 Laboratory safety measurements and variables

Section 6.4 provides details on how AEs based on laboratory tests will be recorded and reported. Conditions that are considered by the investigator(s) to be unequivocally due to disease progression will not be recorded as AEs.

At screening, absolute values of laboratory safety data will not be databased; confirmation that the values meet the inclusion or exclusion criteria will be recorded in the eCRF. From Day 1 onwards, all laboratory safety data will be databased. Confirmation that samples have been taken will be recorded in the eCRF for all samples; data will be recorded into the eCRF.

11.2.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert’s judgement,

significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory data and vital sign will be performed for identification of 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.

11.3 Calculation or derivation of patient reported outcome variables-NA

11.4 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses will be performed at Pharnacokinetics Group, Early Phase Development Department, AstraZeneca K.K. The following PK parameters will be determined using standard non-compartmental methods, based on the individual plasma concentration–time profiles of goserelin following the first dose of ZOLADEX 10.8 mg. The actual sampling times will be used for the PK analysis.

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Area under the plasma concentration – time curve from 0 to time t ($AUC_{(0-t)}$)
- Area under the plasma concentration – time curve from 0 to specifically 12 weeks ($AUC_{(0\text{-}12\ weeks)}$)

11.5 Calculation or derivation of pharmacodynamic variable(s)

11.5.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

Relationship between plasma concentrations of goserelin and E_2 serum concentrations will be assessed in the PK subgroup.

11.5.2 Population analysis of pharmacokinetic/pharmacodynamic variables - NA

11.6 Calculation or derivation of pharmacogenetic variables - NA

11.7 Calculation or derivation of health economic variables -NA

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

A comprehensive statistical analysis plan (SAP) will be prepared prior to database lock, which will provide a more detailed specification of the analyses to be performed and the outputs to be produced. The sponsor will produce the SAP and perform all statistical analyses. Any

deviations from those analyses presented here and/or in the SAP will be detailed in the CSR. All outputs will be produced using .

12.1 Description of analysis sets

Five patient analysis sets will be used in the study as defined in Table 7: the full analysis set (FAS), per protocol set (PPS), safety analysis set, PK subgroup set, and E_2 subgroup set.

Table 7 Definition of analysis sets

Analysis set	Definition
Full analysis set (FAS)	This population comprises all patients randomised to study treatment (regardless of actual treatment(s) received) who had data available for any endpoint post-randomisation. Patients will be included in the analysis according to the treatment to which they were randomised, thus giving an intention to treat analysis.
Per protocol set (PPS)	This population comprises all randomised patients who received at least one dose of study treatment, and who did not significantly violate or deviate from the protocol. Patients will be included in the analysis according to the treatment which they received.
Safety analysis set	This population comprises all randomised patients who received at least one dose of study treatment. Patients will be included in the analysis according to the treatment which they received.
For patients in the PK subgroup:	
PK subgroup set	This population comprises the subgroup of study patients who were randomised to receive and who did receive ZOLADEX 10.8 mg, and who consented to provide samples for PK and additional E_2 analyses, and for whom data are available for any PK endpoint post-randomisation.
E_2 subgroup set	This population comprises the subgroup of study patients who were randomised to receive and who did receive ZOLADEX 10.8 mg, and who consented to provide samples for PK and additional E_2 analyses, and for whom data are available for any E_2 endpoint post-randomisation.

More detailed rules for allocation of patients to the different analysis sets defined in Table 7 will be given in the SAP.

The primary analysis set for evaluation of the primary and secondary efficacy and PD outcome variables (for the main study) will be the FAS. Supportive analyses will also be done using the PPS.

Evaluations of safety outcome variables will be performed using the safety analysis set.

For analyses in the PK subgroup, PK and E_2 analyses will be performed using the PK subgroup set and E_2 subgroup set, respectively.

12.2 Methods of statistical analyses

Formal statistical hypothesis testing will only be performed on the efficacy and PD outcome variables (main study). All confidence intervals (CIs) will be two-sided, 95% intervals. See Section 12.1 for a description of analysis sets used in each analysis.

Summaries presented will include patient inclusion/exclusion, attendance at study visits, baseline and demographic variables, medical history, prior and concomitant medication, and all efficacy and safety endpoints.

Each table, figure and listing will be created for “Japanese centres only”, “Non-Japanese centres only” and for “All centres”

12.2.1 Analysis of efficacy and pharmacodynamic outcome variables (main study)

12.2.1.1 Primary outcome variables

For PFS, the proportion of patients who are progression-free at 24 weeks will be calculated for each treatment group. Non-inferiority of the 12-weekly ZOLADEX 10.8 mg treatment regimen to the 4-weekly ZOLADEX 3.6 mg regimen will be concluded if the lower limit of the 95% CI for the difference (10.8 mg minus 3.6 mg) is above -17.5%. The CI for this difference will be calculated using the score-based method recommended by Newcombe et al 2000.

The choice of this limit is based on a 75% relative efficacy of the 12-weekly ZOLADEX 10.8 mg treatment to the 4-weekly ZOLADEX 3.6 mg regimen, for which a 24-week progression-free proportion of 70% is anticipated.

In the analysis, a subject whose overall response at Visit 4(Week 24) is missing or NE will be treated as non-progression-free subject. Though the time window for Visit 4 is set as 24 weeks+7days (see Table 2), a tumour assessment performed 25 weeks or later will be handled as the assessment at Visit 4. However, in case that the tumour assessment for Visit 4 is performed 23 weeks or earlier, the overall response at Visit 4 will be handled as missing.

12.2.1.2 Secondary outcome variables

The ORRs at 24 weeks will be determined for each treatment, and their difference and 95% CI (derived as for the primary outcome variable) will be presented. Patient without measurable disease at baseline (ie, patients with bone metastases only or with complete remission after prior taxane- or anthracycline-based first line chemotherapy for advanced breast cancer) will not be included in the analysis of ORR.

A comparison of mean E_2 serum concentrations at timepoint(s) post Day 1 will be performed using analysis of covariance (ANCOVA), with treatment group, baseline E_2 serum

concentrations and country as covariates. Least square means and the 95% CI for their difference will be presented.

Further exploratory analyses of efficacy and/or PD outcomes (eg, FSH serum concentrations) may be performed, as deemed appropriate.

Exploratory analyses may investigate whether there is any additional effect of prior chemotherapy for ADVANCED BREAST CANCER use on the efficacy and/or PD outcomes.

12.2.2 Analysis of safety outcome variables (main study)

12.2.2.1 Adverse events

AEs will be classified by MedDRA preferred term (PT) and system organ class (SOC).

All data on AEs that occurred after obtaining informed consent will be listed. AEs that occurred after administration of the investigational product will be summarised by treatment group, SOC, PT and the worst Grade of CTCAE v3.0. Drug related adverse events data will also be summarised in the same manner.

Individual patient data on all SAEs, deaths and AEs leading to discontinuation of the study as well as all AEs assessed, as OAEs will be listed.

12.2.2.2 Clinical laboratory data

Clinical laboratory data will be listed at each observation point and summarised by treatment group using descriptive statistics (n, mean, sd, median, min and max). The listing will also present deviations from the reference ranges established by AstraZeneca. Also graphs of laboratory data will be prepared.

12.2.2.3 Vital signs

Data on vital signs will be listed for each time point and summarised by treatment group using descriptive statistics.

12.2.3 Analysis of the pharmacokinetic subgroup

Analyses of PK outcomes will be performed on samples provided by patients in the PK subgroup set (all of whom received ZOLADEX 10.8 mg).

The plasma concentration–time profiles of goserelin in Japanese and Non Japanese(except for China) patients will be evaluated. From the individual plasma concentration–time profiles of goserelin following the first dose of ZOLADEX 10.8 mg, the following parameters will be derived and analysed using descriptive statistics: C_{max}, T_{max}, $AUC_{(0\text{-}t),}$ and $AUC_{(0\text{-}12\ weeks)}$.

The E_2 concentration-time profiles will also be investigated in the PK subgroup using the E_2 subgroup set. If the data allows, the relationship between goserelin plasma concentrations and E_2 suppression may be investigated, as appropriate.

12.2.4 Testing for treatment-country interaction

For the PFS at 24 weeks and the ORR, Breslow-Day test with a 5% level will be performed to assess homogeneities across countries.

12.2.5 Interim analysis -NA

12.3 Determination of sample size

In a study by Klijn et al 2001 and the trial 0008, the proportion of patients who had not progressed during the first 6 months (24 weeks) of treatment with the combination of ZOLADEX 3.6 mg and tamoxifen was estimated to be approximately 70%. Assuming the proportion of patients who are progression-free at 24 weeks is 70% in both treatment groups in this study (and therefore that there is no underlying difference between the two treatment regimens), and define the limit of non inferiority as an absolute difference of 17.5% between these two proportions, a sample size of 216 patients (108 per group) ensures that 80% power is achieved to conclude non inferiority with a two-sided 95% CI (or in other words, at the one-sided 2.5% level of statistical significance). The non inferiority limit of 17.5% equates to the 12 weekly ZOLADEX 10.8 mg regimen having at least 75% of the efficacy of the 4 weekly ZOLADEX 3.6 mg regimen.

The study will also collect PK (and additional E_2) data from a subgroup of patients allocated to the ZOLADEX 10.8 mg treatment group. It is planned to have at least 20 patients with evaluable PK data for this subgroup (at least 10 Japanese patients from Japan, and at least 10 Non Japanese patients from non-Japanese countries except for China). The sample size for this subgroup is not based on formal sample size considerations. Recruitment to this subgroup will be on an ongoing basis until the required number of patients with evaluable PK data are enrolled. Patient recruitment to the main study may be increased above the planned 216 evaluable patients in order to ensure 10 Japanese and 10 Non Japanese patients with evaluable PK data.

12.4 Data monitoring committee – NA

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator 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 is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator(s) may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician .

Name	Role in the study	Address & telephone number

13.2 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

There is limited experience of ZOLADEX overdose in humans. In cases where ZOLADEX has unintentionally been re-administered early or given at a higher dose, no clinically relevant adverse effects have been seen. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentrations and on the reproductive tract will be evident with higher doses of ZOLADEX. If overdose occurs, this should be managed symptomatically.

Theoretically, overdosage of tamoxifen in humans might cause enhancement of the pharmacological side effects associated with its usage (eg, hot flushes, vaginal bleeding,

vaginal discharge, pruritus vulvae and tumour flare). There have been reports in the literature that tamoxifen given at several times the standard dose may be associated with prolongation of the QT interval of the electrocardiogram. Observations in animals show that extreme overdosage (100 to 200 times the recommended daily dose) may produce oestrogenic effects. There is no specific antidote to overdosage with tamoxifen and treatment must be symptomatic.

In this study, the following constitutes an overdose of study medication:

- >40 mg of tamoxifen in a one day period
- >1 ZOLADEX 3.6 mg injection in a 3-week period, or
- >1 ZOLADEX 10.8 mg injection in an 11-week period

Use of study medication in doses in excess of that specified above should not be recorded in the eCRF 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 SAE forms in the eCRF. Investigators must inform the sponsor of any SAEs within 24 hours of being aware of the SAE (see Section 6.4.4 for reporting of SAEs).

An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRF. In addition, the overdose should be reported on a separate clinical study overdose report form, which will be sent to the sponsor.

An overdose without associated symptoms should not be recorded as an AE in the eCRF. The overdose should be reported on a separate clinical study overdose report form, which will be sent to the sponsor.

13.3 Pregnancy

This study will recruit women of childbearing potential.

ZOLADEX should not be used in pregnancy as there is a theoretical risk of abortion or foetal abnormality if GnRH agonists are used during pregnancy. Potentially fertile women should be examined carefully before treatment to exclude pregnancy. Nonhormonal methods of contraception should be used throughout the study.

When ZOLADEX 3.6 mg is used for assisted reproduction, there is no clinical evidence to suggest a causal association between ZOLADEX and any subsequent abnormalities of oocyte development or pregnancy and outcome.

In the event of suspected pregnancy during the study, a urine test should be repeated. If the results are positive, the sponsor must be notified immediately. Patients who become pregnant at any point during the study will be withdrawn from the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the sponsor on the pregnancy outcomes report form within 24 hours of the investigator(s) being aware of the outcome. Refer to Section 6.4.4 for reporting of SAEs.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigator(s) or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator(s) to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within the timeframe stated in Section 6.4.4 for SAE and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure -NA

14. LIST OF REFERENCES

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Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	ZD9393
Study Code	D8666C00001

An Open Label, Randomised, Parallel Group, Multicentre Study to Compare ZOLADEX™ 10.8 mg Given Every 12 Weeks with ZOLADEX 3.6 mg Given Every 4 Weeks in Pre-menopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer

Sponsor:

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

Change 1

Section of protocol affected:

6.4.4 Reporting of serious adverse events

Previous text:

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as "immediately but no later than the end of the next business day") of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator should notify the serious adverse events in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

Revised text:

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it. The Principal Investigator should notify the serious adverse events in writing to the head of the study site immediately.

Reason for Amendment:

Revision of Astrazeneca procedure and clarification.

Change 2

Section of protocol affected:

13.1 Medical emergencies and AstraZeneca contacts

Previous text:

Name	Role in the study	Address & telephone number

Revised text:

Name	Role in the study	Address & telephone number

Reason for Amendment:

Changes in the study administrative structure at the sponsor.

Change 3

Section of protocol affected:

13.3.1 Maternal exposure

Previous text:

If any pregnancy occurs in the course of the study, then investigator(s) or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

Revised text:

If any pregnancy occurs in the course of the study, then investigator(s) or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Reason for Amendment:

Revision of Astrazeneca procedure and clarification.

Persons who initiated the Amendment: