AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Fulvestrant
Study Code	D6997L00021
Edition Number	1.0

A Randomised, Double-Blind, Parallel-Group, Multicentre Study Comparing the Efficacy and Tolerability of Fulvestrant 500 mg versus Fulvestrant 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

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

A Randomised, Double-Blind, Parallel-Group, Multicentre Study Comparing the Efficacy and Tolerability of Fulvestrant 500 mg versus Fulvestrant 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

National Co-ordinating Investigator

Study centre(s) and number of patients planned

220 postmenopausal patients will be randomised in the study from approximately 20 centres in the mainland China.

Study period			Phase of development
Estimated date of first patient enrolled	Q1	2011	III
Estimated date of last patient enrolled	Q1	2013	
Estimated date of last patient completed	Q4	2013	
Estimated date of data cut-off	Q4	2013	

Objectives and Variables

Objective	Variable
Primary	
To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of progression-free survival.	Progression-Free Survival (PFS)

Secondary

1. To describe the pharmacokinetic profile of fulvestrant 500mg and fulvestrant 250 mg.	CL/F, Vss/F, C_{max}, t_{max}, C_{min}, $AUC_{0-\tau}$ and $t_{1/2}$
2. To compare the objective response rate of patients treated with fulvestrant 500 mg with the objective response rate of patients treated with fulvestrant 250 mg.	Objective Response Rate (ORR = CR + PR defined by RECIST 1.1 criteria)
3. To compare clinical benefit rate of patients treated with fulvestrant 500 mg with the clinical benefit rate of patients treated with fulvestrant 250 mg.	Clinical Benefit Rate (CBR = CR + PR + SD ≥ 24weeks defined by RECIST 1.1 criteria)
4. To estimate the duration of response of patients treated with fulvestrant 500 mg and fulvestrant 250 mg.	Duration of Response (DoR)
5. To estimate the duration of clinical benefit of patients treated with fulvestrant 500 mg and fulvestrant 250 mg.	Duration of Clinical Benefit (DoCB)
6. To assess the tolerability of fulvestrant 500 mg treatment compared with fulvestrant 250 mg treatment.	Frequency and Severity of Adverse Events

Study design

A randomized, double-blind, parallel-group, multicentre study. Eligible patients will be randomised in a 1:1 ratio to receive fulvestrant 500 mg or fulvestrant 250 mg.

The first 30 patients in each arm who consent to the pharmacokinetic(PK) measurements will have pharmacokinetic plasma samples taken.

Target patient population

Postmenopausal women with oestrogen receptor positive advanced breast cancer who have progressed or relapsed on endocrine therapy which can be either an anti-oestrogen or an aromatase inhibitor.

The ratio of post-AI and post-AO patients will be monitored during study recruitment and for consistency with CONFIRM (42.5% post-AI), enrolment of post-AI patients will stop once 100 post-AI patients (45%) have been randomised.

Investigational product, dosage and mode of administration

Fulvestrant 500 mg will be given as two 5 ml intramuscular injections (2 Fulvestrant injections), one in each buttock, on days 1, 15, 29 and every 28 days thereafter.

Comparator, dosage and mode of administration

Fulvestrant 250 mg will be given as two 5 ml intramuscular injections (1 Fulvestrant injection + 1 placebo injection), one in each buttock, on days 1, 15 (2 placebo injections only), 29 and every 28 days thereafter.

After the database lock for the primary analysis, patients will have their treatment unblinded and remain in study, and transferred to open label study drug supplies until they can't receive clinical benefit from the study drug.

After study treatment is unblinded, patient who remains on fulvestrant 250 mg will receive only one 5 ml of fulvestrant 250mg intramuscular injection, as the placebo injection previously required to preserve the double blind nature of the study is no longer needed.

Duration of treatment

Treatment will continue until disease progression, unless any of the criteria for treatment discontinuation are met first.

Statistical methods

Eligible patients will be randomised in a 1:1 ratio to fulvestrant 500mg and fulvestrant 250mg. The primary analysis for PFS will be carried out when at least 150 progression events have been observed.

A criterion has been predefined for declaring consistency with CONFIRM. The results of this study would be considered to be consistent with CONFIRM if the hazard ratio point estimate for the treatment comparison is <1 (i.e. if it is in the same direction as in CONFIRM). With a sample size of 220 patients and 150 progression events, if there is no ethnic difference with the CONFIRM population, there is an 89% chance the HR <1.

The primary statistical analyses of the efficacy variables will be performed by randomised study treatment for 'Full Analysis Set' (FAS) population. In addition, secondary analyses for the primary variable of PFS will be carried out for 'per protocol' (PP) population. Summaries and any analyses on safety variables will be performed by study treatment actually received.

The primary analysis of PFS will be performed using a log-rank test stratified by last therapy received prior to fulvestrant (aromatase inhibitor [AI] vs antioestrogen [AO] therapy). Supporting analysis will be performed using the Cox proportional hazard model to investigate any impact of baseline covariates. Objective response rate (ORR) and clinical benefit rate (CBR) will be analysed using a logistic regression model with treatment factor only. Duration of response (DoR) and duration of clinical benefit (DoCB) will be summarized. No interim analysis will be carried out in this study.

For the PK part, no specific statistical hypothesis will be tested. The patient number per arm will be 30 and these will the first patients who consent to PK plasma samples being taken. The main analysis will take place when the full PK data are available and the whole study database has been locked.

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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)
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AO	Antioestrogen
ASA	Acetylsalicylic Acid (Aspirin)
Assessment	An observation made on a variable involving a patientive judgement (assessment)
AST	Aspartate aminotransferase
ATAC	Arimidex, Tamoxifen Alone or in Combination trial
$AUC_{0-\tau}$	Area under the plasma concentration-time curve from the time of dosing to the end of the dosing interval
BP	Blood Pressure
CBR	Clinical Benefit Rate
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration of drug in a standard dosing interval
C_{min}	Minimum plasma concentration of drug in a standard dosing interval
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DHEA	Dihydroepiandrosterone
DIC	Disseminated Intravascular Coagulation

Abbreviation or special term	Explanation
DoCB	Duration of Clinical Benefit
DoR	Duration of Response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetic acid
Endpoint	A status of the patient that constitutes the 'endpoint' of a patient's participation in a clinical study and that is used as the final outcome.
ER	Oestrogen Receptor
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Hazard Ratio
HR	Heart Rate
HRT	Hormone Replacement therapy
i.m.	Intramuscular
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International Normalisation Ratio
IP	Investigational Product
IS	Internal Standard
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LC-MS-MS	Liquid chromatography mass spectrometry method
LH-RH	Luteinsing Hormone-Releasing Hormone
LMWH	Low Molecular Weight Heparin
LTED	Long-term oestrogen deprivation
Measurement	An observation made on a variable using a measurement device.
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
ml	Millilitres

Abbreviation or special term	Explanation
MRI	Magnetic Resonance Imaging
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OR	Objective Response
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
Principal Investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator.
PRO	Patient Reported Outcome
Q	Quarter
R&D	Research&Development
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 6.4.2).
SD	Stable Disease
SDT	Study Deliver Team
SDV	Source Data Verified
SERM	Selective Estrogen Receptor Modulator
$t_{½}$	terminal plasma half-life
t_{max}	time to C_{max}
TTP	Time to progression
ULRR	Upper Limit of Reference Range
Variable	A characteristic or a property of a patient that may vary e.g., from time to time or between patients
Vss/F	Apparent volume of distribution
w/v	Weight per Volume
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. INTRODUCTION

Investigators should be familiar with the current fulvestrant Investigator's Brochure.

1.1 Background

Breast cancer is one of the most common malignancies in women. It is also one of the most common causes of cancer deaths in women. More than 500,000 women die of breast cancer annually (WHO 2004). It has long been acknowledged that oestrogen acts as an endocrine growth factor for hormone-dependent breast cancer and that hormonal manipulation can affect the progress of this disease (Beatson GT. 1896). The most important factor determining response to hormonal manipulation is the presence of the oestrogen receptor (ER) in the target tissue (Fisher B et al 2001).

Oestrogen deprivation is fundamental to the treatment of breast cancer. In premenopausal women, this can be achieved by the ablation of ovarian function through surgical, radiotherapeutic or medical means, and in postmenopausal women by the use of aromatase inhibitors (AIs). An alternative approach is the inhibition of oestrogen function using antioestrogens, which bind to and compete for the oestrogen receptors (ERs) present in the nuclei of oestrogen-responsive tissue. Tamoxifen, a conventional non-steroidal antioestrogen, compete efficiently with endogenous oestrogen for binding to the ERs and has been the most widely used hormonal treatment for breast cancer in both pre- and postmenopausal women. However, its partial agonist activity leads to incomplete blockage of oestrogen-mediated activity and limits its effectiveness (Furr and Jordan 1984; May and Westley, 1987) as well as unwanted side effects such as endometrial cancer when administered for long periods (EBCTCG 1998;Fisher et al 1998; Fisher et al 1999). The research for novel anti-oestrogen which is devoid of the agonist activity of tamoxifen and can effectively block oestrogen receptor activity resulted in the discovery and clinical development of ZD9238 (fulvestrant, FASLODEX™).

Fulvestrant is a steroidal analogue of oestrogen. Unlike tamoxifen, it has no oestrogen agonist effects (Addo S et al, 2002). Fulvestrant has a novel mode of action since it binds, blocks and accelerates degradation of oestrogen receptor protein, leading to an inhibitor of oestrogen signalling (Robertson et al 2001, Wakeling AE et al 1993).Fulvestrant has demonstrated efficacy in women whose breast cancer has progressed following tamoxifen therapy (Howell et al 2002, Osborne CK et al 2002).

1.2 Rationale for conducting this study

Fulvestrant, at a dose of 250mg every 28 days, is the first oestrogen receptor antagonist with no agonist effects shown to be at least as effective for both TTP (Time to Progression) and OR (Objective Response) as a third-generation aromatase inhibitor in the second-line treatment of advanced breast cancer (Howell et al 2002, Osborne CK et al 2002).In these studies overall survival was also similar between the fulvestrant and anastrozole treatment arms (Pippen J et al 2003). Fulvestrant has received approval in 70 countries worldwide at this dose regimen.

However, evidence from a number of studies suggests that higher dose may be able to enhance efficacy further:

- Data from Study 0036 (Addo S et al, 2002) suggested that a dose-response relationship may exist. In female volunteers given a single intramuscular (i.m.) injection of fulvestrant (250mg, 125mg or placebo), there was a dose-dependent inhibition of ethinyloestradiol-induced endometrial thickening seen at Day 28.

- Results from short term exposure to fulvestrant in Studies 0002 (DeFriend D et al 1994) and 0018 (Robertson et al 2001) showed that expression of ER, progesterone receptor (PgR) and the cell proliferation-related antigen Ki67 are reduced in a dose-dependent manner.

- Data from Studies 0020 (Howell et al 2002) and 0021(Osborne CK et al 2002) suggested that a dose-response effect exists for fulvestrant. Fulvestrant 250mg was shown to be superior to fulvestrant 125mg, which was discontinued as it failed to meet minimum efficacy requirements.

- Evidence from pharmacokinetic modelling indicated that fulvestrant 500 mg dose regiment can achieve higher steady state plasma concentrations compared with fulvestrant 250mg and that steady state concentrations can be achieved earlier than with fulvestrant 250mg.

- Data from Study CONFIRM (A Di Leo et al 2009), a phase III randomised parallel-group trial, demonstrated that fulvstrant 500mg offers a statistically significant longer TTP compared with fulvestrant 250mg (median TTP: 6.5 months vs. 5.5 months; hazard ratio=0.80 [95% CI 0.68 to 0.94]; P=0.006), which seemed to be the consequence of an increase in the rate, and of a prolongation in duration, of disease stabilization. The 50% events overall survival analysis also seemed to favour fulvestrant 500mg, although statistical significance was not reached(hazard ratio=0.84 [95% CI 0.69 to 1.03]; P=0.091). The safety analysis did not raise any relevant concerns in relation to fulvestrant 500mg.

Therefore, this study will compare Fulvestrant 500mg with fulvestrant 250mg in a Chinese population in order to understand the optimal dose for Chinese patients with breast cancer.

1.3 Benefit/risk and ethical assessment

Fulvestrant 250mg is as effective as a third-generation AI (anastrozole) in postmenopausal women with advanced breast cancer who have progressed on prior antioestrogen therapy (median TTP was 166 days for fulvestrant 250mg and 126 days for anastrozole, p=0.4767, Pippen J et al 2003). In Study CONFIRM (A Di Leo et al 2009), fulvestrant 500mg has demonstrated superior efficacy to fulvestrant 250mg in postmenopausal women with advanced breast cancer who have progressed on prior AI or antioestrogen therapy. Median TTP was prolonged by 1.0 month (from 5.5 months for fulvestrant 250mg to 6.5 months for fulvestrant 500mg, p=0.006).

Fulvestrant 250mg is generally well tolerated in postmenopausal women with advanced breast cancer. It has demonstrated a similar safety profile to anastrozole. The safety profile of fulvestrant 500mg is consistent with the known safety and tolerability profile of fulvestrant 250mg with no evidence for dose dependence for any AEs. No adjustment of the dose of fulvestrant is required in the elderly and the patients with Child-Pugh category A and B hepatic impairment.

Overall, the benefit/risk and ethical assessment supports the conduct of this study to understand the optimal dose of fulvestrant in Chinese patients.

2. STUDY OBJECTIVES

This study is to compare the efficacy and tolerability of fulvestrant 500 mg with fulvestrant 250 mg in postmenopausal women with oestrogen receptor positive advanced breast cancer who have progressed or relapsed on prior aromatase inhibitor or antioestrogen therapy.

2.1 Primary objective

Primary Objective	**Variable**
To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of progression-free survival.	Progression-Free Survival (PFS)

2.2 Secondary objectives

Secondary Objective	**Variable**
1. To describe the pharmacokinetic profile of fulvestrant 500mg and fulvestrant 250 mg.	CL/F, Vss/F, C_{max}, t_{max}, C_{min}, $AUC_{0-\tau}$ and $t_{1/2}$
2. To compare the objective response rate of patients treated with fulvestrant 500 mg with the objective response rate of patients treated with fulvestrant 250 mg.	Objective Response Rate (ORR = CR + PR defined by RECIST 1.1 criteria)
3. To compare clinical benefit rate of patients treated with fulvestrant 500 mg with the clinical benefit rate of patients treated with fulvestrant 250 mg.	Clinical Benefit Rate (CBR = CR + PR + SD ≥ 24weeks defined by RECIST 1.1 criteria)
4. To estimate the duration of response of patients treated with fulvestrant 500 mg and fulvestrant 250 mg.	Duration of Response (DoR)
5. To estimate the duration of clinical benefit of patients	Duration of Clinical Benefit

Secondary Objective	Variable
treated with fulvestrant 500 mg and fulvestrant 250 mg.	(DoCB)
6. To assess the tolerability of fulvestrant 500 mg treatment compared with fulvestrant 250 mg treatment.	Frequency and Severity of Adverse Events

2.3 Safety objective

The safety objective of this study is to assess the safety and tolerability of fulvestrant 500 mg treatment compared with fulvestrant 250 mg treatment in postmenopausal women with oestrogen receptor positive advanced breast cancer who have progressed or relapsed on prior aromatase inhibitor or antioestrogen therapy, which has been described in Section 2.2 Secondary objectives.

2.4 Exploratory objectives (Not Applicable)

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a randomised, double-blind, parallel-group, multicentre study to compare two dose levels of fulvestrant. 220 postmenopausal women with oestrogen receptor positive advanced breast cancer who have either relapsed whilst on adjuvant endocrine therapy, or progressed whilst on first endocrine therapy for advanced disease, will enter this study. Eligible patients will be randomised 1:1 to the following treatment groups:

- Fulvestrant 500 mg i.m. every 28 (± 3) days plus an additional 500 mg on day 15 (± 3) of first month only
- Fulvestrant 250 mg i.m. every 28 (± 3) days

Treatment will continue until disease progression, unless any of the criteria for treatment discontinuation are met first. If a patient progresses during the treatment period, the patient must be withdrawn from their randomised treatment and further treatment will be at the investigator's discretion.

All patients will be followed up for disease progression, regardless of whether they have discontinued randomised treatment, unless they have withdrawn consent.

After the database lock for the primary analysis, patients will have their treatment unblinded and remain in study, and transferred to open label study drug supplies until they can't receive clinical benefit from the study drug.

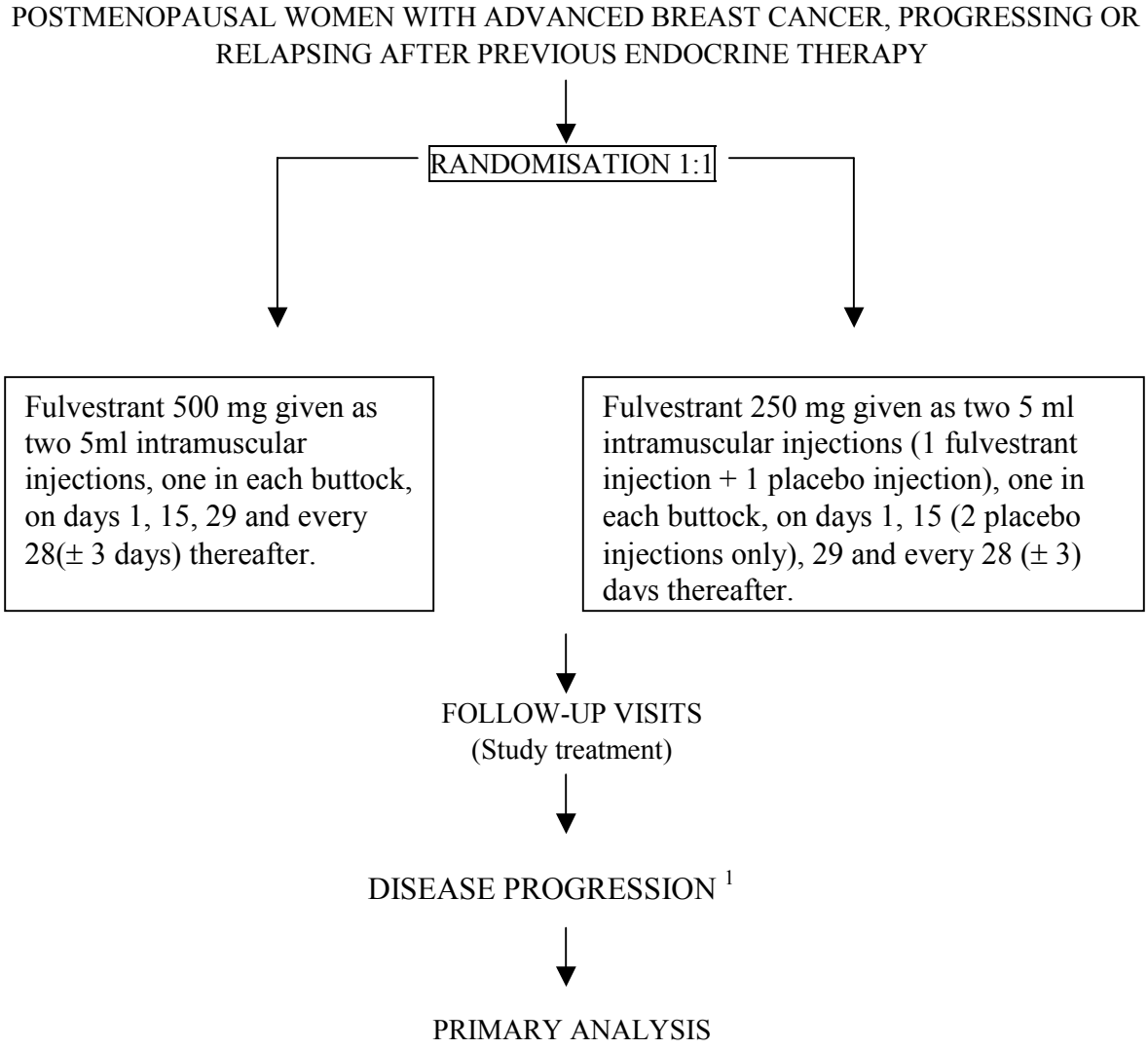
After study treatment is unblinded, patient who remains on fulvestrant 250mg will receive only one 5 ml of fulvestrant 250mg intramuscular injection, as the placebo injection previously required to preserve the double blind nature of the study is no longer needed.

After the primary analysis for PFS, data will no longer be collected on the clinical database, but patients will continue to be followed as per standard clinical practice. After the primary data cut-off, SAEs will still be reported to the AZ Patient Safety department.

First 30 patients in each arm who consent to the pharmacokinetic measurements will have pharmacokinetic plasma samples taken.

All investigators/sub-investigators should adhere to the study plan, procedures and perform tests/observations according to the protocol.

Figure 1 Study flow chart



[1] Up until the time of data cut-off for the analysis of PFS, patients must be followed until evidence of RECIST1.1 defined progression (regardless of whether they have discontinued randomised treatment, unless they have withdrawn consent)

Table 1 Study plan

Study plan	**Screening Phase**	**Treatment Phase**											**Treatment Discontinuation**
Visit	**Screening[a]**	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[c] onwards (every 12 weeks until progression)**	
Week(s)	**-3 to 0**	**0**	**0-1 (Day 5-10)**	**2**	**4**	**4-6 (Day 33-38)**	**8**	**12**	**16**	**20**	**24**	**36 and Onwards**	
Informed consent	X												
Medical history	X												
Demography	X												
Inclusion/exclusion criteria	X												
Concomitant therapy	X	X		X	X		X	X	X	X	X	X	X[d]
ECG[e]	X[e]												
Physical Examination (including WHO Performance Status)	X	X			X		X	X	X	X	X	X	X
Vital Signs (BP, HR)		X			X		X	X	X	X	X	X	X
Weight and height[k]		X[k]			X		X	X	X	X	X	X	X
Haematology/Biochemistry[f]	X	X			X			X			X	X	X
Chest X-ray or CT scan of the chest	X[g]												
Bone scan or skeletal survey	X[i]							X[j]			X[j]	X[j]	X[j]
Tumour assessment[c]	X[g]							X			X	X	X
Randomised Treatment		X		X	X		X	X	X	X	X[h]	X[h]	

Study plan	**Screening Phase**	**Treatment Phase**											**Treatment Discontinuation**
Visit	**Screening[a]**	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[c] onwards (every 12 weeks until progression)**	
Week(s)	**-3 to 0**	**0**	**0-1 (Day 5-10)**	**2**	**4**	**4-6 (Day 33-38)**	**8**	**12**	**16**	**20**	**24**	**36 and Onwards**	
Adverse events	X	X		X	X		X	X	X	X	X	X	X[d]
Informed consent for PK study	X												
PK sample (PK cohort only)[l]		X	X	X	X	X	X	X					X[m]

a Within 3 weeks before randomisation.
b Visit 1/Day 1 should occur no more than 1 week after randomisation and no more than 4 weeks after tumour assessment.
c Assessment by RECIST 1.1 Criteria every 12 ± 2 weeks from Visit 1 until progression. Tumours will be followed using same methodology at each assessment.
d Adverse event (AE) and concomitant therapy follow-up for **8 weeks** after last injection
e An electrocardiogram (ECG) assessment should be recorded within 3 weeks prior to randomisation and repeated should any cardiac adverse events occur.
f Laboratory assessments (haematology and biochemistry) will be performed before randomisation, before treatment (unless treatment is given within 7 days following screening assessments), at weeks 4 and 12, and every 12 weeks thereafter, until withdrawal from randomised treatment.
g within the 4 weeks before treatment
h Treatment continues to be given every 28 (± 3) days
i Patients must have a bone scan within 8 weeks before treatment or a skeletal survey within 4 weeks before treatment. Any hotspots identified on the bone scan must be confirmed by X-ray, computerized tomography (CT) scan or magnetic resonance imaging (MRI), within 4 weeks prior to treatment.
j All patients with metastatic bone lesions at baseline, must have bone scans or skeletal surveys every 12 weeks (+/- 2 weeks) until progression. Additional bone scans or skeletal surveys should be performed if clinically indicated. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
k Height is only captured at Visit 1.
l Pharmacokinetic samples will be collected from a cohort of 60 patients in total. Samples will be taken at day 1, day 15, day 29, day 57 and day 85 just prior to the randomised treatment injections. Two additional samples will also be taken at any time between day 5-10 and between day 33-38.
m A sample will be taken at the treatment discontinuation visit if this occurs before week 12.

3.2 Rationale for study design, doses and control groups

This is a randomised, double-blind, parallel-group, multicentre study to compare the efficacy and tolerability of fulvestrant 500mg with fulvestrant 250mg in postmenopausal women with oestrogen receptor positive advanced breast cancer progressing or relapsing after previous aromatase inhibitor or antioestrogen therapy.

Fulvestrant 250mg dose regimen(250mg given every 28 days), which will be the comparator, is well-tolerated and has demonstrated efficacy in postmenopausal women whose breast cancer has progressed following anti-oestrogen therapy(Howell et al 2002,Osborne CK et al 2002). A higher fulvestrant dose regimen (500mg dose regimen) will be administered at a dose of 500mg every 28 days plus an additional 500mg in the middle of first month only. Fulvestrant 500mg dose regimen has showed superior efficacy to fulvestrant 250mg dose regimen and was well-tolerated with no clinical important differences in tolerability compared with fulvestrant 250mg (A Di Leo et al 2009).

Because of AIs efficacy and the well-tolerated safety profile, postmenopausal patients with advanced breast cancer are increasingly receiving third generation AIs as therapy for first line treatment for advanced disease and as adjuvant therapy of breast cancer (ATAC Trialists' Group 2002). However, inevitably a group of patients will recur or progress under the treatment with AIs. The optimal use of other hormonal therapies in this resistant population has yet to be determined due to limited clinical trial data (Ingle JN 2004), which brings the major challenge of healthcare providers and patients. Preclinical research has found that oestrogen sensitivity may not only be maintained but also enhanced following acquired resistance to long-term oestrogen deprivation (LTED) with AIs. LTED cells display adaptive increases in ER gene expression, resulting in hypersensitivity to low levels of estradiol (Chan CMW et al 2002). This observation suggested that fulvestrant, a pure oestrogen receptor antagonist, may be an appropriate therapeutic option following failure on AIs. And several clinical studies had also demonstrated fulvestrant's efficacy in post-AI failure population. In a phase II study of postmenopausal women with advanced breast cancer who had progressed on prior third-generation AI therapy, fulvestrant provided clinical benefit in 27 of 77 patients(35%)(Ingle JN et al 2006). In Study CONFIRM (A Di Leo et al 2009), the subgroup analysis of TTP favouring fulvestrant 500mg was consistent both in patients who had progressed on an AI (aromatase inhibitor) treatment compared to patients who had progressed on an AO (antioestrogen) treatment (Hazard Ratio=0.85 [95% CI 0.67 to 1.08] and 0.76 [95% CI 0.62 to 0.94] for post-AI and post-AO respectively). Therefore, the patient population recruited into this study will include patients who have progressed on an AI in order to explore the efficacy of fulvestrant in this setting for China population.

This study will also gather PK data from part of recruited patients to describe the pharmacokinetic profile of fulvestrant 250mg and 500mg dosing regimens in Chinese patients and assess inter-individual and residual variability.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient 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.

4.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures

2. Postmenopausal woman, defined as a woman fulfilling any of the following criteria:

   - Having undergone a bilateral oophorectomy
   - Age ≥ 60 years.
   - Age < 60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and oestradiol level in the postmenopausal range (utilising ranges from the local laboratory facility).
   - If taking tamoxifen or toremifene, and age < 60 years, then FSH and plasma oestradiol level in the postmenopausal ranges (utilising ranges from the local laboratory facility).

3. Histological/cytological confirmation of breast cancer

4. Documented positive oestrogen receptor status (ER positive) of primary or metastatic tumour tissue, according to the local laboratory parameters.

5. Requiring hormonal treatment:

(a) Relapsing during, or within 12 months of completion of, adjuvant endocrine therapy (tamoxifen, toremifene or aromatase inhibitors such as anastrozole, letrozole and exemestane), or

(b) Progressing on an endocrine therapy (tamoxifen, toremifene or aromatase inhibitors such as anastrozole, letrozole and exemestane) provided that this endocrine treatment was started at least 12 months after the completion of adjuvant endocrine treatment, or

(c) Progressing on an endocrine therapy (tamoxifen, toremifene or aromatase inhibitors such as anastrozole, letrozole and exemestane) given as first treatment for patients with *de novo* advanced* breast cancer

* Advanced breast cancer: Metastatic disease or locally advanced disease which is not amenable to treatment with curative intent.

6. Patients fulfilling one of the following criteria:

   – Patients with measurable disease as per RECIST 1.1 criteria.

   – Patients with bone lesions, lytic or mixed (lytic + sclerotic), in the absence of measurable disease as defined by RECIST 1.1 criteria.

7. WHO performance status 0, 1 or 2.

For inclusion in the pharmacokinetic research component of the study, patients must fulfil the following criteria:

- Provision of informed consent for pharmacokinetic research component

If a patient declines to participate in the pharmacokinetic research component of the study, 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 consent.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Previous enrolment or randomisation in the present study

3. Presence of life-threatening metastatic visceral disease, defined as extensive hepatic involvement, or any degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not compromised as a result of disease.

4. More than one regimen of chemotherapy for advanced disease

   Note: Patients previously treated with one regimen of chemotherapy *for advanced disease* are allowed as long as their last treatment is an anti-oestrogen or an aromatase inhibitor. That is to mean where chemotherapy has been given for advanced disease, it must have been used early following the diagnosis of that advanced disease, ie, at the beginning of the treatment sequence for that advanced

disease. In this case the chemotherapy must have been followed by endocrine therapy for advanced disease in order to recruit only patients progressing on endocrine therapies.

5. More than one regimen of endocrine therapy for advanced disease.

   Note: Oophorectomy, ovarian ablation, or LH-RH analogue therapy do not count as endocrine treatments in this context and also do not render the patient ineligible for this study.

6. Extensive radiation therapy within the last 4 weeks (greater than or equal to 30% marrow or whole pelvis or spine) or cytotoxic treatment within the past 4 weeks prior to screening laboratory assessment, or strontium-90 (or other radiopharmaceuticals) within the past 3 months.

7. Treatment with a non-approved or experimental drug within 4 weeks before randomisation.

8. Current or prior malignancy within previous 3 years (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix).

9. Any of the following laboratory values :

- Platelets $< 100 \times 10^9$ / L
- Total bilirubin $> 1.5 \times$ ULRR
- ALT or AST $> 2.5 \times$ ULRR if no demonstrable liver metastases or $> 5 \times$ ULRR in presence of liver metastases
- Severe renal impairment (creatinine clearance < 30ml/min)

10. History of :

- bleeding diathesis (i.e., disseminated intravascular coagulation [DIC], clotting factor deficiency), or
- long-term anticoagulant therapy (other than antiplatelet therapy and low dose warfarin – see Section 5.6).

11. History of hypersensitivity to active or inactive excipients of fulvestrant and/or castor oil.

12. Any severe concomitant condition which makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the trial protocol. e.g., uncontrolled cardiac disease or uncontrolled diabetes mellitus.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions should be applied to patients in this trial:

1. Patients who are blood donors should not donate blood during the study and for 12 weeks following their last dose of randomised treatment.

2. Patients who have confirmed disease progression must be discontinued from their randomised treatment.

3. Concomitant treatments listed in Section 5.6.

5.2 Patient enrolment and randomisation

The Principal Investigator (or his/her delegators) will:

1. Obtain signed informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed.

2. As patients are screened for the study after signing and dating the written Informed Consent they must be allocated a 7 digit enrolment code (E-code) with the prefix 'E'.

   The first four digits in the enrolment code will indicate the centre and digits 5-7 the enrolment order for the centre (e.g., the first patient screened in centre number 0125 would be assigned the E-code E0125001, the second patient screened would be E0125002 and so on).

   The enrolment number is the only patient identification number to be used to identify the patient on the CRFs and high level documents. Enrolment numbers should be given in consecutive order. **All screened patients are assigned an E-code irrespective of whether or not they are subsequently randomised to receive study treatment.**

3. Determine patient eligibility. See Sections 4.1 and 4.2.

4. Patients fulfilling the eligibility criteria will be randomised into the study and assigned a randomisation code (patient number). Randomisation codes should be allocated strictly sequentially and each patient pack will be labelled with a randomisation code.

   If a randomisation code is assigned incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The patient will continue

with the allocated randomised code and study material. AstraZeneca (or company representing AstraZeneca) should be notified as soon as the error is discovered. Randomisation of subsequent patients will continue using the first unallocated randomised code in the original sequence.

If a patient withdraws from participation in the study, then their enrolment/randomisation code cannot be reused.

If patients have discontinued their participation in the study then they cannot re-enter into the study.

5.2.1 Procedures for randomisation

Eligible patients will be randomised in a 1:1 ratio (fulvestrant 500mg : fulvestrant 250mg). The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Interactive Voice/Web Response System (IVRS/IWRS) database. The randomisation scheme will be produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers. A biostatistics group at AstraZeneca has responsibility for generating the randomisation scheme.

A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group. The randomisation scheme will be stratified by the last therapy received prior to fulvestrant (AI vs AO therapy).

Based on clinical practice in China, it is anticipated that a significant proportion (>40%) of patients will enter the study having progressed/relapsed on an AI. The ratio of post-AI and post-AO patients will be monitored during study recruitment and for consistency with CONFIRM (42.5% post-AI), enrolment of post-AI patients will stop once 100 post-AI patients (45%) have been randomised.

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as patients are eligible for randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IVRS/IWRS system and follow the procedures as described in the IVRS/IWRS user manual.

5.3 Procedures for handling patients incorrectly enrolled or randomised or initiated on investigational product

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

Patients who are incorrectly enrolled but are not yet randomised or initiated on treatment should be withdrawn from the study.

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the patient 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 patient should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The randomisation schedule, (emergency un-blinding tools), giving details of individual patient treatment will be produced by computer software that incorporates a standard procedure for generating random numbers. The material for the randomised period of treatment will be supplied by Investigational Product Section at AstraZeneca, in containers as detailed in Section 5.5.4.

All study personnel will be unaware of the randomised treatment until all decisions on the evaluability of the data from all patients have been made and documented.

The study drug, fulvestrant, will be supplied by AstraZeneca, in the form of a single-dose in a pre-filled syringe. Each active pre-filled syringe will contain 250 mg of fulvestrant at a concentration of 50 mg/ml in a volume of 5 ml, designated a fulvestrant 5% weight/volume (w/v) injection. The placebo pre-filled syringe will look identical to the active pre-filled syringe and will also have a volume of 5 ml.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

After the database lock for the primary analysis, patients will have their treatment unblinded and remain in study, and transferred to open label study drug supplies until they can't receive clinical benefit from the study drug.

After study treatment is unblinded, patient who remains on fulvestrant 250mg will receive only one 5 ml of fulvestrant 250mg intramuscular injection, as the placebo injection previously required to preserve the double blind nature of the study is no longer needed.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Fulvestrant will be supplied as a castor oil based solution in clear neutral glass pre-filled syringes. Each syringe will contain 250 mg of fulvestrant in 5 ml (Formulation Number F6521).

Matching placebo will be supplied as a castor oil based solution in clear neutral glass pre-filled syringes. Each syringe will contain 5 ml (Formulation Number F6522).

5.5.2 Doses and treatment regimens

Dose

Eligible patients will be randomised 1:1 to the following treatment groups:

- Fulvestrant 500 mg given as two 5 ml intramuscular injections, one in each buttock, on days 1, 15, 29 and every 28 (± 3) days thereafter.

- Fulvestrant 250 mg given as two 5 ml intramuscular injections (1 Fulvestrant injection + 1 placebo injection), one in each buttock, on days 1, 15 (2 placebo injections only), 29 and every 28 (± 3) days thereafter.

After the database lock for the primary analysis, patients will have their treatment unblinded and remain in study, and transferred to open label study drug supplies until they can't receive clinical benefit from the study drug.

After study treatment is unblinded, patient who remains on fulvestrant 250mg will receive only one 5 ml of fulvestrant 250mg intramuscular injection, as the placebo injection previously required to preserve the double blind nature of the study is no longer needed.

Route

All patients will receive two 5ml injections containing either fulvestrant or matching placebo, one into each buttock, on days 1, 15, 29, and every 28 (± 3) days thereafter.

Each injection will be administered into the gluteus maximus muscle using an aseptic parenteral technique, and must be administered slowly over approximately 1-2 minutes. Following administration, the injection site(s) should be assessed by the investigator for any local reaction. The patient should be instructed to report complications to the investigator. Appropriate measures such as the application of heat or cold should be instituted according to basic nursing intervention and institutional policy and pressure should be applied where appropriate – see Section 5.6. Any severe local site reaction should be treated with appropriate medical intervention.

5.5.3 Labelling

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

The label will include the following information: Study code, Randomisation number, Storage Conditions and any other market specific requirements. Two labelled prefilled syringes will be packed into a single dose carton according to the random scheme. All labels will be blinded as per random scheme.

5.5.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

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

All prior treatments for cancer and all drugs given to, or taken by, the patient at entry and during the study must be clearly documented on the appropriate CRF page.

The following treatment restrictions apply:

- Concomitant anticancer treatments are not permitted during the study. Such treatments are prohibited even if they are given for another indication (e.g. megestrol acetate for appetite stimulation, or methotrexate for rheumatological disorders).

- Radiotherapy may be given concomitantly for control of bone pain if therapy was started prior to randomisation. Patients requiring radiation for breast cancer or surgery for a breast cancer site after randomisation will be considered to have progressed, unless the investigator specified otherwise. If the investigator rules out progression, then irradiated or excised lesions will be considered non assessable for response and will be monitored only for disease progression.

- Chronic concomitant bisphosphonate therapy for hypercalcemia, and bisphosphonate treatment for the prevention of bone metastases are not permitted during the study. Bisphosphonate therapy for the treatment of osteoporosis is permitted during the study. Bisphosphonate therapy at the time of randomisation for the management of bone metastases is recommended as standard of care. If bisphosphonate therapy is initiated after randomisation the reason for its use must be clearly documented.

- Sex hormone containing drugs such as hormone-replacement therapy (HRT), progestational agents (megestrol acetate), DHEA, other androgens (e.g., oxandrolone) and SERMs (e.g. raloxifene (Evista) are not permitted during the study. In rare cases where patients suffer severe menopausal symptoms, management with non-hormonal agents, e.g., clonidine or venlafaxine, is recommended. Use of an oestrogen-containing vaginal ring is allowed.

In addition, other drugs than those mentioned above which may affect sex hormone status or disease response, such as systemic ketoconazole, systemic corticosteroids and adrenocortical suppressants are not allowed to begin after randomisation in to the study. However, the patient can continue to receive such drugs if they were taken before randomisation and the investigator is satisfied that the patient's hormonal status is stable.

Topical applications, inhaled sprays, eye drops, local injections and mouth-washes (if not swallowed), containing corticosteroids or ketoconazole are permitted during the study.

- Patients receiving long-term anti-coagulant therapy with warfarin are ineligible for the study unless they are receiving low dose warfarin and have an INR ≤ 1.6. The INR should be checked to ensure that it is ≤ 1.6 prior to each injection. If the INR is > 1.6, the injections should be withheld until the INR has returned to ≤ 1.6. It is advised to apply direct pressure to the injection site in these patients.

- Patients who need to begin anti-coagulant therapy while receiving study treatment may be treated, at the discretion of the investigator, with low molecular weight heparin (LMWH). The LMWH should be temporarily discontinued 12-24 hours prior to each fulvestrant injection and then resumed 12-24 hours later (depending on the particular LMWH used). There is an increased risk of haemorrhage in these patients and the investigator should decide whether that risk is outweighed by the possible benefits of continued treatment. It is advised to apply direct pressure to the injection site in these patients.

  If, in the opinion of the investigator, warfarin is required instead of LMWH, it should be recognised that the risk of intramuscular haemorrhage may be increased. In this situation, the dose of warfarin should be chosen according to the condition being treated and the INR should be monitored. The INR should be checked prior to each injection and the injections may be withheld if the INR > 1.6. It is advised to apply direct pressure to the injection site in these patients.

- Patients receiving antiplatelet therapy (ASA, ticlopidine, clopigrel, …etc.) may be at increased risk of bleeding from intramuscular injection. The investigator should decide whether that risk is outweighed by the possible benefits of continued treatment. It is advised to apply direct pressure to the injection site in these patients.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form. The clinical research associate (CRA) will check these records to confirm the compliance with the protocol administration schedule.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel will account for all received study drugs and return all unused study drugs and used pre-filled syringes to AstraZeneca local depot for destruction. Certificates of delivery and return should be signed.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca (Adverse Event).
- Severe non-compliance to study protocol as judged by the investigator and/or AstraZeneca.
- Confirmed disease progression
- Patients lost to follow-up
- Any other reasons not listed above as per investigator discretion(the reason must be adequately documented)

Specific reasons for discontinuing a patient from the pharmacokinetic research component of the study are:

- Withdrawal of consent to the pharmacokinetic research component of this study. A patient may withdraw from the pharmacokinetic research component of the study at any time, independent of any decision concerning participation in other aspects of the clinical study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment.

Patients who elect not to receive further study treatment (voluntary discontinuation) will continue to have objective tumour assessments until disease progression unless they withdraw their consent from collection of data beyond the point of withdrawal from study treatment.

Patients who withdraw their consent for study participation will no longer receive any protocol mandated assessments. Patient data will not be collected beyond the date of consent withdrawal.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue investigational product 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(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 5.9.

If a patient has confirmed disease progression, they must be discontinued from randomised treatment and further treatment will be given at the investigator's discretion.

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for the linked pharmacokinetic research. It must be established whether the patient:

- Agrees to the blood sample being kept for pharmacokinetic research analyses.
- Withdraws consent for the blood sample to be kept for pharmacokinetic research analysis and wishes the sample to be destroyed. Destruction of the sample will only be possible so long as the particular sample is traceable. In the event that pharmacokinetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the blood sample for pharmacokinetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients 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); all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

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 investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator 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. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

6.2 Data collection and enrolment

Investigators should refer to the Study Plan (Table 1) for the list of procedures and assessments to be performed at screening and their relative timings prior to randomisation.

Before entering the study, patients will be assessed to ensure that they meet the eligibility criteria (see Sections 4.1 and 4.2). Patients not meeting these criteria should not be entered into the study.

Written informed consent must be obtained prior to any study specific assessments. Procedures that are part of standard of care may occur before informed consent is obtained.

Each patient will undergo screening procedures within 3 weeks prior to randomisation except for baseline tumour assessments (see below).

The data listed below will be collected on the relevant CRFs:

- date of birth and race
- past medical history, including all significant conditions which have existed previously even if now resolved
- physical examination to assess all conditions which are current and ongoing
- ECG
- WHO performance status
- haematology and biochemistry

  Patients with any elevation of bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase (ALP) above upper limit of reference range (ULRR) at screening must have a CT scan or ultrasound of the liver to assess involvement with hepatic metastases.
- concurrent therapy
- Tumour burden and tumour assessments (as per RECIST 1.1 criteria (see Appendix C))
  - Tumour assessment data must be available for confirmation of disease before randomisation. All patients must have a chest x-ray or a computerized

tomography (CT) scan of the chest within 4 weeks before treatment. And a screening skeletal survey or isotopic bone scan within 8 weeks before treatment. Patients with an abnormal isotopic bone scan or skeletal survey must have further baseline confirmation with assessment by X-ray (or by CT scan, or magnetic resonance imaging [MRI] as appropriate) for clinical evaluation and tumour assessment within 4 weeks prior to treatment. (A skeletal survey done within 4 weeks of treatment does not require further confirmation by X-ray.)

- Up to 5 target lesions (no more than 2 lesions per organ) can be selected at screening; these target lesions, which must be measurable (as defined in Appendix C), will be monitored by the investigator throughout the study, and tumour measurements will be collected.

- Previously irradiated lesions will not be considered measurable.

- All other (non-target) lesions will also be monitored throughout the study, and an overall assessment of non-target lesions will be made and recorded as "present", "present with progression" or "absent".

- proven evidence of ER positive breast cancer

  If possible, the status of the PgR receptor should also be recorded. If the status of this receptor is not available historically, if possible a test should be done for the missing receptor data for the purposes of this study.

Screening data will be used as baseline measurements, except for haematology and biochemistry, which must be repeated before study treatment if study treatment does not commence within 7 days after the screening sample was taken. The most recent assessment before first dosing should be entered onto the Visit 1 CRF pages.

Day 1/Visit 1 is the day on which the patient first receives her randomised study treatment (i.e., the first day to receive study treatment, not the day of randomisation).

The patient should be treated within 7 days following randomisation.

Subsequent visits should occur within ± 3 days of the protocolled visit times except for tumour assessments, which can occur ± 2 weeks of the specified time point.

6.3 Efficacy

Following initial randomised trial treatment on day 1, subsequent visits and assessments, including day 15, should occur ± 3 days of the protocolled visit times except for tumour assessments which can occur ± 2 weeks of the specified visit date. Patients will be considered lost to follow-up if they miss their visit and have no information available for more than 24 weeks.

Efficacy for all patients will be assessed by objective tumour assessments every 12 weeks using the RECIST 1.1 criteria (Appendix C) except for those patients with bone only disease.

All patients will be assessed until evidence of one of the following:

- Progression of disease
- Death

For patients with measurable disease the RECIST 1.1 criteria will be used to determine PFS, the objective tumour assessments (CR and PR), as well as the best overall objective tumour response; details are given in Appendix C. The definitions (RECIST 1.1) for measurable, non-measurable, target and non-target, and the objective tumour response criteria (CR, PR, SD or progression of disease) are presented in Appendix C.

For patients with bone only disease, progression will be defined as described in Section 6.3.1.

Up to 5 target lesions (no more than 2 lesions per organ) can be selected at screening; these target lesions, which must be measurable (as defined in Appendix C), will be monitored by the Investigator throughout the study, and tumour measurements will be collected. All other (nontarget) lesions will also be monitored throughout the study, and an overall assessment of nontarget lesions will be made and recorded as “present”, “present with progression” or “absent”.

A patient is determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions (see Appendix C). Death will be regarded as a progression event in those patients who die before disease progression.

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the CRF page in the same order as they were recorded at screening. Details of any new lesions will also be collected. Response and progression will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

Tumour markers must not be used to assign progression or objective response (see RECIST 1.1, Appendix C).

Objective tumour response will be determined according to RECIST 1.1, and these responses will be used in the summaries of PFS, ORR, CBR, DoR and DoCB.

Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment. Further tumour assessments will be made for all patients at all time points defined in the study plan (Table 1).

It is important to follow the assessment schedule as closely as possible because PFS is the primary variable and biases in analysis can occur if one treatment group is examined more

often or sooner than the other. If an unscheduled radiological and clinical tumour assessment is performed, and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan). This is in order to minimize any unintentional bias caused by some patients being monitored at a different frequency than other patients.

Patients who are withdrawn from study treatment for reasons other than disease progression will continue to have objective tumour assessments every 12 weeks until progression is documented. Adherence to the study plan should be observed whenever possible.

6.3.1 Progression-Free Survival (PFS)

For patients with measurable disease, the RECIST 1.1 criteria will be used to determine a patient's PFS (see Appendix C).

According to RECIST 1.1, a patient is determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions. Progression of target lesions is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded, and in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

In the absence of measurable disease at baseline (as per RECIST 1.1 criteria), the following will be considered progression among patients with lytic or mixed (lytic-blastic) bone lesions:

- The appearance of one or more new lytic lesions in bone
- The appearance of one or more new lesions outside of the bone
- Unequivocal progression of existing bone lesions and/or other non-target lesions

For patients with both measurable disease (as per RECIST 1.1 criteria), and documented lytic or mixed bone lesions at baseline, the definition of progression will be based on the RECIST 1.1 criteria in addition to the criteria defined above for patients with lytic or mixed bone lesions without measurable disease.

Note: Pathologic fracture, new compression fracture or complications of bone metastases will not be considered as evidence of disease progression, unless one of the above mentioned criteria is fulfilled.

The date of progression is the date of the investigation/procedure (imaging, biopsy, etc) that led to the diagnosis of progression. If more than one investigation/procedure is performed, and assuming that more than one confirms progression, the date of progression is the date when the first investigation/procedure was performed. The date of the progression in the case of a biopsy refers to the date of the biopsy itself and not the date of the pathology report. In the case of more than one procedure, where the first one had unclear results that have been confirmed later, that date of progression is the date of the investigation/procedure with clear,

definitive results. Progression should not be backdated to the earlier procedure. If a patient dies prior to reporting progression, the date of progression should be considered as the date of death.

Patients without a PFS event at the time of the primary analysis will be censored at the date of their last objective assessment. This includes patients lost to follow up or who have withdrawn consent. The PFS for patients without post baseline tumour assessments will be censored at time zero days.

6.3.2 Objective Response Rate (ORR)

Only patients with measurable disease at baseline, as per RECIST 1.1, will be assessed for objective response. The RECIST 1.1 criteria will be used to perform the objective tumour assessments and best overall objective tumour response. **Tumour markers will not be utilised for this purpose** (see RECIST 1.1 Criteria for details, Appendix C).

Categorization of the objective tumour response assessments will be based on the RECIST 1.1 criteria for target and nontarget lesions. Response will be classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a patient's best overall response will be determined from the start of treatment until progression.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks from the date of randomisation.

6.3.3 Clinical Benefit Rate (CBR)

The RECIST 1.1 criteria will be used to perform the objective tumour assessments and best overall objective tumour response. **Tumour markers will not be utilised for this purpose** (see RECIST 1.1 Criteria for details, Appendix C).

6.3.4 Duration of Response (DoR)

DoR will be calculated for those patients who have a best response of CR and PR based on RECIST 1.1 criteria (Appendix C).

6.3.5 Duration of Clinical Benefit (DoCB)

Duration of clinical benefit will be calculated for those patients with a best response of CR, PR or SD ≥ 24 weeks.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is 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.

The term AE is used to include both serious and non-serious AEs.

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

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Method of detecting AE/SAEs

At each visit the method of detecting AEs and SAEs will be by:

- information volunteered by the patient or carer
- open-ended and non-leading verbal questioning of the patient at every visit such as the following: *How are you feeling? Have you had any (other) medical problems since your last visit?*
- observation by the investigational team, other care providers or relatives

Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and up to **8 weeks** after the last injection of study medication

Follow up of AEs/SAEs

After the initial AE/SAE report, the investigator is required to follow up proactively each patient and provide further information to AstraZeneca on the patient's condition. During the study all AEs/SAEs should be followed up to resolution, or until the condition stabilizes, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- the date when the AE started and stopped
- CTCAE grade
- whether the AE is serious or not
- investigator causality rating against the Investigational Product (yes or no)
- action taken with regard to investigational product
- AE caused patient's withdrawal from study *(*yes or no*)*
- outcome

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

- AE met criteria for serious AE
- Investigator became aware of serious AE
- AE is serious due to
- of hospitalisation
- of discharge

- Probable cause of death
- of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

The grading scales found in the revised National Cancer Institute CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

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. 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 patient or care provider 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 CRF. 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 and vital signs 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 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 patient'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. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Adverse events related to elective surgery and surgery for breast cancer

A hospitalisation for elective surgery or surgery for breast cancer should not be recorded as an adverse event or as a serious adverse event. However, complications of surgery should be recorded as adverse events or as serious adverse events if they fulfil any of the criteria (see Section 6.4.1 and 6.4.2).

Deaths

All deaths that occur during the study must be reported as follows:

Death, clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF, but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as an 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.

New Cancers

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this 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.

Interactions

Current experience with fulvestrant has not shown potential for drug-drug interaction.

However, for the purpose of this study if, in the opinion of the investigator, an interaction between fulvestrant and a concomitant drug or between concurrent drugs has occurred, this should be reported as an adverse event. Information should be provided as to which drugs the interaction has occurred between. Any adverse event that occurs as a consequence of the interaction and fulfils the criteria for seriousness must be reported to AstraZeneca immediately, on the same day as per other serious adverse events. Adverse events (serious and non serious) arising as the result of an interaction should be recorded on an adverse event form with an indication that the event is a result of an interaction. For example 'hypotension related to drug-drug interaction'.

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 CRF.

If any SAE occurs in the course of the study, then investigators 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 to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five 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 ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

6.4.5 Laboratory safety assessment

Blood samples for determination of clinical chemistry and haematology will be taken at the times indicated in the Study Plan (see Table 1). Local hospital laboratory will be utilised for the analysis of haematology and biochemistry values.

The following laboratory variables will be measured:

Table 2 Biochemistry (serum gel tube)

Alanine aminotransferase (ALT)	Creatinine
Aspartate aminotransaminase (AST)	Total bilirubin
Alkaline phosphatase (ALP)	

Table 3 Haematology (ethylene diamine tetra-acetic acid [EDTA] coated tube)

White blood cell count (total)	Absolute Neutrophil Count (ANC)
Haemoglobin	Platelet count

For blood volume see Section 7.1

6.4.6 Physical examination

Physical examinations will be performed at the times indicated in the study plan (see Table 1), which will also include the WHO performance status.

WHO performance status will be recorded as follows:

0 = Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia

1 = Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains patients who are fully active, as in Grade 0, but only with the aid of analgesics

2 = Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, unable to carry out any self-care and confined totally to bed or chair.

6.4.7 ECG

ECG is only recorded routinely at screening and in the event of a cardiac adverse event. The same method of assessment should be used throughout. ECG will be evaluated locally and the results recorded on the relevant CRF page. Any clinically significant abnormal findings observed and recorded during the study will be recorded as AEs.

6.4.8 Vital signs

Vital signs (heart rate and blood pressure) are performed at the times indicated in the study plan (see Table 1).

6.5 Patient reported outcomes (PRO) (Not Applicable)

6.6 Pharmacokinetics

First 30 patients in each arm who consent to the pharmacokinetic measurements will have pharmacokinetic plasma sample taken at the time points shown in Table 1.

6.6.1 Collection of samples

A 4 ml blood sample will be taken into a lithium heparin tube at the specified time points to enable the measurement of fulvestrant plasma drug level for pharmacokinetic analysis. Samples will be taken at day 1, day 15(±3 days), day 29(±3 days), day 57(±3 days), day 85(±3 days), just prior to the fulvestrant injection(s). Two additional samples will also be taken at any time between day 5-10 and between day 33-38.A sample will also be taken at the treatment discontinuation visit if this occurs before week 12. The time and date of sample collection will also be recorded.

The sample should be kept mobile and centrifuged as soon as possible after collection by spinning for 10 minutes at 1000G. The plasma should be taken off immediately and stored in a plain tube at -20°C.The tubes of plasma should be sent to Covance, Shanghai for analysis of fulvestrant concentrations. Samples will be protected from light at all times. The plasma samples must be kept at a temperature of -20°C or below (using a freezer or dry ice) while being shipped and should be packed securely to avoid breakage during transit. Samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours to allow for delays in shipment. Samples must be shipped as quickly as possible.

AZ or a third party selected by AZ will provide materials (test tubes, labels, etc.) used in the collection, storage and shipment of blood samples.

For blood volume see Section 7.1.

6.6.2 Labelling of plasma PK samples

PK blood sample tubes will be clearly labelled with the study number, patient number, visit number, date and actual time of collection. The date and time of collection will also be recorded on the lab data collection form provided. Any samples collected outside of the acceptable time windows will have an explanatory comment added to the source documents.

Pre-printed labels and sample registration forms will be provided for plasma drug level samples detailing study number, patient number, visit number, actual sample time and date.

A label will be completed and affixed to a plain tube at the time of plasma preparation. Identical data will be recorded on the sample registration form.

It is important that sample registration forms are completed accurately and that each tube can be accurately and easily identified.

6.6.3 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by Covance, Shanghai on behalf AstraZeneca, using a validated, highly sensitive and specific, liquid chromatography mass spectrometry method (LC-MS-MS), using deuterated fulvestrant as the internal standard (IS). Concentration of fulvestrant will be calculated from peak area ratios[fulvestrant/IS] by reference to calibration series constructed by adding known amounts of fulvestrant to control plasma and extracting these standards in parallel with the test samples. Quantification will be by reference to a least squares linear regression line generated from the standard sample.

6.7 Pharmacodynamics (Not Applicable)

6.8 Pharmacogenetics (Not Applicable)

6.9 Health economics (Not Applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood drawn from each patient will depend on the length of time the patient receives study medication. Table 4 is a guide to the approximate volume of blood that will be drawn from each patient, based on the assumption that each patient will receive study treatment for 24 weeks. Actually, when the blood samples are assessed at the local hospital laboratory, necessary volumes of blood samples will be collected at each medical centre.

Table 4 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3.5	5	17.5
	Haematology	2	5	10
Pharmacokinetic (PK cohort only)		4	7	28
Total				55.5

7.2 Handling, storage and destruction of biological samples

The samples will be used up after analyses as described here.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

7.4 Chain of custody of biological 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 biological samples from the patients while in storage at the centre until shipment or disposal and keeps documentation of receipt of arrival.

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 biological samples

If a patient withdraws consent to the use of donated biological 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.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, 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 patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the 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 Biological Samples.

8.2 Patient data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee (EC) 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 patients. The investigator 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 should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients 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 patient 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, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient 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 patient

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

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of 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 is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to 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 are to 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.

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. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient 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 patients 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.
- Discuss where the identification of data will be recorded eg, medical record(s), CRF and other associated documents. This will be documented in a Clinical Study Agreement.
- Discuss the specific requirements of the pharmacokinetic research part of the study with the investigator(s) (and other personnel involved with the study).

9.2 Training of study site personnel

Before the first patient 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 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 CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

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

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 for location of source data.

Source data refers to data generated as a result of the patient's inclusion in the study and includes all related medical examinations and other records.

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, or equivalent, 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 patients and in all other respects, not relating to study conduct or treatment of patients, 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 patients are enrolled.

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

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

The study is expected to start in Q1 2011 and to end by Q4 2013.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with fulvestrant.

Study investigators will be notified by AstraZeneca when recruitment is complete.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by Cognizant -AstraZeneca Data Management Centre.

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. 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 defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the Cognizant-AstraZeneca Data Management Centre

The data collected through third party sources will be obtained and reconciled against study data.

When all data have been coded, validated, electronically signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Progression-Free Survival (PFS)

PFS is defined as the time from randomisation to the time of the earliest objective disease progression (defined in Section6.3.1), including death from any cause. Patients who have not progressed or died at the time of the data cut-off date or who have been lost to follow-up will be right-censored at the date of their last disease assessment.

For details of the primary statistical analysis of PFS see Section 12.

11.1.2 Objective Response Rate (ORR)

ORR is defined as the proportion of all treated patients with measurable disease at baseline who have a best objective tumour response of either CR or PR.

Confirmation of response is not required and therefore the following categories of best objective response will be derived:

CR: Single visit response of CR

PR: Single visit response of PR

SD : Stable disease recorded at least8 weeks after the date of randomisation

PD: Progression, or death in the absence of CR/PR or SD

NE: No evidence of CR/PR or SD or PD or death (e.g. early censored patients)

11.1.3 Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients in the FAS who have a best objective tumour response of CR, PR or SD ≥ 24 weeks. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks from the date of randomisation.

11.1.4 Duration of Response (DoR)

Duration of response will be defined in two ways:

(i) From date of first documentation of the response (CR or PR) until the date of disease progression or death from any cause.

(ii) From date of randomisation until the date of disease progression or death in the absence of progression from any cause.

Any patient who has not progressed or died by the date of data cut-off, or who have been lost to follow up, will be right-censored in the analysis at the date of their last disease assessment.

11.1.5 Duration of Clinical Benefit (DoCB)

Duration of clinical benefit will be defined as from date of randomisation until the date of disease progression or death from any cause, measured only in those patients who achieved a confirmed CR, PD or SD≥24 weeks. DoCB should be in those patients with CB.

Any patients who has not progressed or died by the date of data cut-off, or who have been lost to follow up, will be right-censored in the analysis at the date of their last disease assessment.

11.2 Calculation or derivation of safety variable(s)

Any new medical condition reported during the study will be recorded as an AE. Only those findings that are in addition to the condition being treated will be recorded as AEs (see Section 6.4.3for recording of AEs). Conditions that are considered by the investigator to be unequivocally disease-related will not be recorded as AEs.

11.2.1 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/vital signs/ECG data 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 (Not Applicable)

11.4 Calculation or derivation of pharmacokinetic variables

The objectives of the PK analyses for this study are to derive parameters that describe the PK of fulvestrant 250 mg and 500 mg dosing regimens in Chinese patients and assess inter-individual and residual variability. The primary parameters to be reported are CL/F and Vss/F and derive secondary parameters Cmax, tmax, Cmin, AUC0-τ, and t ½.

The concentration-time data from these studies will be analysed using a non-linear mixed effects model approach, a technique that is particularly useful for sparse data from a large number of individuals when the link between the individual parameters and the observed data are nonlinear. NONMEM will be used by the Clinical Pharmacology & DMPK group at AstraZeneca in addition to other supportive software such as R and Excel. Data from this study will be combined with data from studies 20 and 21 where further PK assessments will be undertaken.

The fixed effects describe the structural model or general form of the data. Random effects describe by the variation between individuals through individual specific regression parameters, which may be due to dependence on certain covariates and/or random but persistent variation. The residual error model captures random deviations between observed values and those predicted by the model. Model selection will be based on goodness of fit criteria including change of at least 6.64 (p=0.01) in the objective function value with 1 df, diagnostic plots, parameter, standard error and correlation estimates.

Secondary parameters will be derived for each individual from the final population model. Cmax, tmax, Cmin, and AUC0-τ will be derived following the 1st month of dosing and at steady-state. The table below details the calculation of the secondary PK parameters:

Table 5 Calculation of secondary PK parameters

Parameter	
t ½	Effective half-life: ln (2) x (Vss/F) / (CL/F)
C_{max}	The maximum individual predicted concentration in the central compartment (where the derivative approaches zero) in a standard dosing interval i.e. 28 days
t_{max}	The time of C_{max}

Parameter	
C_{min}	The individual predicted concentration at the end of the dosing interval (actual time immediately prior to the next dose or 672 hours, if longer)
$AUC_{0-\tau}$	Integration of the area under the concentration-time curve from the time of dosing to the end of the dosing interval (tau) i.e. 28 days or less if the dose is administered a few days prior day 28

A summary of the results, table of parameters and plots demonstrating the fit of the model to the data for this study may be presented in the CSR. Full details of the pharmacokinetic analysis will be reported separately in the Pharmacokinetic Report.

11.5 Calculation or derivation of pharmacodynamic variable(s) (Not Applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not Applicable)

11.7 Calculation or derivation of health economic variables (Not Applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

Full details of the analyses will be provided in the Statistical Analysis Plan which will be finalised before database lock.

The primary objective of the study is to compare the efficacy of 500 mg fulvestrant with 250 mg fulvestrant in terms of progression free survival, assessed by the primary variable, PFS, as defined in Section 11.1.

A secondary objective of the study is to describe the pharmacokinetic profile of fulvestrant 500mg and fulvestrant 250 mg in postmenopausal women with oestrogen receptor positive advanced breast cancer who have progressed or relapsed on endocrine therapy, using the PK parameters defined in Section 11.4.

The further objective of the study is to compare objective response rate, clinical benefit rate, duration of clinical benefit and duration of response of 500 mg fulvestrant with 250 mg fulvestrant, assessed by the secondary variables, ORR, CBR, DoCB and DoR, as defined in Section 11.1. And also to assess tolerability of fulvestrant 500 mg compared with fulvestrant 250 mg, assessed by adverse events as defined in Section 11.2.

12.1 Description of analysis sets

Full Analysis Set (FAS)

The primary statistical analysis of the efficacy of 500 mg fulvestrant compared to 250 mg fulvestrant will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Therefore efficacy data will be summarised and analysed on an FAS basis. This approach will be used when assessing progression-free survival, objective response rates, clinical benefit rates, duration of clinical benefit and duration of response.

Per protocol (PP)

In addition, a per protocol (PP) analysis excluding significant protocol violators and deviators will be carried out for the primary variable of PFS using the model with treatment factor only.

Pharmacokinetics

First 30 patients in each arm who consent to the pharmacokinetic(PK) measurements will have pharmacokinetic plasma samples taken. The patients who have actually received the study medication and have evaluable plasma levels of 500 mg fulvestrant and 250 mg fulvestrant will be included for pharmacokinetic analysis.

Safety

When assessing tolerability of 500 mg fulvestrant against 250 mg fulvestrant, safety population, a subset of the FAS population that includes all patients who received at least one dose of study medication will be used to produce summaries based on study treatment actually received.

12.2 Methods of statistical analyses

The primary analysis on the primary variable of PFS will be performed using a stratified log-rank test in the FAS population.

Following a request from the Chinese State Food and Drug Administration(SFDA) to perform subgroup analyses of patients on the basis of the last therapy received prior to fulvestrant (AI vs AO therapy), the randomisation scheme and primary analysis have been stratified to ensure that a similar proportion of post AI and post AO patients are in each treatment group. Section 12.2.6 provides further details of the planned subgroup analyses.In addition to the stratified log rank test for PFS based on the FAS population, a Cox regression model will also be performed with factors fitted for treatment and other baseline covariates (adjusted model).

The conclusions will be based on the log rank test analysis as this is considered as the primary analysis. If the log rank test and the adjusted analysis yield different results, the consequence of covariate adjustments will be explored.

A secondary Per Protocol analysis of PFS will be performed using a stratified log-rank test in order to assess the reliability of the conclusions from the primary FAS analysis. For objective

response rate and clinical benefit rate, a logistic regression model will be fitted with treatment factor only. Duration of response and duration of clinical benefit will be summarised using the Kaplan-Meier method.

12.2.1 Progression-free Survival

For the primary analysis of PFS, to assess efficacy of 500 mg fulvestrant against 250 mg fulvestrant, the following analysis will be carried out:

Formal treatment comparisons will be analysed using a stratified log-rank test as a primary method.

In addition, a secondary analysis using the Cox regression model will be performed to investigate any impact of baseline covariates. The following baseline covariates will be fitted in the Cox regression model:

- Age (≤ 65 vs. >65)
- Response to last endocrine therapy received prior to fulvestrant (responsive / not responsive)
- Receptor status at diagnosis (both ER+ & PgR+ vs. ER+ & PgR other)
- Visceral involvement (Yes/No)
- Last therapy received prior to fulvestrant (Aromatase Inhibitor (AI)/ Anti-Oestrogen(AO))
- Measurable disease (Yes/No)

The effects of centre and treatment by centre interaction will be investigated if possible; however, it is recognised that this investigation may be limited if recruitment at most centres is low, which will cause problems with computational convergence. No analysis will be performed for individual centres or a subgroup of centres.

12.2.2 Pharmacokinetics

All PK parameters will be listed (CL/F, Vss/F etc). Only C_{max}, t_{max}, C_{min}, $AUC_{0-\tau}$ and $t_{1/2}$ may be summarised.

12.2.3 Objective Response Rate and Clinical Benefit Rate

Assessments of tumour response will be based on the RECIST 1.1 criteria for patients with measurable disease at baseline.

ORR is defined as the proportion of responders (CR and PR). CBR is defined as the proportion of responders plus those with SD≥24 weeks.

Treatment comparison in ORR and CBR will be analysed using a logistic regression model with treatment factor only. Results will be expressed as the odds ratio together with the corresponding 95 % CI and p-value. The estimate of the difference in ORRs (500 mg fulvestrant vs. 250 mg fulvestrant) and the corresponding 2-sided 95% CI will also be presented.

The best objective response of CR, PR, SD≥24 weeks, SD<24 weeks, and progression will be summarised.

12.2.4 Duration of Response and Duration of Clinical Benefit

Duration of response and duration of clinical benefit will be summarised using the Kaplan-Meier method by randomised treatment. Kaplan-Meier plots and Kaplan-Meier estimates of median DoR and DoCB will be presented for each treatment.

12.2.5 Tolerability

AE and lab variables will be summarised by treatment actually received. AE data will be summarised in MedDRA by preferred term and system organ class. The number of patients who withdraw or die due to AEs will be summarised.

12.2.6 Subgroup analysis

A subgroup analysis based on FAS will be performed for subgroup patients of last therapy prior to fulvestrant (AI vs AO therapy) for the variable of PFS at the request of the SFDA. The same analysis as detailed in Section 12.2 will be performed on this subgroup with only treatment factor fitted to the models. No adjustment for other covariates will be made.

The subgroup analysis will be exploratory in nature as the study is not appropriately powered to perform a formal subgroup analysis. Consequently, any results obtained from this analysis should be interpreted with caution.

12.2.7 Interim analyses

No interim analysis will be performed for this trial.

12.3 Determination of sample size

The study will randomised 220 postmenopausal women with oestrogen receptor positive advanced breast cancer and it is expected to obtain at least 100 evaluable postmenopausal women per treatment group so as to meet the SFDA's requirements for registration trials. The 220 patients will be randomised in a 1:1 ratio to fulvestrant 500mg and fulvestrant 250mg. The primary analysis for PFS will be carried out when at least 150 progression events have been observed.

A criterion has been predefined for declaring consistency with CONFIRM. The results of this study would be considered to be consistent with CONFIRM if the hazard ratio point estimate for the treatment comparison is <1 (i.e. if it is in the same direction as in CONFIRM). With a

sample size of 220 randomised patients and 150 progression events, if there is no ethnic difference with the CONFIRM population, there is an 89% chance the HR <1.

For the PK part, no specific statistical hypothesis will be tested. Because of the long apparent t1/2, intensive sampling for fulvestrant is problematic. For this reason sparse sampling is preferred and has been used in other fulvestrant PK studies (Pritchard KI et al 2010; Ohno.S et al 2010). The sparse data will be analyzed by a mixed effect compartmental model (not non-compartmental analysis). Based on experience from prior fulvestrant PK studies, this study plans to recruit approximately 30 patients per arm for PK analysis for comparison with existing PK data for fulvestrant. Recruitment into the PK analysis will be on the basis of the first 30 patients per group who consent to the analysis.

12.4 Data monitoring committee

No data monitoring committee will be used in this study.

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 may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Name	Role in the study	Address & telephone number

13.2 Overdose

An overdose is defined as a dose administered to a patient that is in excess of the randomised dose for patients.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators 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 to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, 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 or life threatening events and within 4 calendar days of initial receipt for all other SAEs. For other overdoses (i.e. without symptoms or with non-serious adverse events) reporting to the Patient Safety data entry site should be done within 5 calendar days.

For fulvestrant, there is no human experience of overdosage to date. Animal studies suggest that no effects other than those related directly or indirectly to antioestrogenic activity were evident with higher doses of fulvestrant. Thus, it indicates that overdose should be managed symptomatically.

13.3 Pregnancy

Only postmenopausal women are eligible to participate in this study. Pregnancy should be ruled out prior to study start in the case of doubt. However, if for any reason a pregnancy occurs it should be reported to AstraZeneca immediately using specific pregnancy reporting forms.

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Clinical Study Protocol Appendix B

Drug Substance	Fulvestrant
Study Code	D6997L00021
Edition Number	1.0

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance Fulvestrant

Study Code D6997L00021

Appendix Edition 1.0

Appendix C
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

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LIST OF TABLES

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D6997L00021 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT/MRI/plain x-ray and is suitable for repeated assessment.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) or Clinical examination and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination***
- Brain metastasis***

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as Non-Target Lesions (NTL).

** Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

*** Skin lesions assessed by clinical examination and brain lesions are considered as NTL in general AstraZeneca practice.

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D6997L00021 study it is recommended that CT examinations of the neck, chest, abdomen, pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the D6997L00021 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest X-ray

In the D6997L00021 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

In the D6997L00021 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D6997L00021 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D6997L00021 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

In the D6997L00021 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the D6997L00021 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D6997L00021 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D6997L00021 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. In the D6997L00021 study follow-up assessments will be performed every 12 ± 2 weeks from Visit 1 until progression. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

4.3 Non-Target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no TL/NTLs at baseline).

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

5.1 CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method. >>

Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should

be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

5.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247