**Amended Clinical Study Protocol**

| | |
|---|---|
| Drug Substance | Fulvestrant |
| Study Code | D6997C00002 |
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| Date | |

# A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

**Sponsor:** AstraZeneca AB, 151 85 Södertälje, Sweden

**AstraZeneca Research and Development site representative** _____ _____



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

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
|---|---|---|---|
| 1 | | | |
| 2 | | | |

| Administrative change No. | Date of Administrative Change | Local Administrative change No. | Date of local Administrative Change |
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| 1 | | | |
| 2 | | | |

# PROTOCOL SYNOPSIS

## A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

**International Coordinating Investigators**

**Study centre(s) and number of patients planned**

A total of 720 postmenopausal patients will be recruited from approximately 150 centres in North America (Data Cut off date for primary analysis (and 50% Survival analysis)4 and 30 patients per centre.

| Study period | | Phase of development |
|---|---|---|
| Date of first patient enrolled | February 2005 | III |
| Date of last patient enrolled | August 2007 | |
| Data Cut off date for primary analysis (and 50% Survival analysis) | 28th February 2009 | |
| Estimated data Cut off date for 75% Survival Analysis and end of clinical data collection | 2011* | |
| Estimated date of last patient completing the study (end of study) | 2012** | |

*Patients may remain on open label study treatment and be followed as per standard clinical practice after the 75% Survival Analysis until any of the criteria for discontinuation are met
**Estimated date when the last patient discontinues study treatment

**Objectives and Variables**

| Objective | Variable |
|---|---|
| **Primary** | |
| To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression. | Time to Progression (TTP) |
| **Secondary** | |
| **1.** 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 criteria) |
| **2.** 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 criteria) |
| **3.** To compare duration of response of patients treated with fulvestrant 500 mg with the duration of response of patients treated with fulvestrant 250 mg. | Duration of Response (DoR) |
| **4.** To compare the duration of clinical benefit of patients treated with fulvestrant 500 mg with the duration of clinical benefit of patients treated with fulvestrant 250 mg. | Duration of Clinical Benefit (DoCB) |
| **5.** To compare the overall survival of patients treated with fulvestrant 500 mg with the overall survival of patients treated with fulvestrant 250 mg. | Overall Survival (OS) |
| **6.** To assess the tolerability of fulvestrant 500 mg treatment compared with fulvestrant 250 mg treatment. | Frequency and Severity of Adverse Events |
| **7.** To assess the quality of life (QoL) of patients treated with fulvestrant 500mg as compared to fulvestrant 250 mg in a subgroup of patients. | Trial outcome index (TOI) derived from the FACT-B questionnaire. Data will be collected from a subgroup of patients. |

**Study design**

Randomised, double-blind, parallel-group, multicentre study. Eligible patients will be randomised 1:1 to receive either fulvestrant 500 mg or fulvestrant 250 mg.

**Target patient population**

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.

**Investigational product, dosage and mode of administration**

Fulvestrant 500 mg will be given as two 5 ml intramuscular injections, one in each buttock, on days 0, 14, 28 and every 28 days thereafter.

Following the database lock for the primary analysis, patients will have their treatment unblinded and be transferred to open label supplies

**Comparator, dosage and mode of administration**

Fulvestrant 250 mg will be given as two 5 ml intramuscular injections, one in each buttock, on days 0, 14, 28 and every 28 days thereafter.

Following the database lock for the primary analysis, patients will have their treatment unblinded and transferred to open label supplies. Patients who are currently receiving the fulvestrant 250 mg, in consultation with their physician and the provision of re-consent to the open label follow-up phase of the study, will be given the option to be transferred to fulvestrant 500 mg.

After study treatment is unblinded, any patient not wishing to be transferred to fulvestrant 500 mg, who remains on fulvestrant 250 mg, will receive only one 5 ml intramuscular injection, as the placebo injection previously required to preserve the double blind nature of the study is no longer required

**Duration of treatment**

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

**Statistical methods**

The formal statistical analysis for TTP will be carried out when at least 632 progression events have been observed. The initial Overall Survival (OS) analysis will be performed after 632 progression events, or when at least 50% of patients have died, whichever occurs later. A further OS analysis will be performed when approximately 75% of patients have died.

The primary statistical analyses of the efficacy variables will be performed by randomised study treatment for 'intention to treat' (ITT) population. In addition, secondary analyses for

the primary variable of TTP 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 TTP will be performed using a log-rank test. 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. Overall survival (OS) will be analysed using a log rank test as above for TTP. Duration of response (DoR) and duration of clinical benefit (DoCB) will be summarized.

No interim analysis will be carried out in this study.

The decision as to whether or not the primary study objective has been achieved will be made upon the superiority test for TTP using the log-rank test in ITT population.

**Translational research sub-study**

An optional part of this study will involve the collection of archival tumour samples (paraffin-embedded blocks) from either the primary tumour or a metastatic site for the purposes of translational research. The main aims of this research will be to explore the correlation between HER pathway activation and response to fulvestrant.

Provision of the archival tumour samples will be optional for all patients and will require patient consent.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event (see definition in Section 4.7.1.1) |
| AI | Aromatase inhibitor |
| ANC | Absolute Neutrophil Count |
| Assessment | An observation made on a variable involving a subjective judgement (assessment) |
| AUC | Area Under the Curve |
| ASA | Acetylsalicylic Acid (Aspirin) |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BCS | Breast Cancer Subscale |
| ER | Oestrogen Receptor |
| CBR | Clinical Benefit Rate |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration of drug |
| CR | Complete Response |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Clinical Research Organisation |
| $C_{ss}$ | Steady State Concentration |
| CT | Computed Tomography |
| DCIS | Ductal carcinoma in situ |
| DIC | Disseminated Intravascular Coagulation |
| DHEA | Dihydroepiandrosterone |
| DNA | Deoxyribonucleic acid |
| DoCB | Duration of Clinical Benefit |
| DoR | Duration of Response |
| ECG | Electrocardiogram |
| EDTA | Ethylene diamine tetra-acetic acid |
| EGF-R | Epidermal Growth Factor Receptor |

| Abbreviation or special term | Explanation |
|---|---|
| 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 |
| EWB | Emotional Well Being (FACT-B) |
| FACT-B | Functional Assessment of Cancer Therapy for Breast Cancer |
| FACT-G | Functional Assessment of Cancer Therapy - General |
| FSH | Follicle Stimulating Hormone |
| FWB | Functional Well Being (FACT-B) |
| GCP | Good Clinical Practice |
| h | Hours |
| HER | Human Epidermal Growth Factor Receptor |
| HRT | Hormone Replacement therapy |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IGF | Insulin-like Growth Factor |
| i.m. | Intramuscular |
| International Co-ordinating investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally. |
| INR | International Normalisation Ratio |
| IRB | Institutional Review Board |
| ITT | Intention to Treat |
| LD | Longest Diameter |
| 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 |
| MRI | Magnetic Resonance Imaging |
| NCI CTC | National Cancer Institute, Common Toxicity Criteria |

| Abbreviation or special term | Explanation |
|---|---|
| NCR | No Carbon Required |
| ng | Nanogram |
| OAE | Other Significant Adverse Event (i.e., adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 4.7.1.1 |
| OR | Objective Response |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| Outcome variable | A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective. |
| pMAP Kinase | Mitogen Activated Protein Kinase |
| Parameter | A quantity (usually unknown) that characterizes the distribution of a variable in a population of patients. |
| PCR | Polymerase Chain Reaction |
| PD | Progressive Disease |
| PgR | Progesterone Receptor |
| 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. |
| PK | Pharmacokinetic |
| PP | Per Protocol |
| PWB | Physical Well Being (FACT-B) |
| QoL | Quality of Life |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| SAE | Serious adverse event (see definition in Section 4.7.1.1). |
| SAP | Statistical Analysis Plan |
| SERM | Selective Estrogen Receptor Modulator |
| SD | Stable Disease |
| SWB | Social Well being (FACT-B) |
| TMA | Tissue Micro Array |
| TOI | Trial Outcome Index (FACT-B) |
| TTP | Time to progression |
| ULRR | Upper Limit of Reference Range |

| Abbreviation or special term | Explanation |
|---|---|
| Variable | A characteristic or a property of a patient that may vary e.g., from time to time or between patients |
| WHO | World Health Organisation |
| w/v | Weight per Volume |

# 1. INTRODUCTION

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

## 1.1 Background

Breast cancer is one of the most common female cancers and the most common cause of cancer deaths in women. It comprises 18% of all female cancers worldwide (Mcpherson K et al 2000). The incidence varies among populations with about half of all cases occurring in North America and Western Europe. Oestrogen acts as an endocrine growth factor for at least one third of breast cancers. It has long been acknowledged that many cancers are hormone dependent and that hormonal manipulation can affect the progress of the disease. Early recognition of the effects of hormonal manipulation on metastatic breast cancer was observed as early as 1896 following removal of the oestrogenic stimulus by bilateral oophorectomy (Beatson GT. 1896). The most important factor that determines response to hormonal manipulation is the presence of the oestrogen receptor in the target tissue (Fisher B et al 2001).

The anti-oestrogen AstraZeneca ZD6157 (tamoxifen, NOLVADEX™) is the most widely used hormonal treatment for breast cancer in both pre- and postmenopausal women. This drug has been used to treat patients with breast cancer in advanced disease, as an adjuvant therapy after surgery, and for the treatment of ductal carcinoma in situ (DCIS), and to reduce the risk of breast cancer development in women at high risk (Fisher B et al 1998). Despite the demonstrated efficacy in these patient populations, de novo resistance or acquired resistance may occur after prolonged treatment, which limits the effectiveness of tamoxifen in many patients. In at least some patients the disease progresses during therapy because tumour growth may also be stimulated by tamoxifen (Wiebe VJ et al 1993). The reasons for tamoxifen resistance include not only tamoxifen-stimulated tumour growth, but also by the absence or loss of oestrogen receptors (ER), by cross talk amongst growth factor signalling pathways, and by altered expression of receptor-interacting proteins. Some tumours spontaneously become hormone-independent despite the presence of oestrogen receptors; in others, tumours that are initially oestrogen-receptor-positive become oestrogen-receptor-negative over time (Encarnacion CA et al 1993, Hull et al 1983). At least two-thirds of the tumours that become resistant to tamoxifen continue to express oestrogen receptors, and many of these tumours regress when second line hormonal therapy is initiated. After progression of disease on an anti-oestrogen, further hormonal therapy is sought.

Because the major source of oestrogen in postmenopausal women is aromatase-mediated conversion of circulating androstenedione to oestrone in peripheral tissues, an alternate approach to the management of advanced breast cancer in postmenopausal women has been through the use of aromatase inhibitors (AI). The development of oral, selective, non-steroidal AI has lead to the introduction into clinical practice of well-tolerated agents with clear evidence of clinical benefit.

The third generation oral AIs, ie, AstraZeneca ZD1033 (anastrozole, ARIMIDEX™), letrozole (FEMARA™, Novartis), and the steroidal, type I inhibitor, exemestane (AROMASIN™, Pharmacia & Upjohn), have now been tested in phase III trials where each has been shown to be more effective than megestrol acetate (MEGACE™, Bristol-Myers Squibb) (Buzdar AU et al 1998; Buzdar A et al 2001; Dombernowsky P et al 1998; Kaufmann M et al 2000). They also have been shown to be more effective than tamoxifen in advanced breast cancer (Bonneterre J et al. 2001; Mouridsen H et al 2001; Paridaens R et al 2004).

The search for an anti-oestrogen which is devoid of the agonist activity of tamoxifen and which can effectively block oestrogen receptor activity resulted in the discovery and clinical development of ZD9238 (fulvestrant, FASLODEX™). Fulvestrant has demonstrated efficacy in women whose breast cancer has progressed following tamoxifen therapy (Howell et al 2002, Osborne CK et al 2002). Fulvestrant is a new oestrogen receptor antagonist, without known agonistic properties that down-regulates cellular levels of the ER in a dose-dependent manner (Howell et al 2000, Robertson et al 2001, Wakelin AE et al 1991).

## 1.2 Rationale for this study

This study will assess the relationship between fulvestrant dose and efficacy. Fulvestrant, at a dose of 250 mg every 28 days, is the first oestrogen receptor antagonist shown to be at least as effective for both TTP and OR 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).

This dose and schedule has received regulatory approval in the USA and European Union. However, evidence from a number of studies suggests that higher doses may be able to enhance efficacy further. There is a hypothesis that greater efficacy may be achieved using an increase in fulvestrant dose which is based on:

- Data from studies 9238IL/0020 (Howell et al 2002) and 9238IL/0021 (Osborne CK et al 2002) suggesting that a dose-response effect exists for fulvestrant. These studies also included a lower dose arm (125 mg fulvestrant every 28 days) which was discontinued because it failed to meet the minimum efficacy requirements.

- Data from study 9238IL/0036 (Addo S et al, 2002) also suggest that a dose-response relationship may exist. In female volunteers given a single i.m. injection of fulvestrant, there was a dose-dependent inhibition of ethinyloestradiol-induced endometrial thickening seen at day 28.

- Results from short term exposure to fulvestrant in Studies 9238IL/0002 (DeFriend D et al 1994) and 9238IL/0018 (Robertson et al 2001) showing that expression of ER, PgR and the cell proliferation-related antigen Ki67 are reduced in a dose-dependent manner and suggesting that the maximum effect has not been reached.

- Pharmacokinetic modeling (see Figure 2) providing evidence that an increase in fulvestrant dose and dosing schedule will result in a:

- decreased time to steady state plasma levels
- higher AUC and $C_{max}$
- higher trough level and therefore maintenance of a higher exposure throughout the dosing interval

Therefore, this study will compare the current dose and dosing schedule of fulvestrant (250 mg every 28 days) with a higher dose (500 mg every 28 days + an additional 500 mg on day 14 of the first month only).

### 1.2.1 Rationale for the translational research study on tumour tissue samples

In previous studies it has been shown that the HER family receptor signalling pathway cross-communicates with the oestrogen receptor pathway and regulates the ligand-independent activity of the oestrogen receptor (Gruber CJ et al 2002; Pietras RJ et al 1995). In hormone receptor positive HER-2 positive breast cancer cells, tamoxifen works as an agonist and promotes tumour growth. Early clinical data seem to support these pre-clinical findings (Osborne CK et al 2003).

Recently reported pre-clinical data suggest that oestrogen-dependent cell lines carrying HER-2 over-expression retain a significant level of sensitivity to fulvestrant, although the use of trastuzumab (anti-HER-2 monoclonal antibody) in combination with fulvestrant elicits a more profound and durable antitumour effect on the same breast cancer cell lines (Pietras RJ et al 2003).

These pre-clinical and early clinical data support the following hypotheses that will be explored in the context of the present study :

- Fulvestrant might be more active in tumours carrying a “non-activated” HER-pathway. In tumours carrying the HER pathway activation the combination of fulvestrant with anti-HER pathway compounds might be investigated in future studies.
- The 500 mg fulvestrant dose might be more effective than the 250 mg dose only in the cohort of tumours carrying the HER pathway activation.

To explore these hypotheses, archival tumour samples from patients participating in the clinical trial will be collected and molecular markers belonging to the HER pathway (i.e. membrane receptors, phosphorylated receptors, down stream effectors) will be evaluated using different techniques such as immunohistochemistry, fluorescence in-situ hybridisation, and PCR. In addition, a centralised testing for ER, PgR and Ki-67 will be performed.

Tumour samples will be collected only for those patients who have given their written informed consent. Details regarding the logistics of tumour samples collection are reported in Section 4.10.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| Primary Objective | Variable |
|---|---|
| To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression (TTP). | Time to Progression (TTP) |

## 2.2 Secondary objectives

| Secondary Objective | Variable |
|---|---|
| **1.** 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 criteria) |
| **2.** 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 criteria) |
| **3.** To compare duration of response of patients treated with fulvestrant 500 mg with the duration of response of patients treated with fulvestrant 250 mg. | Duration of Response (DoR) |
| **4.** To compare the duration of clinical benefit of patients treated with fulvestrant 500 mg with the duration of clinical benefit of patients treated with fulvestrant 250 mg. | Duration of Clinical Benefit (DoCB) |
| **5.** To compare the overall survival of patients treated with fulvestrant 500 mg with the overall survival of patients treated with fulvestrant 250 mg. | Overall Survival (OS) |
| **6.** To assess the tolerability of fulvestrant 500 mg treatment compared with fulvestrant 250 mg treatment. | Frequency and Severity of Adverse Events |

| Secondary Objective | Variable |
|---|---|
| **7.** To assess the quality of life (QoL) of patients treated with fulvestrant 500mg as compared to fulvestrant 250 mg in a subgroup of patients. | Trial outcome index (TOI) derived from the FACT-B questionnaire. Data will be collected from a subgroup of patients. |

# 3. STUDY PLAN AND PROCEDURES

## 3.1 Overall study design and flow chart

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

This is a randomised, double-blind, parallel-group, multicentre, phase III study to compare two dose levels of fulvestrant. 720 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 be recruited.

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 14 (± 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 and survival, regardless of whether they have discontinued randomised treatment, unless they have withdrawn consent. Details of the first subsequent systemic breast cancer therapy received following discontinuation of randomised treatment (regimen and start and end date), as well as the best response to this therapy (according to the investigator's best judgment as per the RECIST criteria), will be collected.

There will be an Independent Data Monitoring Committee (IDMC) responsible for the review of safety data as detailed in Appendix D.

Following the primary analysis for TTP (and 50% survival analysis which was performed at the same time), all patients, regardless of whether they are still receiving randomised treatment, will enter the survival follow-up phase and be followed as per standard clinical practice. Patients remaining on randomised treatment will have their treatment unblinded and transferred to open label supplies. Patients who are currently receiving fulvestrant 250 mg, in consultation with their physician and the provision of re-consent to the open label follow-up phase of the study, will be given the option to be transferred to fulvestrant 500 mg.

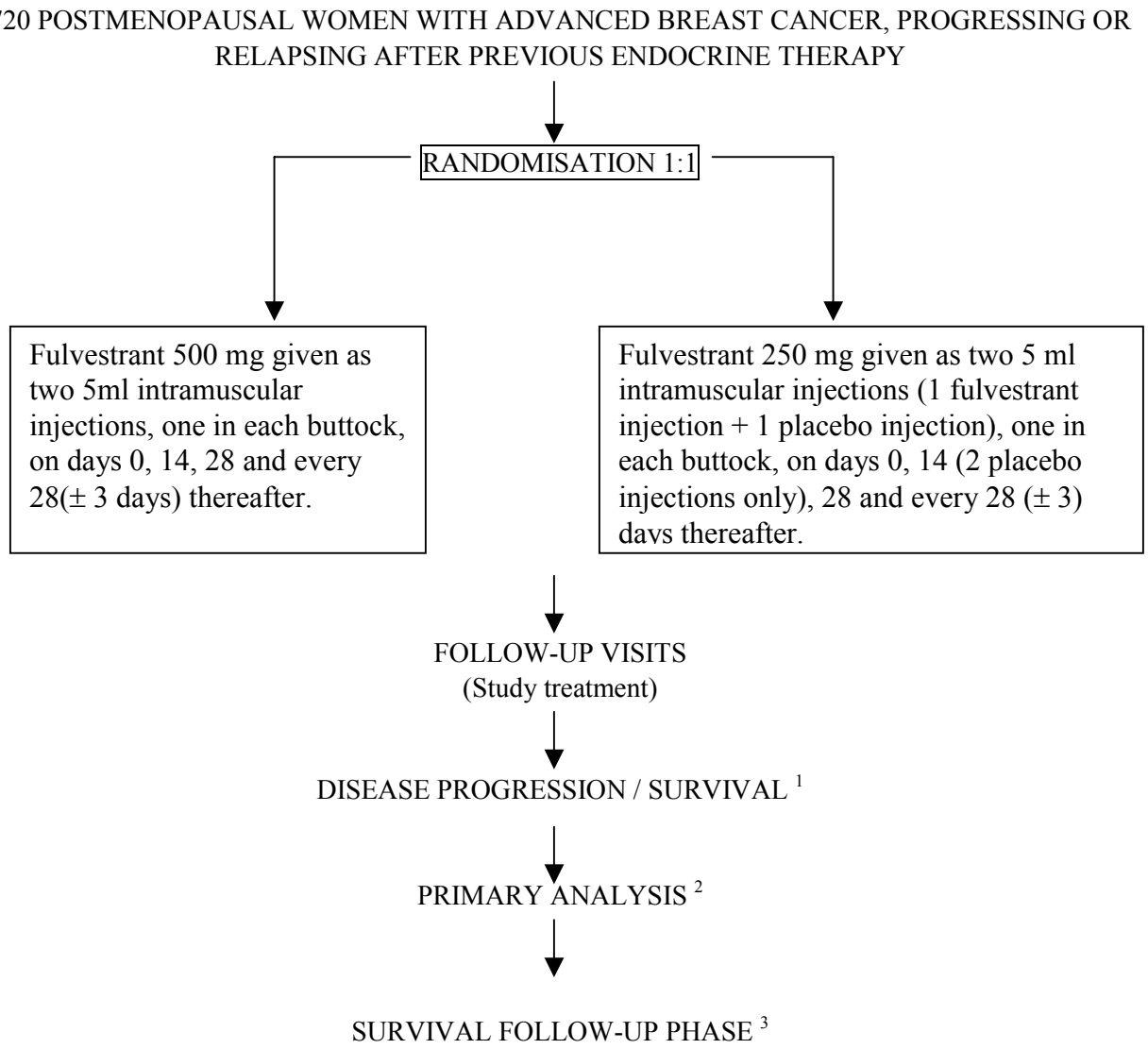
An additional survival analysis after approximately 75% of patients have died will be performed. After this analysis, data will no longer be collected on the clinical database, but patients will continue to be followed as per standard clinical practice, on open label supplies,

until any of the criteria for discontinuation are met. The study will be closed after the last patient discontinues study treatment

An optional part of this study will involve the collection of archival tumour samples (paraffin-embedded blocks) from either the primary tumour or a metastatic site for the purposes of translational research. The main aims of this research will be to explore the correlation between HER pathway activation and response to fulvestrant. Provision of the archival tumour samples will be optional for all patients and will require patient consent.

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

2. After the primary analysis has occurred, all patients will enter the survival follow-up phase of the study.

3. Patients in the follow-up phase still receiving randomised treatment will be unblinded and transferred to open-label supplies. Following IDMC advice, patients who are currently receiving fulvestrant 250 mg will be given the option to transfer

to fulvestrant 500 mg. A survival analysis at approximately 75% deaths will be performed, and following this, data will no longer be entered onto the clinical study database. The study will be closed after the last patient discontinues study treatment.

## Table 1 Study plan (Before primary Analysis)

| Study plan | Screening Phase | Treatment Phase | | | | | | | | | Treatment Discontinu -ation [j] | Survival Phase [j] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | Screening[a] | 1[b] | 2 (Day 14) | 3 | 4 | 5 | 6 | 7 | 8 | 9[c] onwards (every 12 weeks until progression) | | |
| Week(s) | -3 to 0 | 0 | 2 (Day 14) | 4 | 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,j] | |
| 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[p] | | X[p] | | 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[k] | | | | | X[l] | | | X[l] | X[l] | X[l] | |
| Tumour assessment[c] | X[g] | | | | | X | | | X | X | X | |
| Randomised Treatment | | X | X | X | X | X | X | X | X[i] | X[i] | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X[d] | |
| Survival contact | | | | | | | | | | | | X[h,j] |
| Informed consent for tissue biomarker research | X | | | | | | | | | | | |
| Optional tumour tissue samples for biomarker analysis (if available)[m] | | X | | | | | | | | | | |
| FACT-B Quality of Life Questionnaire[n] | | X | | X | X | X | X | X | X | | X[o] | |

[a] Within 3 weeks before randomisation.

[b] Visit 1/Day 0 should occur no more than 1 week after randomisation and no more than 4 weeks after tumour assessment.

[c] Assessment by RECIST Criteria every 12 ± 2 weeks from Visit 1 until progression. Tumours will be followed using same methodology at each assessment. For patients with an objective response of CR or PR, confirmations of response by repeat imaging must be performed at 4 weeks (or as soon as possible thereafter) following the date of response.

[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] Contact for survival after progression every 12 weeks until death or until the final survival analysis endpoint has been met, whichever occurs first.

[i] Treatment continues to be given every 28 (± 3) days

[j] First subsequent systemic breast cancer therapy received following discontinuation of randomised treatment and details of response to treatment will be collected.

[k] 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.

[l] 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.

[m] A tumour block (paraffin-embedded tumour tissue), if available, from either the primary tumour or a metastatic site will be sent to the central laboratory in those patients who give separate consent.

[n] Quality of life will be collected at baseline and at every 4 weeks for the first 24 weeks. QoL will be collected in selected countries/centres, for approximately 100 patients.

[o] A QoL questionnaire should also be completed at the treatment discontinuation visit if this occurs before 24 weeks.

[p] Height is only captured at Visit 1.

**Table 2 Study Plan (Survival Follow-up Phase)**

| Visit | Survival Follow-Up Phase |
|---|---|
| **Pts receiving randomised treatment** | Visits as per standard clinical practice |
| Serious Adverse Events [b] | X |
| Randomised treatment [c] | X |
| Survival status [a] | X |
| **Pts who have discontinued randomised treatment** | Visits as per standard clinical practice |
| Best response to 1st subsequent breast cancer therapy [d] | X |
| Survival status [a] | X |

a All patients will continue to have their survival status monitored every 12 ± 2 weeks until the final survival analysis when approximately 75% of patients have died.

b During the survival follow up phase, SAEs need only be reported for patients still receiving randomised treatment. SAEs for these patients should be collected for up to 8 weeks after the last injection of fulvestrant. SAEs to be sent directly to AZ Patient Safety.

c Fulvestrant study treatment may continue to be given/dispensed for as long as the patient receives clinical benefit. Following IDMC advice after the primary analysis, patient's treatment will be unblinded and patients who are currently receiving fulvestrant 250 mg will be given the option to transfer to fulvestrant 500 mg.

d Details of the best overall response (CR, PR, SD ≥ 24 weeks, PD as defined by the Investigator) to the first subsequent systemic breast cancer therapy will be collected

## 3.2 Rationale for study design, doses and control groups

In 2 large randomised trials with the primary efficacy endpoint of TTP, fulvestrant was shown to be similar in efficacy to the AI, ARIMIDEX™ (Robertson et al 2003). Median TTP was 5.5 months for fulvestrant and 4.1 months for anastrozole. Overall response rates showed a numerical advantage for fulvestrant (19.2%) over anastrozole (16.5%). CBR (complete response [CR] + partial response [PR] + stable disease (SD) ≥24 weeks) were 43.5% for fulvestrant and 40.9% for anastrozole. Median duration of response was 16.7 months for fulvestrant and 13.7 months for anastrozole. Overall survival was similar, 27.4 months for fulvestrant and 27.7 months for anastrozole. Both treatments were well tolerated. Since regulatory approval in the USA, fulvestrant has now been approved in the EU for the treatment of oestrogen receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-oestrogen therapy.

Because of AI efficacy and the well-tolerated safety profile, patients with advanced breast cancer increasingly receive 3rd 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 aromatase inhibitors.

The optimal use of other hormonal therapies in this resistant population has yet to be determined. Oestrogen sensitivity may not only be maintained but also enhanced following acquired resistance to long-term oestrogen deprivation (LTED) with AIs. The rationale for the treatment of advanced breast cancer progressing on an AI with fulvestrant, rather than tamoxifen, or exemestane is derived from preclinical data demonstrating that hormone sensitive MCF-7 breast cancer cells treated by LTED eventually adapt and become hypersensitive to very low levels of oestradiol (Chan CMW et al 2002;Masamura S et al 1995; Santen R et al 2001). An adaptive increase in ER expression and function (Jeng M-H et al 1998), and "cross-talk" between various growth factor receptor signalling pathways and ER occurs with ER becoming activated and super-sensitised by a number of different intracellular kinases, including mitogen-activated protein kinases and insulin-like growth factor (IGF)/AKT pathway (Campbell RA et al 2001; Shim WS et al 2000; Stephen RL et al 2001).

An ongoing trial has assessed the efficacy of fulvestrant as third-line treatment in AI failures progressing after both tamoxifen and AIs. In 32 patients who were followed for at least 6 months, and were evaluable for response there were 2 PR (6%) and 9 (28%) with SD ≥24 weeks with fulvestrant for an overall clinical benefit of 34% (Perey L et al 2002). These data suggest that fulvestrant may be a potential alternative treatment option for postmenopausal women with advanced breast cancer progressing on non-steroidal AIs.

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

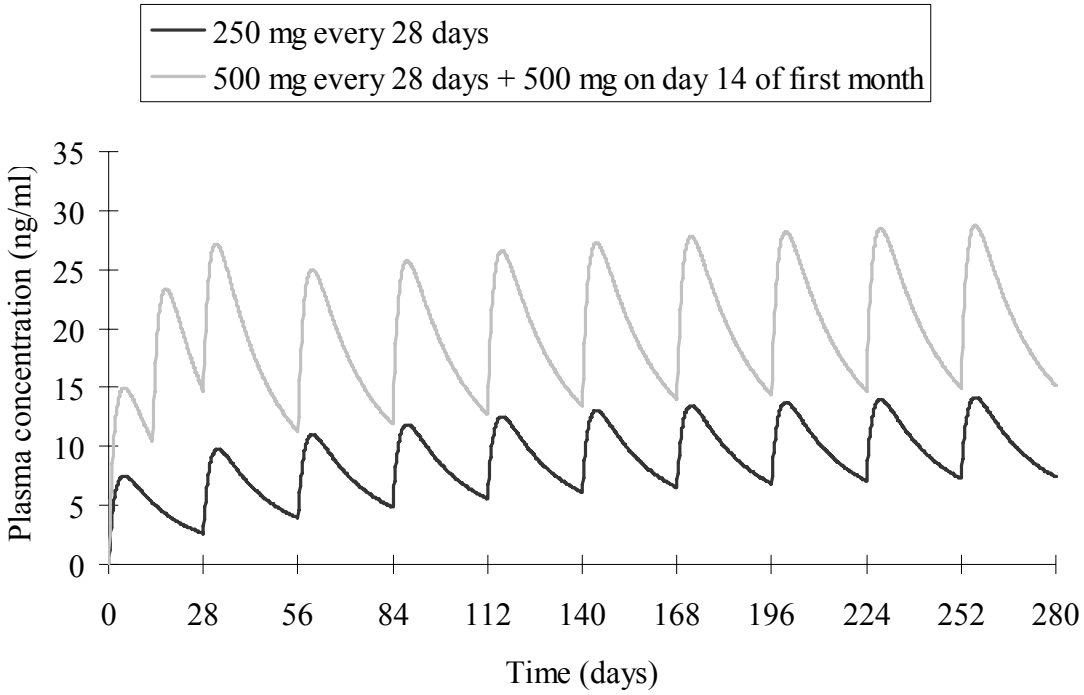
### 3.2.1 Rationale for the higher fulvestrant dose

At present, no dose-ranging trials to assess efficacy beyond the 250 mg every 28 days dosing schedule have been completed. The delivery of a higher dose of fulvestrant in a 5 ml volume is currently constrained by the limits of the formulation, and what is perceived as being a clinically acceptable schedule of administration. However, because of the favourable safety profile of fulvestrant, administration of a higher dose (volume) may be acceptable if it is paired with greater efficacy. The delivery of a higher dose, as predicted by pharmacologic modelling, may lead to the rapid achievement of steady state (and maintenance of $C_{trough}$) (see Figure 2), and higher plasma concentrations.

In this study, higher fulvestrant dose arm will be administered at a dose of 500 mg every 28 days + an additional 500 mg dose on day 14 of the first month only in an attempt to decrease the time to achieve steady-state levels and increase efficacy. Phase III pharmacokinetic (PK) sampling data has demonstrated that a 250 mg dose administered every 28 days requires 3 to 6 months (90 to 180 days) before approaching steady-state drug concentrations (Figure 2). Earlier achievement of steady-state plasma concentrations may be important to avoid early "progression-events".

The expected mean peak plasma concentration ($C_{max}$) for 500 mg fulvestrant is approximately 27 ng/mL, around day 18 after the second fulvestrant administration on day 14. Over the next 10 months, $C_{max}$ will be expected in the range of 26 – 28 ng/mL. The trough plasma concentrations at steady state are expected to be approximately 15 ng/mL compared to approximately 7 ng/mL for the 250 mg every 28 days injection.

**Figure 2** **Population-predicted profiles of fulvestrant 250 mg and the fulvestrant 500 mg treatment regimens**




The predicted exposure during the first month of dosing the 500 mg loading regimen is 1.5 fold higher than the steady state exposure (approximately 10800 ng.h/ml vs 7245 ng.h/ml) achieved with the standard every 28 day administration of the 250 mg intramuscular dose (See Table 3). In previous trials, some patients were treated on the standard 250 mg every 28 day schedule for more than 10 months achieving a high total exposure over the course of the study. This did not result in any worsening of the adverse event profile over time. In addition, fulvestrant has previously been given at a dose of 10 mg intravenously over 1 hour to volunteers (Study 9238IL/0026). The mean peak plasma concentration after intravenous (iv) administration was 140 $ng.ml^{-1}$, with 1 volunteer having a peak drug level of 260 $ng.ml^{-1}$ at the end of 1 hour. Plasma levels of fulvestrant were above 30 $ng.ml^{-1}$ for about 1.5 hours and volunteers were monitored for an additional 48 hours after the dose with no significant adverse reactions reported.

In addition, when contrasted with the pre-clinical toxicology information (Table 3) no issues are predicted.

This information, together with the estimated low inter-patients variability of 28%, suggest that the exposure predicted for the high dose regimen in terms of the anticipated $C_{max}$ and AUC is not expected to cause major safety concerns.

A more detailed rationale for the higher dose of fulvestrant can be found in Appendix E.

**Table 3 Ratio of animal/human exposure to fulvestrant on the basis of mean AUC(0-28) and Cmax values following multiple doses**

| Parameter | Rat (male) | Rat (female) | Dog | Human[a] | Human[b] (predicted) |
|---|---|---|---|---|---|
| Dose | 10 mg/rat/15 days | 10 mg/rat/15 days | 40 mg/kg/28 days | 250 mg/28 days | 500 mg /28 days + 500 mg on day 14 of first month only |
| AUC ng.h/ml | 46,656 | 92,688 | 36000 | 7245 | 10800 |
| AUC Ratio [c] | 4.3 | 8.6 | 3.3 | 0.7 | 1.0 |
| $C_{max}$ ng/ml | 105 | 372 | 88 | 14.6 | 28 |
| $C_{max}$ Ratio [c] | 3.8 | 13.3 | 3.1 | 0.5 | 1.0 |

[a] Studies 0021 and 0020 (steady-state parameter estimates).
[b] Based on proposed high dose regimen (500 mg) in this study (parameters over the 1st four weeks).
[c] Relative to predicted human exposure in the high dose regimen (500 mg)

### 3.2.2 Rationale for Comparator

In this study, fulvestrant 250 mg given every 28 days will be the comparator. This dose and schedule is well-tolerated and has demonstrated efficacy in women whose breast cancer has progressed following anti-oestrogen therapy (Howell et al 2002, Osborne CK et al 2002).

The results from two phase III trials showed that fulvestrant was at least as effective for both TTP and OR as anastrozole in the second-line treatment of advanced breast cancer. Both fulvestrant and anastrozole were well-tolerated. The only statistically significant difference was in the incidence of joint disorders (including arthralgia and arthritis) which was lower in the fulvestrant-treated patients (Robertson et al 2003). In these studies, overall survival was similar between the fulvestrant and anastrozole treatment arms (Pippen J et al 2003).

## 3.3 Selection of study population

### 3.3.1 Study selection record

Before entering the study, patients will be assessed to ensure that they meet the eligibility criteria listed below. Patients not meeting these criteria should not be entered into the study. Investigators must keep a record of patients who were considered for enrolment but were never randomised, eg patient screening log. This information is necessary to establish that the patient population was selected without bias. The patient screening log should be filed in the Investigator study file at each centre.

### 3.3.2 Inclusion criteria

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

1. Provision of written informed consent

2. Histological/cytological confirmation of breast cancer

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

4. 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.

5. Patients fulfilling one of the following criteria:

- Patients with measurable disease as per RECIST criteria. This is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.

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

6. Postmenopausal woman, defined as a woman fulfilling any 1 of the following criteria:

- Age ≥ 60 years.

- Age ≥ 45 years with amenorrhoea ≥ 12 months with an intact uterus.

- Having undergone a bilateral oophorectomy.

- FSH and oestradiol levels in postmenopausal range (utilising ranges from the local laboratory facility).

- In patients who have previously been treated with an LH-RH analogue, the last depot must have been administered more than 4 months prior to randomisation, menses must not have restarted, and FSH and oestradiol levels must also be in the postmenopausal range (utilising ranges from the local laboratory facility).

7. WHO performance status 0, 1 or 2.

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

1. Provision of informed consent for translational research component

   If a patient declines to participate in the translational 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.

### 3.3.3 Exclusion criteria

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

1. 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.

2. 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.

3. 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.

4. 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.

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

6. 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).

7. Any of the following laboratory values:

- Platelets < 100 × 109 / L
- Total bilirubin > 1.5 × ULRR
- ALT or AST > 2.5 × ULRR if no demonstrable liver metastases or > 5 × ULRR in presence of liver metastases

8. 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 3.7).

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

10. 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.

### 3.3.4 Restrictions

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 3.7.

### 3.3.5 Discontinuation of patients from treatment or assessment

#### 3.3.5.1 Criteria for Discontinuation

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

1. Voluntary discontinuation by the patient who are at any time free to discontinue their participation in the study, without prejudice to further treatment.

2. Safety reasons as judged by the investigator and/or AstraZeneca (Adverse Event).

3. Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.

4. Confirmed disease progression

5. Patient lost to follow-up

6. Any other reasons not listed above as per investigator discretion (the reason must be adequately documented)

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

1. withdrawal of consent to the translational research component of this study. A patient may withdraw from the translational 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, and be followed for survival 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, nor will they be followed for survival. Patient data will not be collected beyond the date of consent withdrawal.

#### 3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and about the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up for 8 weeks after the last injection (see Section 4.7.1.2).

The reason for withdrawal and the date of withdrawal from the study must be documented on the CRF provided. If the patient withdraws from the study every effort should be made to measure the tumour at the time of withdrawal. If a patient discontinues randomised treatment prior to disease progression, and does not withdraw consent, they should continue to be followed up for progression and survival.

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.

#### 3.3.5.3 Procedures for discontinuation from translational research aspects of the study

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

- Agrees to the tissue sample being kept for translational research analyses in the future.
- Withdraws consent for the sample to be kept for translational research analysis in the future 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 translational 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 tissue sample for translational 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.

## 3.4 Treatments

### 3.4.1 Identity of investigational product and comparators

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).

### 3.4.2 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 0, 14, 28 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 0, 14 (2 placebo injections only), 28 and every 28 (± 3) days thereafter.

After the database lock for the primary analysis, in line with the IDMC advice, patients will have their treatment unblinded and transferred to open label supplies. Patients who are currently receiving fulvestrant 250 mg will be given the option transfer to fulvestrant 500 mg.

After study treatment is unblinded, any patient not wishing to transfer to fulvestrant 500 mg, who remains on fulvestrant 250 mg, will receive only one 5 ml 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 0, 14, 28, 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 3.7. Any severe local site reaction should be treated with appropriate medical intervention.

### 3.4.3 Labelling

The pre-filled syringes will be labelled. Each syringe will go into a light excluding carton, and packed according to the random scheme. Each of these cartons will have a tear-off label and this label is to be removed at time of dispensing and affixed into the CRF. All labels will contain at least the following information, Study code, Randomisation number, Storage Conditions and any other market specific requirements. All labels will be blinded as per random scheme.

### 3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product pack label and investigator brochure.

### 3.4.5 Accountability

For US centres only, the investigator or the sub-investigators named on the Food and Drug Administration (FDA) Form-1572 will prescribe investigational materials. For centres in other countries, the investigator or his/her representative will prescribe investigational

materials. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol without prior AstraZeneca approval.

The investigator must maintain accurate records accounting for the receipt of the investigational materials (AstraZeneca (or company representing AstraZeneca) provides a copy of the Drug Shipment Request/Certificate of Delivery for this purpose) and for the disposition of the material. This record keeping consists of a dispensing record including the identification of the patient to whom the drug is dispensed, the quantity and the date of dispensing.

Upon authorization by AstraZeneca (or company representing AstraZeneca), used pre-filled syringes should be destroyed by high temperature incineration or by standard institutional procedure. Unused study drug will be destroyed by the same method after authorization by AstraZeneca (or company representing AstraZeneca). The investigator or his representative must sign off on all locally destroyed drugs using the Drug Destruction Form provided. If drug destruction on site is not feasible, AstraZeneca (or company representing AstraZeneca) will provide instructions on return of drug. It is essential that the investigator accounts for all drugs, but the task of maintaining accurate records may be delegated to a pharmacist.

## 3.5 Method of assigning patients to treatment groups

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).

This number is the patient’s unique identifier and is used to identify the patient on the CRFs. 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.**

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 patient discontinues from the study, the randomisation code (patient number) will not be reused, and the patient will not be allowed to re-enter the study.

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.

The actual treatment given to individual patients will be determined by a randomisation schedule. Patients will be allocated treatment in balanced blocks. The actual treatments will be prepared and packed by Investigational Product Section, AstraZeneca into individual patient packs (See Section 3.4.3). Complete blocks of study material will be dispensed to each centre.

## 3.6 Blinding and procedures for unblinding the study

### 3.6.1 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 3.4.3.

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.

### 3.6.2 Methods for un-blinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists at the study centre.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation. The investigator(s) must document and report to AstraZeneca (or company representing AstraZeneca) any breaking of the treatment code. 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.

After the database lock for the primary analysis, in line with the IDMC advice, patients will have their treatment unblinded and transferred to open label supplies. Patients who are currently receiving fulvestrant 250 mg will be given the option to transfer to fulvestrant 500 mg.

After study treatment is unblinded, any patient not wishing to transfer to fulvestrant 500 mg, who remains on fulvestrant 250 mg, will receive only one 5 ml intramuscular injection, as the placebo injection previously required to preserve the double blind nature of the study is no longer needed.

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## 3.7 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(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the case report form (CRF).

Details of the first subsequent systemic breast cancer therapy received following discontinuation of randomised treatment (regimen and start and end date), as well as the best response to this therapy (according to the investigator's best judgment as per the RECIST criteria), will be collected.

## 3.8 Treatment compliance

The investigator or pharmacy must retain records of the administered pre-filled syringes. The CRA will check these records to confirm the compliance with the protocol administration schedule.

# 4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

## 4.1 Primary variable

The primary variable for this study is time to progression (TTP), which is defined as the time from randomization to the time of the earliest objective disease progression, including death from any cause. Further detail is given in Section 4.6.1. TTP is used as the basis for the sample size calculation (see Section 6.5).

## 4.2 Screening and demographic measurements

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 3.3.2 and 3.3.3). 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 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 10 target lesions (no more than 5 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 unless there is definite progression at such lesions immediately before entry, or if more than 12 weeks has elapsed between treatment and entry.

  – 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+ve 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 0/Visit 1 is the day on which the patient first receives her randomised study treatment (ie, 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.**

## 4.3 Patient-Reported Outcomes (PROs)

The methods for collecting Patient Reported Outcomes (PRO) data are presented below.

QoL will be assessed for a sub-group of patients. This sub-group will initially include all patients in a number of selected countries. The QoL analysis will require a minimum of 100 patients and selection of participating countries will be based on availability of the translated questionnaires and suitability of investigators.

QoL will be assessed in both treatment groups using the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire (Appendix G).

The patient should complete a questionnaire at the scheduled clinic visit at baseline, and at each 4-weekly visit for 24 weeks or until progression, whichever occurs earlier. The patient should also complete a questionnaire at their treatment discontinuation visit if this occurs prior to 24 weeks. If any scheduled QoL assessment is not completed the reason for non-completion should be recorded.

Each centre participating with QoL assessments should allocate responsibility for QoL assessment to a specific individual (e.g., a research nurse). The AstraZeneca designee will provide training for the relevant personnel in the administration of QoL questionnaires to help avoid the key problem of missing data. Before patients are randomised, they must be informed of the rationale for the study and the study details, including the QoL questionnaire. The patients should be instructed on how to complete the questionnaire and if necessary assisted with completion of a training questionnaire that must be destroyed after completion.

It is important that the value and relevance of QoL data is explained carefully to participating patients so that they are motivated to comply with data collection. There is research evidence that patients with breast cancer value the opportunity to provide information on their QoL . The research nurse or appointed individual should also stress that the information is confidential. Therefore, if the patient has any medical problems she should discuss them with the doctor or research nurse separately from their QoL assessment.

The instructions for completion of questionnaires are:

- It must be completed before any investigations or discussions about the status of the patient's disease with the clinic staff.
- The patient must complete it herself without any intervention from family, friends, centre staff etc.
- The only exception to this is if the patient is blind or illiterate. In this case the questionnaire may be read to the patient verbatim, however the reader must not aid in the interpretation of questions or in the selection of answers.
- Only one answer to every question should be checked.

- Centre personnel should not review the responses to the questionnaire with the patient nor with any other centre staff.

- Following completion, the nurse or appointed individual may quickly scan the questionnaire for completeness and should confirm verbally with the patient that the questionnaire has been completed fully.

### 4.3.1 Methods of assessment

FACT-B consists of the FACT-G (general) QoL tool for cancer patients plus the Breast Cancer Subscale (BCS). FACT-G was developed by Pietras RJ (Cella DF et al 1993) using a standardized approach to derivation and reduction. It is a self-report instrument that measures multi-dimensional QoL. It consists of four domains: physical well-being, social well-being, emotional well-being, and functional well-being. The BCS was developed specifically for patients with breast cancer and is used in addition to FACT-G to measure overall QoL in these patients. FACT-B was chosen for use in this study because it has good psychometric properties, has been shown to be valid and responsive to change and known group differences (Brady MJ et al 1997), and is relatively simple and quick (up to 10 minutes) for patients to complete. FACT-B is in use in a number of large breast cancer treatment studies within the US and Europe.

### 4.3.2 Derivation or calculation of outcome variables

The main outcome measure from the FACT-B will be the Trial Outcome Index (TOI), which is a summary score of the following subscales:

- Physical well-being (PWB)

- Functional well-being (FWB)

- Breast cancer subscale (BCS)

The TOI is recommended as an efficient and precise summary measure of the physical and functional well-being of patients in clinical trials (Brady MJ et al 1997).

The following measures will also be derived from the FACT-B;

- The total FACT-B score comprising the sum of the scores from all the sub-scales; PWB, FWB, SWB, EWB, BCS.

- The total FACT-G score which comprises the sum of the scores from the PWB, FWB, SWB and EWB subscales

## 4.4 Health Economic measurements and variables (Not Applicable)

## 4.5 Pharmacokinetic measurement and variables (Not Applicable)

## 4.6 Efficacy and Pharmacodynamic measurement and variables

Following initial randomised trial treatment on day 0, subsequent visits and assessments, including day 14, 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 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 without evidence of progression

For patients with measurable disease the RECIST criteria will be used to determine TTP, the objective tumour assessments (CR and PR), as well as the best overall objective tumour response; details are given in Appendix C. The revised (May 1999) WHO definitions (RECIST) 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 4.6.1.1.

Up to 10 target lesions (no more than 5 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, Appendix C).**

Objective tumour response will be determined using a computer program, and these responses will be used in the summaries of TTP, ORR, CBR, DoR and DoCB. Bone only disease patients will only be included in the TTP summaries.

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 TTP is the primary variable and biases in analysis can occur if 1 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. After progression, patients should be followed up for survival every 12 weeks as outlined in the study plan, unless the patient withdraws consent. Adherence to the study plan should be observed whenever possible.

### 4.6.1 Time To Progression

#### 4.6.1.1 Methods of assessment

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

According to RECIST, 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 the longest diameter (LD) of target lesions taking as references the smallest sum of LD recorded.

In the absence of measurable disease at baseline (as per RECIST criteria), the following will be considered progression among patients with lytic or mixed (lytic + sclerotic) 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

For patients with both measurable disease (as per RECIST criteria), and documented lytic or mixed bone lesions at baseline, the definition of progression will be based on the RECIST 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.

#### 4.6.1.2 Derivation or calculation of outcome variable

TTP is defined as the time from randomisation to the time of the earliest objective disease progression (defined in Section 4.6.1.1), 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 TTP see Section 6.4.1

### 4.6.2 Objective Response Rate (ORR)

#### 4.6.2.1 Method of Assessment

Only patients with measurable disease at baseline, as per RECIST, will be assessed for objective response. The RECIST 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 Criteria for details, Appendix C).

Categorization of the objective tumour response assessments will be based on the RECIST 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.

**For patients with an objective response of CR or PR, confirmations of response by repeat imaging must be performed at 4 weeks (or as soon as possible thereafter) following the date of response.**

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.

#### 4.6.2.2 Derivation or calculation of outcome variable

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.

A best response of CR means that a response of CR is recorded at one visit and confirmed by repeat imaging at not less than 4 weeks later.

A best response of PR means that a response of PR is recorded at one visit and confirmed by repeat imaging at not less than 4 weeks later.

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.

### 4.6.3 Overall Survival (OS)

#### 4.6.3.1 Methods of assessment

After withdrawal from the study treatment, patients should be followed up for survival every 12 weeks, as outlined in the study plan, unless the patient withdraws consent.

#### 4.6.3.2 Derivation or calculation of outcome variable

The overall survival (or time to death) is defined as the number of days from randomisation to death from any cause. Patients who are alive by the date of the data cut-off or who have been lost to follow-up will be right-censored in the analysis at their last contact date, that is, the date when the patient was last known to be alive.

### 4.6.4 Clinical Benefit Rate (CBR)

#### 4.6.4.1 Methods of assessment

The RECIST 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 Criteria for details, Appendix C).

#### 4.6.4.2 Derivation or calculation of outcome variable

CBR is defined as the proportion of all treated patients with measurable disease at baseline who have a best objective tumour response of CR, PR or SD ≥ 24weeks.

### 4.6.5 Duration of Clinical Benefit (DoCB)

#### 4.6.5.1 Method of assessment

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

#### 4.6.5.2 Derivation or calculation of outcome variable

Duration of clinical benefit will be defined as from date of randomisation until the date of disease progression or death 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

### 4.6.6 Duration of Response (DoR)

#### 4.6.6.1 Methods of assessment

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

#### 4.6.6.2 Derivation or calculation of outcome variables

Duration of response will be defined in two ways:

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

2. From date of randomization until the date of disease progression or death 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.

### 4.6.7 Translational research analyses

In patients with available tumour samples from either the primary tumour or a metastatic site (in the latter case the sample will have been obtained before treatment with the study drug), a molecular marker research will be carried out provided that the patient has given her written informed consent. The main aim of this sub-study will be the identification of a patient cohort which might derive the largest benefit from the use of the 500 mg dose of fulvestrant. In this context the evaluation of a panel of molecular markers involved in the HER pathway seems to be of interest because of the cross-talks existing between the ER and the HER pathway.

HER family receptors ( EGF-R, HER-2, HER-3, HER-4), phosphorylated receptors, and downstream effectors such as pMAP Kinase and pAKT will be evaluated. In addition ER, PgR and Ki-67 will also be tested. The tumour samples will not be used for genetic testing.

Since this is a complex area of investigation, which is rapidly evolving and as yet not completely understood, data obtained in this study will not be definitive but potentially can be used in hypothesis generation.

Any data obtained from analysis of tumour tissue will be used for research only, and patient confidentiality will be preserved internally and in any presentations or publications. The samples will be available to scientists either within AstraZeneca or at laboratories/research

institutes contracted to AstraZeneca and/or the translational research coordinating centre and patient confidentiality will be preserved. Each patient will have a unique identifier called the patient E-code. A master list is retained at each centre linking initials to patient E-code.

It is not proposed that the analysis of results from a specific patient are made available routinely to either the subject of the treating physician, however, group results from this study will be published. The patient will be informed of this in the patient information sheet.

Samples will be retained for 10 years and data for 15 years in line with AstraZeneca's current policy.

#### 4.6.7.1 Derivation or calculation of outcome variables

The tumour tissue study will be retrospective and hypothesis-generating. Accordingly no calculation of the sample size is feasible. The main study aim will be the evaluation of the interaction between the tumour biological phenotype (ie. HER pathway activated or inactivated) and fulvestrant clinical activity. The latter will be evaluated separately in the two treatment cohorts receiving either 250 or 500 mg of the study drug.

## 4.7 Safety measurements and variables

The methods for collecting safety data are described below.

### 4.7.1 Adverse events

#### 4.7.1.1 Definitions

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

**Adverse event**

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. **Any events that are unequivocally because of progression of disease must not be reported as an AE. Adverse events of bone pain (ie not related to disease progression) should be reported as an adverse event.**

**Serious adverse event**

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol. **Any serious events that are unequivocally because of progression of disease must not be reported as an SAE.**

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

**Other Significant Adverse Events (OAE)**

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

#### 4.7.1.2 Recording of adverse events

Any detrimental change in a patient's condition subsequent to their entering the study should be considered an AE.

**(i) Method of detecting AE/SAEs**

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

(a) information volunteered by the patient or carer

(b) 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?*

(c) observation by the investigational team, other care providers or relatives

**(ii) Time period for collection of AEs/SAEs**

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to 8 weeks after the last injection of study medication. During the survival follow up phase only SAEs for patients still on study treatment (and up to 8 weeks after the last injection of study medication), will be recorded and reported to Quintiles who will inform the appropriate AstraZeneca Patient Safety Department. These should be reported within the timelines stated in Section 4.7.1.3 in the Clinical Study Protocol.

**(iii) Collection of AE data**

All AEs will be recorded on the CRFs provided. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment, other treatment given, and follow-up tests) and outcome, should be provided along with the investigator's assessment of causality (the relationship to the study treatment). AEs will also be graded according to the NCI CTC version 3.

**(iv) Causality**

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study medicinal product and the AE (see Appendix B for guidelines on interpretation of causality).

**(v) Intensity**

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For instance nausea that persists for several hours may be considered severe nausea, but not an 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 an SAE. The following definitions will be used in this study:

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

The degree of severity will also be recorded by means of the National Cancer Institute, Common Toxicity Criteria (CTC) criteria (version 3) for all events with an assigned CTC grade.

**(vi) Disease progression**

Where there is deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or constitutes an AE. In such cases, unless the AstraZeneca or reporting physician considers that the study treatment contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered to be disease progression and not an AE. Expected progression and signs and symptoms of the disease/disorder being studied, unless more severe in intensity or more frequent than expected for the patient's condition, should not be reported as an AE or SAE, but documented elsewhere in the CRF.

Any events that are unequivocally due to progression of disease must **not** be reported as an AE.

**(vii) 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 for seriousness (see Section 4.7.1.1).

**(viii) Deaths**

All deaths that occur during the study, or within the protocol defined follow-up period after the last injection of study treatment, 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.

**(ix) 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.

**(x) Abnormal laboratory values/vital signs**

The reporting of laboratory /vital signs abnormalities as both laboratory findings and adverse events should be avoided. They should not be reported unless any criterion for a SAE is fulfilled, the laboratory /vital signs abnormalities causes the patient to discontinue from the study, or the investigator insists the abnormality should be reported as an AE. If an abnormal laboratory value /vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

**(xi) Pregnancy**

Only postmenopausal women are eligible to participate in this study (see Section 9.4.). However, if for any reason a pregnancy occurs it should be reported to AstraZeneca immediately using specific pregnancy reporting forms.

**(xii) Overdose**

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

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3. All symptoms associated with the overdose should be reported as AEs.

AEs that occur in association with an overdose should be reported in the same manner as other AEs, following the procedures described in the protocol.

Please refer to Section 9.3.

**(xiii) 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.

**(xiv) Handling unresolved AE/SAEs at completion/withdrawal**

Any SAEs that are ongoing when the patient completes the study, or at patient discontinuation from the study, must be followed until resolution or until the patient is lost to follow up, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

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

**(xv) Interactions**

Current experience with fulvestrant has not shown potential for 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'.

**(xvi) Review of safety data by the Independent Data Monitoring Committee (IDMC)**

The procedures for the review of safety data by the IDMC are described in Appendix D.

#### 4.7.1.3 Reporting of serious adverse events

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

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

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

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

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 case report form. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The adverse event dictionary used at the beginning of this study will be MedDRA v 5.1. Any new versions released will be implemented as appropriate.

### 4.7.2 Laboratory safety measurements and variables

#### 4.7.2.1 Methods of assessment

During the conduct of this study, a central laboratory (Quintiles Laboratories) will be utilised for the analysis of haematology and biochemistry values in order to assure standardisation of assessments and meaningful comparisons between the two treatment arms. However, the local laboratory in each centre may be used to perform any laboratory assessments required by the investigator as part of the routine medical management of the patient.

For the purpose of assessing eligibility, patients may be screened within 3 weeks prior to randomisation by a local laboratory. However, all patients must have a baseline haematology and biochemistry evaluation performed by the central laboratory within 7 days prior to treatment. For participating centres, the central laboratory will be performing all laboratory safety measurements for this study. For centres in countries where use of the main study central laboratory is not possible, a local Central Laboratory may be used if available, if not, a centre-specific local laboratory may be used.

The central laboratory may be used to determine eligibility if performed in time to allow review of the results within 7 days before randomisation and treatment. Results from the local laboratory may be used to determine eligibility should the investigator wish to treat the patient prior to the receipt of the results form the central laboratory. Further samples will be assessed at the timepoints detailed in the study plan (see Table 1).

The central laboratory will supply all venepuncture equipment, sample containers and labels. Procedures for sampling, handling and shipping of these samples will be provided in the Laboratory Handbook for Investigators to be provided to each site.

The following laboratory parameters will be investigated. See Section 4.8 for the total volume of blood samples to be collected.

**Table 4 Biochemistry (serum gel tube)**

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

**Table 5 Haematology (ethylene diamine tetra-acetic acid [EDTA] coated tube)**

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



#### 4.7.2.2 Derivation or calculation of outcome variables

Section 4.7.1.2 (x) provides details of how AEs based on laboratory tests will be recorded and reported.

### 4.7.3 Vital signs, ECG and physical examination

#### 4.7.3.1 Methods of assessment

Vital signs (heart rate and blood pressure) and physical exam are performed at each dosing visit with the exception of visit 2.

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.

Physical examinations will be performed and 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.

#### 4.7.3.2 Derivation or calculation of outcome variables

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 4.7.1.2 for recording of AEs). Conditions that are considered by the investigator to be unequivocally disease-related will not be recorded as AEs.

## 4.8 Volume of blood sampling and handling of biological samples

The total volume of blood drawn from each patient will depend on the length of time the patient receives study medication. Table 6 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.

**Table 6 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (ml) | No. of samples | Total volume (ml) |
|---|---|---|---|---|
| Safety | Biochemistry | 3.5 | 5 | 17.5 |
| | Haematology | 2 | 5 | 10 |
| **Total** | | | | **27.5** |

During the survival follow up phase, no further central laboratory blood samples will be taken for this protocol.

### 4.8.1 Analysis of biological samples

#### 4.8.1.1 Biochemistry samples

The analyte stability limits defined by Quintiles Laboratories will be applied to all analyses performed on behalf of AstraZeneca. Quintiles Laboratories will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by Quintiles Laboratories may be amended in accordance with its Standard Operating Procedures. Quintiles Laboratories will inform AstraZeneca (or company representing AstraZeneca) of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

If Quintiles Laboratories chooses to sub-contract the analytical work to another laboratory, Quintiles Laboratories must assure itself and provide assurance to AstraZeneca (or company representing AstraZeneca) that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported. The other laboratory will inform AstraZeneca (or company representing AstraZeneca) of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

## 4.9 Genetic measurements and co-variables

For those centres considering the collection of blood samples for genetic analysis: Patients will be invited to contribute a single 9 ml blood sample for extraction of DNA for potential genetic analysis. Patients' participation in this genetic component is voluntary and any patient's decision not to participate will not exclude them from the main clinical study.

Further details regarding blood sample collection, storage, extraction of DNA and analysis are available in Appendix F.

## 4.10 Collection of tissue samples

A tumour block (paraffin-embedded tumour tissue) from either the primary tumour or a metastatic site (in the latter case the sample will have been obtained before that the study drug has been started) will be sent to the coordinating centre for each patient participating in the tumour tissue study, provided that the patient has given her written informed consent.

All tumour samples from a given participating centre will be submitted to the coordinating centre after which the translational research study accrual will be closed.

Available samples will have to be sent by courier to the following address :

Faslodex translational research study c/o

Upon receipt of the tumour block, appropriate data will be recorded in the translational research study data-base and, immediately after, the sample will be processed in order to extract a core biopsy that will be incorporated in a tissue micro-array (TMA). After the completion of this operation the tumour block will be immediately returned to the participating centre.

It is foreseen that the time elapsing from the date of the tumour block receipt at the coordinating centre and the date the tumour block will be mailed back to the participating centre will be four weeks.

TMA sections will be sent from the coordinating centre to a central laboratory with large experience in the evaluation of those biological markers that will be investigated in the translational research study. If the patient will withdraw her consent to the translational research study, the corresponding sample will be removed from consideration for any future study use (see Section 3.3.5.3).

Biological data will be entered in the translational research study database. The latter will be located at the coordinating centre in (see address above) where data management and statistical analysis will also be performed.

For any additional information regarding this study please contact at the address indicated above or at the following e-mail address :



# 5. DATA MANAGEMENT

Case Report Forms will be provided for the recording of data. The forms will be 4 level NCR (no carbon required) paper. Data is to be recorded legibly onto the case report forms in black or blue ballpoint ink. Corrections should be made legibly and initialled and dated by approved personnel; the reasons for significant changes must be provided. Correction fluid or covering labels must not be used. The top original, 1st and 2nd copy of each completed form will be collected. The top original and the 1st copy will be sent to data management personnel at the CRO, the 2nd copy will be retained by the monitor. The 3rd copy will be retained at the investigator site.

Any electronic data will be electronically loaded into the database by the CRO and checked for validity.

The method of distribution of data queries will be documented in the study Data Management Plan. The original signed data query will be returned to the CRO. The monitor will retain one copy and the other retained at the investigator site. On receipt of the data query by data management at the CRO the database will be edited appropriately.

## 5.1 Reporting of Translational Research Results

Results from any translational research performed will be reported separately from the clinical trial report. AstraZeneca and the translational research coordinating centre will not provide individual results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient's tissue will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before un-blinding of the data, or in instances where the data are not blinded, database lock.

## 6.2 Description of outcome variables in relation to objectives and hypotheses

The primary objective of the study is to compare the efficacy of 500 mg fulvestrant with 250 mg fulvestrant. This will be assessed by the primary variable of time to progression, which is defined in Section 4.6.1.

A secondary objective of the study is to compare objective response rate, overall survival, clinical benefit rate, duration of clinical benefit and duration of response of 500 mg fulvestrant with 250 mg fulvestrant. The secondary variables ORR, OS, CBR, DoCB and DoR are defined in Section 4.6 and TOI in Section 4.3.

A further secondary objective of the study is to assess tolerability of fulvestrant 500 mg compared with fulvestrant 250 mg. Tolerability will be assessed by adverse events, which are defined in Section 4.7.1.1.

## 6.3 Description of analysis sets

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 intention-to-treat (ITT) basis. This approach will be used when assessing time to progression, objective response rates, overall survival, clinical benefit rates, duration of clinical benefit and duration of response. Analyses on QoL data will be carried out using the ITT population as primary and will also be performed by study treatment actually received as supportive.

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

A subgroup analysis based on ITT will be performed for patients who are both ER+ and PgR+ for the variables of TTP, ORR, OS and CBR.

When assessing tolerability of 500 mg fulvestrant against 250 mg fulvestrant summaries will be produced based on study treatment actually received.

## 6.4 Method of statistical analysis

The hypothesis being tested in this study is:

$H_0$: 500 mg fulvestrant is no different than 250 mg fulvestrant

$H_1$: 500 mg fulvestrant is different from 250 mg fulvestrant

The hypothesis testing for treatment differences will be performed for TTP, ORR, OS and CBR. The superiority of 500 mg fulvestrant will be declared if the two-sided p-value for the treatment comparison is ≤ 0.05

No formal analysis will be performed on DoR or DoCB.

The primary analysis on the primary variable of TTP will be performed using a log-rank test (equivalent to the Cox's proportional hazards regression model with treatment factor only) in ITT population.

In addition to the log rank test for TTP (unadjusted model with treatment factor only) a Cox's regression model will also be performed with factors fitted for treatment and other baseline covariates (adjusted model).

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

A secondary Per Protocol analysis of TTP will be performed using a log-rank test in order to assess the reliability of the conclusions from the primary ITT analysis.

For objective response rate and clinical benefit rate, a logistic regression model will be fitted with treatment factor only. For overall survival the log rank test will be performed (as described above for TTP). Duration of response and duration of clinical benefit will be summarised using the Kaplan-Meier method.

### 6.4.1 Time to Progression

For the primary analysis of TTP, 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 log-rank test (equivalent to the Cox's proportional hazards regression model with treatment factor only) 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.

### 6.4.2 Objective Response Rate and Clinical Benefit Rate

Assessments of tumour response will be based on the RECIST 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 – 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 or progression will be summarised.

### 6.4.3 Overall Survival

The formal treatment comparison for OS will be performed using a log rank test only after the proportion of reported deaths exceeds 50% of the total number of patients to be randomised across the 2 treatment groups (i.e., at least 360 deaths). Prior to that, survival will be summarised only and will not be subjected to inferential statistical analysis.

A further OS analysis will be performed when approximately 75% of randomised patients have died. The primary OS analysis will be a log rank test to estimate the hazard ratio of 500 mg fulvestrant to 250 mg fulvestrant together with the corresponding 95% CI and p-value. A secondary analysis will be the Cox proportional hazards regression model with treatment factor and the baseline covariates specified in Section 6.4.1.

OS will be summarised using the Kaplan-Meier method. Kaplan-Meier plots and Kaplan-Meier estimates of median time to death and percentage of patients alive at six-monthly intervals will be presented for each treatment group.

Further details will be provided in the Statistical Analysis Plan for the follow-up OS analysis

### 6.4.4 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.

### 6.4.5 Quality of life

The FACT-B quality of life instrument is to be used for this trial and the number of patients required for the analysis is based on the trial outcome index (TOI) within the FACT-B. This measure is the sum of the functional well being, physical well being and breast cancer subscale dimensions of the questionnaire.

Analyses on QoL data will be carried out using the ITT population as primary and will also be performed by study treatment actually received (i.e. patients who received at least one dose of the medication to which they were randomised) as supportive.

All FACT-B items will be scored such that a higher score represents a better QoL.

The TOI, total FACT-B and the FACT-G will be analysed longitudinally using a model with baseline covariates (as detailed in Section 6.4.1) to examine the difference in the TOI between the fulvestrant 500mg and fulvestrant 250mg groups.

The above QoL endpoints for each treatment group at each time point will be summarised using descriptive statistics and will also be presented graphically.

Also, an analysis of the time to deterioration in QOL will be carried out in the same way as the analysis of time to progression. QOL information will be collected at 4, 8, 12, 16, 20 and 24 weeks and this discrete data collection will be accounted for in the analysis by replacing the proportional hazard model with the discrete logistic model (by using the TIES = DISCRETE option in the MODEL statement of PHREG in SAS). For an individual patient a deterioration in QOL is defined as a decrease in TOI from baseline of 5 points or more. If a subject has not shown a reduction of 5 points or more at the time of analysis then the observation will be right censored using the last QOL assessment date. Covariates will be included as above.

Missing data handling for the TOI and FACT-B scales:

The reason for missing data will be identified. If data is missing at random, the technique outlined below will be used. If there is any evidence that the missing data is systematic, missing values will be handled to ensure that any possible bias is minimised. If there are

missing items, subscale scores will be prorated. The sum of the subscale is multiplied by the number of items in the subscale. This is then divided by the number of items actually answered. This is an accepted way of scoring the subscales provided that more than 50% of the questions are answered. If 50% or more of the questions are not answered, the subscale will be considered as missing. If any of the scores on the scales (PWB, FWB, BCS) comprising the TOI is missing, then the TOI score will be considered missing.

### 6.4.6 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.

### 6.4.7 Exploratory analysis

A subgroup analysis based on ITT will be performed for patients who are both ER+ and PgR+ for the variables of TTP, ORR, OS and CBR. The same analysis as detailed in Section 6.4 will be performed on this subgroup with only treatment factor fitted to the models. No adjustment for covariates will be made.

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

## 6.5 Determination of sample size

The sample size calculation is based on the primary variable, TTP, and assumes exponential survival times. The sample size is driven by the number of required events. In order to detect a hazard ratio of ≤0.8 (or ≥1.25) for 500 mg fulvestrant compared to 250 mg fulvestrant, at a 2-sided significance level of 5%, with 80% power, approximately 632 events are required to have occurred in the study (i.e., 632 patients to have progressed or died)

The median time to progression for 250 mg fulvestrant in this patient population is estimated to be 5.5 months (Robertson et al 2003). A hazard ratio of 0.8 would equate to a prolongation in median TTP for 500 mg fulvestrant over 250 mg fulvestrant of 1.38 months (i.e., a median TTP of 6.88 months for 500 mg fulvestrant compared to median TTP of 5.5 months for 250 mg fulvestrant).

If 720 patients are recruited over a period of 36 months, it is anticipated that the required 632 events would be observed approximately 6 months following the end of recruitment.

The initial survival analysis will be performed after the proportion of reported deaths exceeds 50% of the total number of patients required. If 50% of deaths occur before the 632 progression events then the survival analysis will not be carried out until the 632 progression events are observed and the data is unblinded for the TTP analysis. A further overall survival analysis will be performed when approximately 75% of randomised patients have died.

## 6.6 Interim analyses

No interim analysis will be performed for this trial.

## 6.7 Independent Data Monitoring Committee (IDMC)

The composition and terms of reference of the IDMC are presented in Appendix D.

# 7. STUDY MANAGEMENT

## 7.1 Monitoring

Before first patient into the study, a representative of AstraZeneca (or company representing AstraZeneca) will visit the investigational study site to:

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca (or company representing 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
- to discuss the specific requirements of the translational research part of the study with the investigator(s) (and other personnel involved with the study)

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

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms (CRFs), and that investigational product 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). This will require direct access to all original records for each patient (eg, clinic charts).

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

## 7.2 Audits and inspections

Authorised representatives of AstraZeneca (or company representing AstraZeneca), a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca (or company representing AstraZeneca) audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

## 7.3 Training of staff

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

## 7.4 Changes to the protocol

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

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

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

AstraZeneca (or company representing AstraZeneca) will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her IRB or IEC, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

## 7.5 Study agreements

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

## 7.6 Study timetable and termination

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

- signed Clinical Study Protocol and other agreements between AstraZeneca (or company representing AstraZeneca) and the Principal Investigator/Study Site.
- approval of the study by the IRB/IEC
- approval of the study, if applicable, by the regulatory authority.

The first patient was recruited in February 2005, and recruitment was completed in August 2007. Study Investigators, were notified by AstraZeneca (or company representing AstraZeneca) when the study recruitment was completed.

Following the primary Analysis for TTP (and 50% survival analysis which was performed at the same time), all patients, regardless of whether they are still receiving randomised treatment, will enter the survival follow-up phase and be followed as per standard clinical practice.

Patients remaining on randomised treatment will have their treatment unblinded and transferred to open label supplies. An additional survival analysis after approximately 75% of patients have died will be performed. After this analysis, data will no longer be collected on the clinical database but patients will continue to be followed as per standard clinical practice on open label supplies until any of the criteria for discontinuation are met. The study will be closed after the last patient discontinues study treatment.

# 8. ETHICS

## 8.1 Ethics review

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

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve

all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC annually, as local regulations require.

This study will be conducted under an FDA IND at centres in the US only, and at each centre in the US, the Principal Investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

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

## 8.2 Ethical conduct of the study

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

## 8.3 Written informed consent

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

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

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

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca (or company representing AstraZeneca).

## 8.4 Patient data protection

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

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca/designee will be identified by *randomisation code / study code / initials*.

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

# 9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

## 9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact the Clinical Study Team Leader. If the Clinical Study Team Leader is not available, contact the Clinical Study Team Physician or the Clinical Study Team Drug Safety Physician at the AstraZeneca Research and Development site shown below.

| Role in the study | Name | Address & telephone number |
|---|---|---|
| CST Leader responsible for the protocol at central R&D site | | AstraZeneca |
| CST Physician responsible for the protocol at central R&D site | | AstraZeneca |
| CST Global Patient Safety Physician responsible for the protocol at central R&D site | | AstraZeneca |

## 9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

## 9.3 Procedures in case of overdose

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRF as an AE of 'Overdose' unless there are associated symptoms or signs

- An Overdose with associated SAEs should be recorded as the SAE diagnose/symptoms on the relevant AE forms in the CRF.

- An Overdose with associated non-serious AEs should be recorded as the AE diagnose/symptoms on the relevant AE forms in the CRF. In addition, the Overdose should be reported on the separate AZ 'Clinical Study Overdose Report Form.'

- An Overdose without associated symptoms should not be recorded as an AE in the CRF. The Overdose should be reported on the separate AZ 'Clinical Study Overdose Report Form.'

No specific antidote is available in the event of overdose. Should overdose occur, routine supportive measures should be taken.

## 9.4 Procedures in case of 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.

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# Appendix A
# Signatures

## ASTRAZENECA SIGNATURE(S)

# A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

This Clinical Study Protocol Amendment has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

_____ _____

Date
(Day Month Year)

## ASTRAZENECA SIGNATURE(S)

# A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

This Clinical Study Protocol Amendment has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

_____ _____

Date
(Day Month Year)

## ASTRAZENECA SIGNATURE(S)

# A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

This Clinical Study Protocol Amendment has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative** _____ _____

Date
(Day Month Year)

# SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

## A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy

This Clinical Study Protocol Amendment has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

**Signature:**

Date
(Day Month Year)

AstraZeneca

| Clinical Study Protocol: Appendix B | |
|---|---|
| Drug substance: | ZD9238 (Fulvestrant) |
| Study Code: | D6997C00002 (9238IL/0064) |
| Appendix Edition No: | 1 |
| Appendix Date: | |

# Appendix B
# Additional Safety Information

# 1. 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**

Out-patient 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.

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

# 2. 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.

AstraZeneca

| Clinical Study Protocol: Appendix C | |
|---|---|
| Drug substance: | ZD9238 (Fulvestrant) |
| Study Code: | D6997C00002 (9238IL/0064) |
| Appendix Edition No: | 1 |
| Appendix Date: | |

# Appendix C
# Objective Tumour Response Criteria (RECIST)

# 1. INTRODUCTION

The introduction explores the definitions, assumptions, and purposes of tumour response criteria. Below, guidelines that are offered may lead to more uniform reporting of outcomes of clinical trials. Note that although single investigational agents are discussed, the principles are the same for drug combinations, non-investigational agents, or approaches that do not involve drugs.

Tumour response associated with the administration of anticancer agents can be evaluated for at least three important purposes that are conceptually distinct:

- Tumour response as a prospective end point in early clinical trials. In this situation, objective tumour response is employed to determine whether the agent/regimen demonstrates sufficiently encouraging results to warrant further testing. These trials are typically phase II trials of investigational agents/regimens (*see* section 1.2), and it is for use in this precise context that these guidelines have been developed.

- Tumour response as a prospective end point in more definitive clinical trials designed to provide an estimate of benefit for a specific cohort of patients. These trials are often randomised comparative trials or single-arm comparisons of combinations of agents with historical control patients. In this setting, objective tumour response is used as a surrogate end point for other measures of clinical benefit, including time to event (death or disease progression) and symptom control (*see* section 1.3).

- Tumour response as a guide for the clinician and patient or study subject in decisions about continuation of current therapy. This purpose is applicable both to clinical trials and to routine practice (see section 1.1), but use in the context of decisions regarding continuation of therapy is not the primary focus of this document.

However, in day-to-day usage, the distinction among these uses of the term "tumour response" can easily be missed, unless an effort is made to be explicit. When these differences are ignored, inappropriate methodology may be used and incorrect conclusions may result.

## 1.1 Response outcomes in daily clinical practice of oncology

The evaluation of tumor response in the daily clinical practice of oncology may not be performed according to predefined criteria. It may, rather, be based on a subjective medical judgment that results from clinical and laboratory data that are used to assess the treatment benefit for the patient. The defined criteria developed further in this document are not necessarily applicable or complete in such a context. It might be appropriate to make a distinction between "clinical improvement" and "objective tumour response" in routine patient management outside the context of a clinical trial.

## 1.2 Response outcomes in uncontrolled trials as a guide to further testing of a new therapy

"Observed response rate" is often employed in single-arm studies as a "screen" for new anticancer agents that warrant further testing. Related outcomes, such as response duration or proportion of patients with complete responses, are sometimes employed in a similar fashion. The utilisation of a response rate in this way is not encumbered by an implied assumption about the therapeutic benefit of such responses, but rather implies some degree of biologic antitumour activity of the investigated agent.

For certain types of agents (ie cytotoxic drugs and hormones), experience has demonstrated that objective antitumour responses observed at a rate higher than would have been expected to occur spontaneously can be useful in selecting anticancer agents for further study. Some agents selected in this way have eventually proven to be clinically useful. Furthermore, criteria for "screening" new agents in this way can be modified by accumulated experience and eventually validated in terms of the efficiency by which agents so screened are shown to be of clinical value by later, more definitive, trials.

In most circumstances, however, a new agent achieving a response rate determined *a priori* to be sufficiently interesting to warrant further testing may not prove to be an effective treatment for the studied disease in subsequent randomised phase III trials. Random variables and selection biases, both known and unknown, can have an overwhelming effect in small, uncontrolled trials. These trials are an efficient and economic step for initial evaluation of the activity of a new agent or combination in a given disease setting. However, many such trials are performed, and the proportion that will provide false-positive results is necessarily substantial. In many circumstances, it would be appropriate to perform a second small confirmatory trial before initiating large resource-intensive phase III trials.

Sometimes, several new therapeutic approaches are studied in a randomised phase II trial. The purpose of randomisation in this setting, as in phase III studies, is to minimise the impact of random imbalances in prognostic variables. However, randomised phase II studies are, by definition, not intended to provide an adequately powered comparison between arms (regimens). Rather, the goal is simply to identify one or more arms for further testing, and the sample size is chosen so to provide reasonable confidence that a truly inferior arm is not likely to be selected. Therefore, reporting the results of such randomised phase II trials should not imply statistical comparisons between treatment arms.

## 1.3 Response outcomes in clinical trials as a surrogate for palliative effect

### 1.3.1 Use in non-randomised clinical trials.

The only circumstance in which objective responses in a non-randomised trial can permit a tentative assumption of a palliative effect (ie beyond a purely clinical measure of benefit) is when there is an actual or implied comparison with historical series of similar patients. This

assumption is strongest when the prospectively determined statistical analysis plan provides for matching of relevant prognostic variables between case subjects and a defined series of control subjects. Otherwise, there must be, at the very least, prospectively determined statistical criteria that provide a very strong justification for assumptions about the response rate that would have been expected in the appropriate "control" population (untreated or treated with conventional therapy, as fits the clinical setting). However, even under these circumstances, a high rate of observed objective response does not constitute proof or confirmation of clinical therapeutic benefit. Because of unavoidable and non-quantifiable biases inherent in non-randomised trials, proof of benefit still requires eventual confirmation in a prospectively randomised, controlled trial of adequate size. The appropriate end points of therapeutic benefit for such a trial are survival, progression-free survival, or symptom control (including quality of life).

### 1.3.2 Use in randomised trials

Even in the context of prospectively randomised phase III comparative trials, "observed response rate" should not be the sole, or major, end point. The trial should be large enough that differences in response rate can be validated by association with more definitive end points reflecting therapeutic benefit, such as survival, progression-free survival, reduction in symptoms, or improvement (or maintenance) of quality of life.

# 2. MEASURABILITY OF TUMOuR LESIONS AT BASELINE

## 2.1 Definitions

At baseline, tumour lesions will be categorised as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan [see section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

(*Note:* Tumour lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.)

## 2.2 Specifications by methods of measurements

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumour effect of a treatment.

### 2.2.1 Clinical examination

Clinically detected lesions will only be considered measurable when they are superficial (eg skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.

### 2.2.2 Chest x-ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

### 2.2.3 CT and MRI

CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumours of the chest, abdomen, and pelvis, while head and neck tumours and those of the extremities usually require specific protocols.

### 2.2.4 Ultrasound

When the primary end point of the study is objective response evaluation, ultrasound should not be used to measure tumour lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

### 2.2.5 Endoscopy and laparoscopy

The utilisation of these techniques for objective tumour evaluation has not yet been fully or widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may be available only in some centres. Therefore, utilisation of such techniques for objective tumour response should be restricted to validation purposes in specialised centres. However, such techniques can be useful in confirming complete histopathologic response when biopsy specimens are obtained.

### 2.2.6 Tumour markers

Tumour markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all tumour lesions have disappeared. Specific additional

criteria for standardised usage of prostate-specific antigen and CA (cancer antigen) 125 response in support of clinical trials are being validated.

### 2.2.7 Cytology and histology

Cytologic and histologic techniques can be used to differentiate between partial response and complete response in rare cases (eg after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). New techniques to better establish objective tumour response will be integrated into these criteria when they are fully validated to be used in the context of tumour response evaluation.

# 3. TUMOUR RESPONSE EVALUATION

## 3.1 Baseline evaluation

### 3.1.1 Assessment of overall tumour burden and measurable di sease

To assess objective response, it is necessary to estimate the overall tumour burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion (as defined in section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

### 3.1.2 Baseline documentation of "target" and "nontarget" lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterise the objective tumour response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

## 3.2 Response criteria

### 3.2.1 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: complete response—the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

### 3.2.2 Evaluation of nontarget lesions

This section provides the definitions of the criteria used to determine the objective tumour response for nontarget lesions: complete response—the disappearance of all nontarget lesions and normalisation of tumour marker level; incomplete response/stable disease—the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

(*Note:* Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel [or study chair].)

### 3.2.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 3.3.1). Table 1 provides overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions.

(*Notes:*

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.

- Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status).

### 3.2.4 Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up of every other cycle (ie 6-8 weeks) seems a reasonable norm. Smaller or greater time intervals than these could be justified in specific regimens or circumstances.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the phase II trial has, as a goal, the response rate or the time to an event (disease progression/death). If time to an event is the main end point of the study, then routine re-evaluation is warranted of those patients who went off the study for reasons other than the expected event at frequencies to be determined by the protocol. Intervals between evaluations twice as long as on study are often used, but no strict rule can be made.

**Table 1 Overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions**

| Target lesions[a] | Nontarget lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Incomplete response/StD | No | PR |
| PR | Non-PD | No | PR |
| StD | Non-PD | No | StD |
| PD | Any | Yes or no | PD |
| Any | PD | Yes or no | PD |
| Any | Any | Yes | PD |

[a]CR complete response; PR partial response; StD stable disease; and PD progressive disease See text for more details.

## 3.3 Confirmatory measurement/duration of response

### 3.3.1 Confirmation

The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in non-randomised trials where response is the primary end point. In this setting, to be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol (see section 3.3.3).

(*Note:* Repeat studies to confirm changes in tumour size may not always be feasible or may not be part of the standard practice in protocols where progression-free survival and overall survival are the key end points. In such cases, patients will not have "confirmed response." This distinction should be made clear when reporting the outcome of such studies.)

### 3.3.2 Duration of overall response

The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for complete response until the first date that recurrent disease is objectively documented.

### 3.3.3 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for disease progression is met (taking as reference the smallest measurements recorded since the treatment started). The clinical relevance of the duration of stable disease varies for different tumour types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of stable disease. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

(*Note:* The duration of response or stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency that should take into account many parameters, including disease types and stages, treatment periodicity, and standard practice. However, these limitations to the precision of the measured end point should be taken into account if comparisons among trials are to be made.)

## 3.4 Progression-free survival/time to progression

This document focuses primarily on the use of objective response end points. In some circumstances (eg, brain tumours or investigation of non-cytoreductive anticancer agents), response evaluation may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, progression-free survival/time to progression can be considered valuable alternatives to provide an initial estimate of biologic effect of new agents that may work by a non-cytotoxic mechanism. It is clear though that, in an uncontrolled trial proposing to utilise progression-free survival/time to progression, it will be necessary to document with care the basis for estimating what magnitude of progression-free survival/time to progression would be expected in the absence of a treatment effect. It is also recommended that the analysis be quite conservative in recognition of the likelihood of confounding biases, eg, with regard to selection and ascertainment. Uncontrolled trials using progression-free survival or time to progression as a primary end point should be considered on a case-by-case basis, and the methodology to be applied should be thoroughly described in the protocol.

# 4. RESPONSE REVIEW

For trials where the response rate is the primary end point, it is strongly recommended that all responses be reviewed by an expert or experts independent of the study at the study's completion. Simultaneous review of the patients' files and radiologic images is the best approach.

(*Note:* When a review of the radiologic images is to take place, it is also recommended that images be free of marks that might obscure the lesions or bias the evaluation of the reviewer[s].)

# 5. REPORTING OF RESULTS

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response**,** 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (*Note:* By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (eg, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

## 6. RESPONSE EVALUATION IN RANDOMISED PHASE III TRIALS

Response evaluation in phase III trials may be an indicator of the relative antitumour activity of the treatments evaluated but may usually not solely predict the real therapeutic benefit for the population studied. If objective response is selected as a primary end point for a phase III study (only in circumstances where a direct relationship between objective tumour response and a real therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applicable to phase II trials (RECIST guidelines) should be used.

On the other hand, some of the guidelines presented in this special article might not be required in trials, such as phase III trials, in which objective response is *not* the primary end point. For example, in such trials, it might not be necessary to measure as many as 10 target lesions or to confirm response with a follow-up assessment after 4 weeks or more. Protocols should be written clearly with respect to planned response evaluation and whether confirmation is required so as to avoid *post-hoc* decisions affecting patient evaluability

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| Clinical Study Protocol: Appendix D | |
|---|---|
| Drug substance: | ZD9238 (Fulvestrant) |
| Study Code: | D6997C00002 |
| Appendix Edition No: | 1 |
| Appendix Date: | |

# Appendix D
# Independent Data Monitoring Committee (IDMC)

# INDEPENDENT DATA MONITORING COMMITTEE (IDMC) COMPOSITION AND TERMS OF REFERENCE

**Approved by:**

Clinical Study Physician

Signature .....

Date .....

Statistician

Signature .....

Date .....

Clinical Study Team Leader

Signature .....

Date .....

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## LIST OF ABBREVIATIONS

The following abbreviations are used in this appendix.

| Abbreviation | Explanation |
|---|---|
| IDMC | Independent Data Monitoring Committee |
| SAE | Serious Adverse Event |

## LIST OF APPLICABLE PERSONNEL

The following personnel are relevant to this appendix.

| | |
|---|---|
| IDMC Members | International Coordinating Investigators |
| Statistician | Clinical Study Team Leader |
| Clinical Team Members | Clinical Study Team Physician |

# 1. PRINCIPLES

An Independent Data Monitoring Committee (IDMC) will be established in order to assess the progress of the clinical trial, including the safety data, at regular intervals. Based on the information reviewed by the IDMC at regular intervals, the IDMC will recommend to AstraZeneca whether to continue, modify or stop the trial. The IDMC will act according to the operating procedures detailed in this document and will maintain written records of its meetings.

The choice of the members of the IDMC is agreed upon by the International Coordinating Investigators of the trial. No participants in the trial or pharmaceutical industry representatives may be among the members of the IDMC. The composition of the IDMC should be multidisciplinary, including physicians and statisticians who agree with the objectives of the trial and are free of any conflict of interest that might be related to the particular trial. The members of the committee should be at least two medical oncologists and one statistician.

The IDMC members should be aware that the information included in the interim reports is confidential and must not be disclosed, even partially or indirectly, either orally or in writing.

If the IDMC considers that the clinical trial should continue, the committee will actively encourage and give recommendations in order to pursue the trial and to complete patient entry as quickly as possible with the aim of exerting a positive influence on the trial. If the IDMC considers otherwise, this situation is discussed in section 2.4 of this document.

# 2. PROCEDURE

## 2.1 Composition and Nomination

The AstraZeneca Clinical Study Team Physician in agreement with the International Coordinating Investigators will nominate the IDMC members. After nomination of the committee the Clinical Study Team Physician will:

- Contact the nominated members and invite them to be part of the IDMC.
- Consult with the International Coordinating Investigators before nominating any replacement members if necessary.

The Clinical Study Team Leader of the trial will:

- Collect and archive signed Conflict of Interest Disclosure and Confidentiality Declaration Form from each IDMC member

During the first meeting of the IDMC, the members of the committee will elect a Chairman.

## 2.2 Interim Reports

After consultation with the independent statistician of the IDMC, fields relevant to the safety of the patients enrolled in the trial will be extracted from the database and provided to him/her, together with the randomisation scheme and SAS programs to help him/her produce adverse event information per treatment arm. This unblinded data will only be made available for the members of the IDMC.

The first *Report* will be produced when safety data is available for the first 30 patients (approximately 15 patients form each treatment arm) who have safety data for at least 3 months. Recruitment of additional patients to the study will not be interrupted and will continue while the safety data are being collected and the *Report* is being prepared. AstraZeneca commits to provide the data to the IDMC statistician within 5 weeks of the 30$^{th}$ patient completing 3 months of treatment

The second *Report* will be produced when safety data are available for the first 60 patients (approximately 30 patients from each treatment arm) who have safety data for at least 3 months. Recruitment of additional patients to the study will not be interrupted and will continue while the safety data are being collected and the *Report* is being prepared. AstraZeneca commits to provide the data to the IDMC statistician within 5 weeks of the 60$^{th}$ patient completing 3 months of treatment. Those patients who are recruited whilst the IDMC review data from the first 60 patients will be closely monitored in the same manner to ensure their safety. By the time the 60$^{th}$ patient has been treated for 3 months, a cohort of the earlier patients will have had a prolonged exposure (>3 months) that may provide reassurance of any association of long-term exposure and toxicity.

Unless otherwise requested by the IDMC Chairman, more *Reports* will be produced at approximately 9 month intervals after the second *Report.*

The data supplied for the above IDMC meetings will contain all safety data that has been entered onto the database. It will have been source data verified against the patient records at each study site, but will not necessarily have been fully validated.

If requested, AstraZeneca will provide the IDMC's recommendation to Regulatory Authorities.

The Clinical Study Team Physician in collaboration with the AstraZeneca Drug Safety Physician will provide the IDMC members with all narratives of serious adverse events (SAE) received by AstraZeneca. In addition, each *Report* will include:

- An appendix assessing the progress of the Trial worldwide
- Any other available safety information requested by the IDMC

The Trial Clinical Study Leader will be responsible for confidential distribution of any *Report* to the IDMC members.

The data used for the *Report* will include at least all data received by AstraZeneca until 2 weeks prior to a scheduled meeting, irrespective of whether or not the data has been completely validated.

In addition, the following may be submitted to the IDMC prior to a scheduled meeting:

- Any safety issue provided by one or more of the International Coordinating Investigators
- Any issue provided by the AstraZeneca Clinical team, eg, information emerging from other clinical trials that might be relevant to this trial.
- Note: Any amendments of the Trial protocol will be approved by the Trial International Coordinating Investigators, by the AstraZeneca Clinical Team and IDMC before being submitted to the Ethics Committees in each institution.

## 2.3 Planning of Meetings

Depending on the material to be discussed, there may be either a physical meeting of the IDMC or a telephone conference. The IDMC Chairman will decide whether a physical meeting or a telephone conference should be carried out and notify AstraZeneca.

AstraZeneca, in agreement with the International Coordinating Investigators will:

- Contact the IDMC members to find a suitable date/location for the meeting
- Provide the independent statistician with the necessary database, the SAS programs and the randomisation scheme.
- Prepare a *Report* based on the data collected up to 2 weeks prior to sending the data to the IDMC statistician.
- Distribute the *Report* confidentially to each member at least 2 weeks prior to a scheduled meeting

## 2.4 Conduct of Meetings

IDMC meetings will include the following sessions (or telephone conferences):

- An **open session** where the IDMC can seek information from invited representatives (as requested by the IDMC Chairman or as proposed by the Coordinating Investigators or by AstraZeneca) such as any of the Principal Investigators, representatives of any of the participating institutions, regulatory

bodies, etc. Neither per-randomised-treatment data nor safety information included in the *Report* will be disclosed during this session.

- *Presentation of the report*: The Clinical Study Team Physician and Statistician will attend this session of the meeting to present the interim report, provide clarifications and answer questions from the IDMC members. The Clinical Study Team Physician will invite other members of the AstraZeneca Trial team, if appropriate.

- After presentation of the *Report*, the following **closed session** will be limited to the members of the IDMC. The data will be discussed and the IDMC will either:

1. Recommend that the trial should be continued unchanged
2. Recommend that the trial should be modified
3. Recommend that the trial should be stopped
4. Recommend early disclosure of results
5. Request further information

- The closed session will be followed by a **second open session** with the Clinical Study Team Physician and Statistician, in which recommendations of the IDMC are discussed.

- Optionally, at the request of either the IDMC Chairman or one of the International Coordinating Investigators, one or more of the International Coordinating Investigators will attend the second open session. Only if the IDMC gives any recommendation other than *continuing the trial unchanged* can any relevant information be provided to justify the recommendation. Unblinded information about safety should only be revealed in case of recommending discontinuation or modification of the trial.

- Within two weeks of the IDMC Meeting, the IDMC Chairman will send the IDMC recommendation/outcome in writing to the Clinical Study Team Physician who will distribute it to the International Coordinating Investigators.

## 2.5 Record Keeping

The Trial Clinical Study Team Leader will be responsible for archiving:

- Composition of the IDMC
- Any correspondence related to the IDMC
- Signed Conflict of Interest Disclosure Form from each IDMC member

- Signed Confidentiality Declaration from each IDMC member
- Copy of all documentation supplied by AstraZeneca to the IDMC
- Written records of any meeting of the IDMC including:
  - Date and Time
  - IDMC members
  - Invited members
  - Any recommendations from the IDMC following their meetings/telephone conferences
  - The *Reports* and any recommendation of the IDMC will be made available for review to the International Principal Investigators.

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| Clinical Study Protocol: Appendix E | |
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| Drug substance: | ZD9238 (Fulvestrant) |
| Study Code: | D6997C00002 (9238IL/0064) |
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# Appendix E
# Rationale for fulvestrant dose

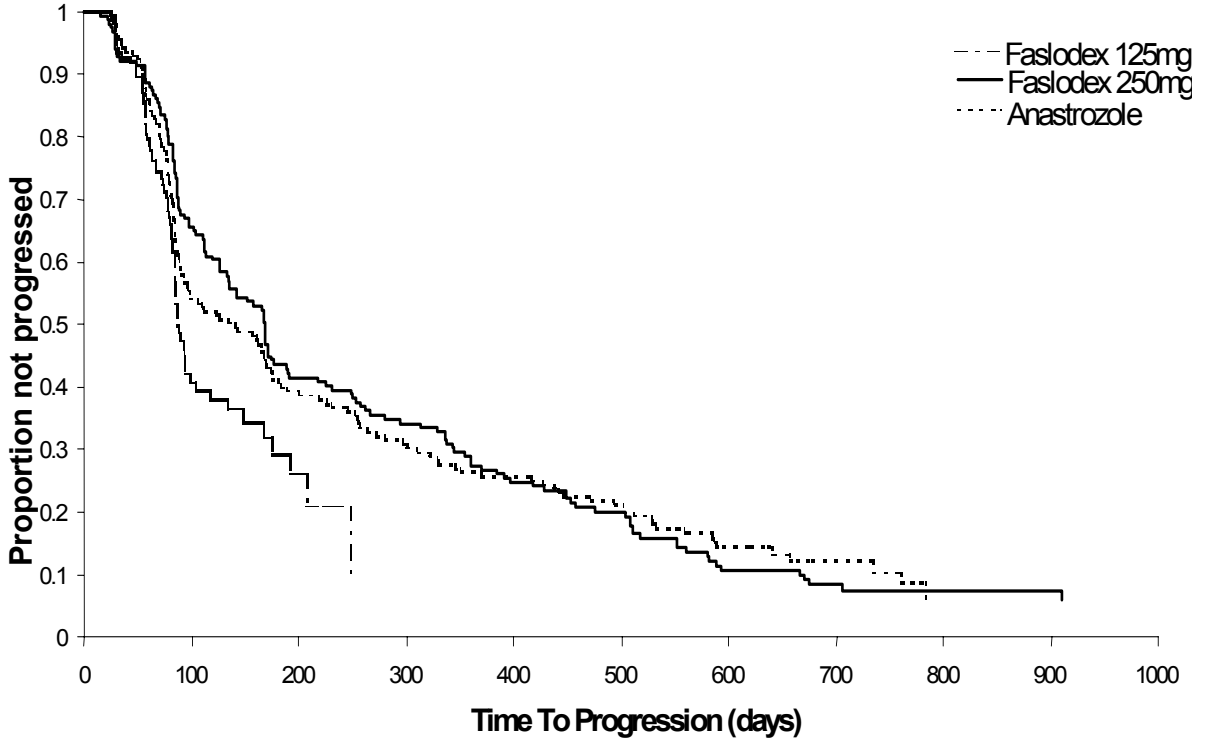
**Rationale for fulvestrant dose**

Fulvestrant competes with oestradiol for, and binds to, the oestrogen receptor (ER). Binding to the ER makes the receptor complex unstable, thus accelerating the degradation of the ER, and resulting in what is otherwise referred to as 'downregulation'. Because fulvestrant does not alter the synthesis or stability of ER mRNA, synthesis of new ER protein continues and complete elimination of ER protein does not occur. This is a dynamic process in which existing receptors must be bound and degraded at a rate much greater than their synthesis in order to overcome the stimulus to cell growth.

The rapid achievement and maintenance of a fulvestrant plasma concentration higher than that achievable with the current schedule would potentially increase the ability to bind to more receptors, and enhance the downregulation and degradation of the receptor protein which continues to be produced. Hence, the rapid and sustained achievement of a higher systemic exposure may produce further receptor degradation and results in greater efficacy. At present, no dose-ranging trials to assess efficacy beyond the 250 mg/month dosing schedule have been completed. The delivery of a higher dose of fulvestrant in a 5 mL volume is currently constrained by the limits of the formulation, and what is perceived as being a clinically acceptable schedule of administration. However, because of the favourable safety profile of fulvestrant, administration of a higher dose (volume) may be acceptable if it is paired with greater efficacy. The delivery of a higher dose, as predicted by pharmacologic modelling, may lead to the rapid achievement of steady state (and maintenance of $C_{trough}$).

Trial 9238IL/0020 and trial 9238IL/0021 assessed the efficacy of fulvestrant 250 mg, 125 mg, and anastrozole 1 mg. In line with the protocol design, an assessment of the first 30 patients recruited to the fulvestrant 125 mg arm and treated for three months, demonstrated that this dose was inferior in efficacy when compared to the 250 mg arm and was discontinued (Figure 1: Howell et al, 2002; Osborne et al, 2002). Recruitment to the fulvestrant 125 mg treatment group had continued during the 3-month minimum follow-up period for the first 30 patients. During this period, a total of 161 patients were recruited across both trials. The comparison between fulvestrant 250 mg and fulvestrant 125 mg demonstrated a significant advantage for fulvestrant 250 mg. The hazard ratio of 0.59 (C.I. 0.44 – 0.80, $p < 0.001$) for the comparison indicates that patients receiving fulvestrant 250 mg are estimated to be 41% less likely to experience disease progression in a given time period compared with patients receiving fulvestrant 125 mg.

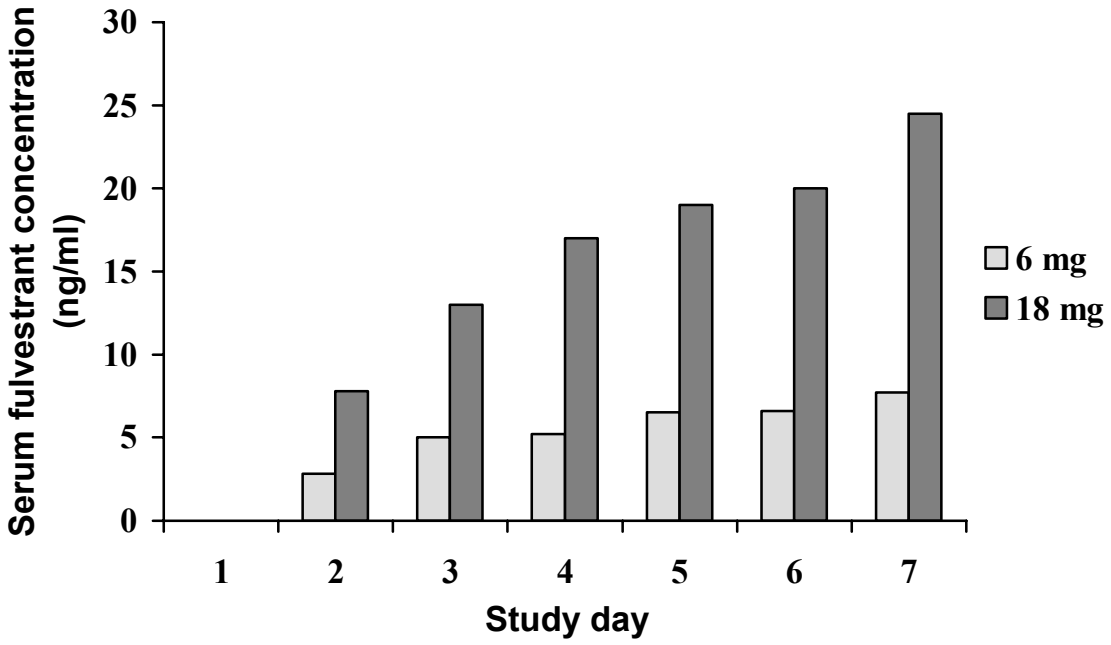
**Figure 1** **Time to progression on anastrozole, fulvestrant 125 mg and fulvestrant 250 mg in postmenopausal women with advanced breast cancer progressing after antiestrogen therapy (Trials 9238IL/0020 and 9238IL/0021).**




The rationale for the potential of a higher dose of fulvestrant to downregulate the ER to a greater extent is further supported by the results of Trial 9238IL/0002 (trial 0002) (DeFriend et al, 1994). In this trial 56 patients were randomised to either a control group (n = 19), or a treatment group (n = 37), in which daily i.m. injections of the short-acting formulation of fulvestrant at doses of 6 mg (n = 21) or 18 mg (n = 16) for 7 days prior to primary breast surgery were received. An antiproliferative effect on tumour tissue was observed to occur by day 7 of treatment. Over this time period, there was a three-fold drug accumulation.

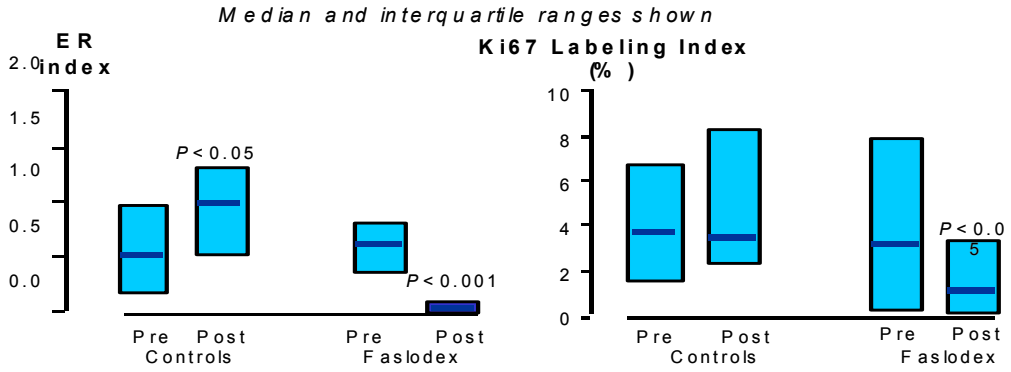
Expression of oestrogen receptors (ER), progesterone receptors (PgR), the oestrogen-induced protein pS2, and the cell proliferation-related antigen Ki67 were determined, and trough serum concentrations of fulvestrant were measured. The trough serum concentration of fulvestrant was dose dependent with an approximately 3-fold drug accumulation (of from ≈ 11 ng/mL to ≈ 26 ng/mL for the 18 mg dose) over this short treatment period (Figure 2)

**Figure 2** **Serum fulvestrant concentrations (ng/ml) after daily administration of 2 doses of i.v. short acting fulvestrant formulation (Trial 9238IL/0002).**




Given that this was short-term exposure, steady state levels were not reached by the end of the 7 days. In patients with ER-positive tumours treatment with fulvestrant, when data from the 6 mg and 18 mg dose were combined, was associated with significant reductions (> 90%) in the tumour expression of ER (median ER index, 0.72 before *vs* 0.02 after treatment; $P < 0.001$), PgR (median progesterone receptor index, 0.50 before *vs* 0.01 after treatment; $P < 0.05$), and Ki67 (median Ki67 labelling index, 3.2 before *vs* 1.1 after treatment; $P < 0.05$) (Figure 3).

**Figure 3 Antiproliferative effects of Faslodex (Trial 9238IL/0002).**




In another trial of similar design (9238IL/0018), performed with the LA formulation, 201 patients were randomised to be treated pre-surgically with a single injection of fulvestrant in a dose ranging from 50-250 mg and then assessed on day 14-22 (Robertson et al, 2001). A dose-dependent reduction in ER and PgR expression was seen. Compared to placebo, a 39% reduction in ER score occurred in those treated with 50 mg (P = 0.0255), 50% reduction with 125 mg (P = 0.0006), and 59% with 250 mg (P= 0.0001) (Figure 4). Reduction in the mean PgR score was 12% with 50 mg (P = 0.1455), 52% with 125 mg (P = 0.0030), and 67% with 250 mg (P = 0.0002) (Figure 5). Reduction in median Ki67 LI score was 25% with 50 mg (P = 0.0460), 28% with 125 mg (P = 0.0014), and 49% with 250 mg (P = 0.0002) (Figure 6). Although these results were not as profound as those seen in Trial 0002, possibly due to a higher exposure in Trial 0002 with the short acting formulation, the statistical significance supports the dose-response relationship. A further reduction of ER, PgR and Ki67 expression may be possible with a higher dose.

**Figure 4** **Post-treatment mean ER H-score (Trial 9238IL/0018).**

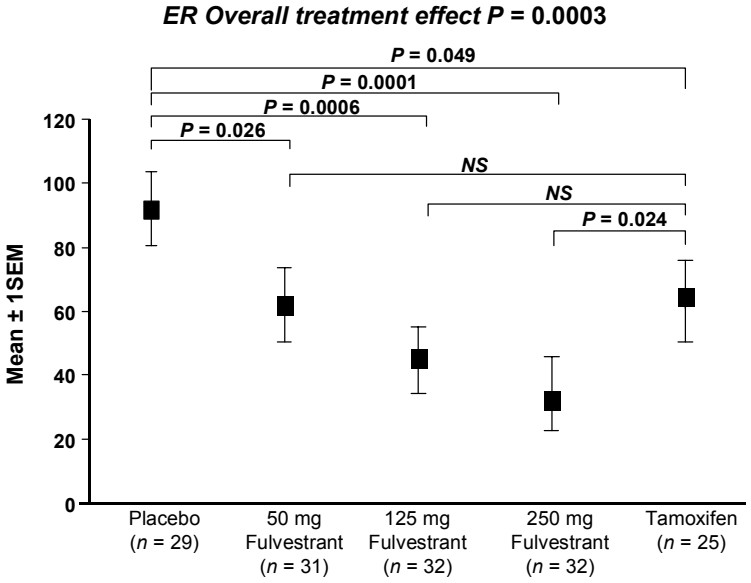



**Figure 5** **Post-treatment mean PgR H-score (Trial 9238IL/0018).**

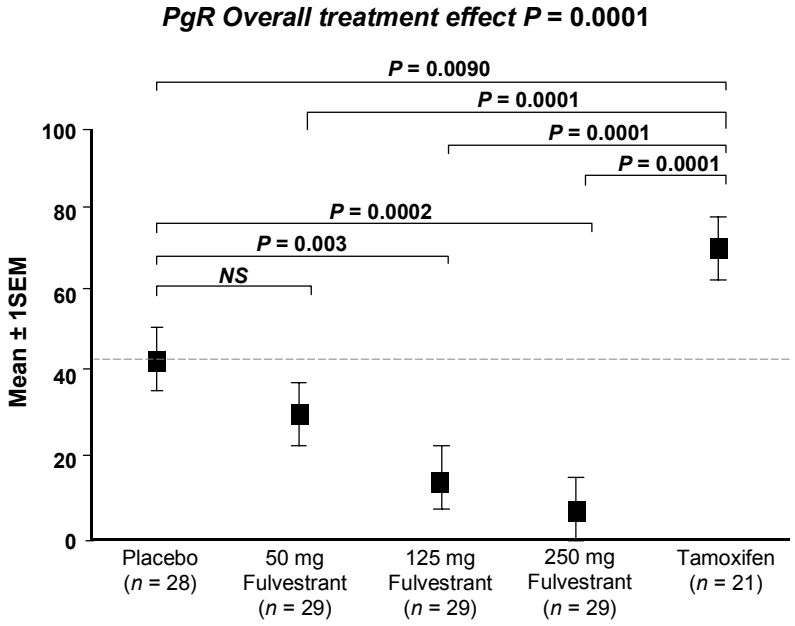
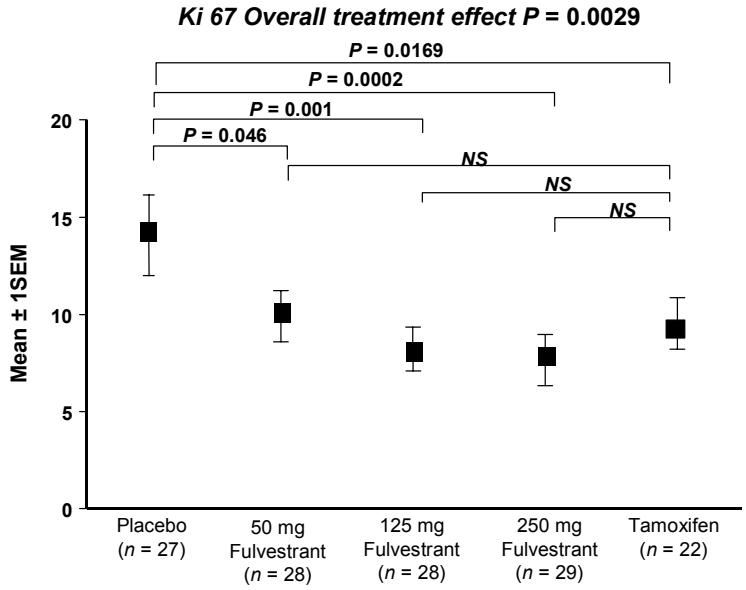


**Figure 6** **Post treatment antiproliferative effect (Ki67 labeling index) (Trial 9238IL/0018).**




In Trial 0002, in which downregulation of the ER was >90%, the overall fulvestrant exposure from the short-acting formulation was 7 × 18 mg, i.e. total dose of 126 mg. Because the effective "half life" of the short acting formulation was about 30 hours, by day 7 most of the patients should have been close to steady state and about 85% of the total dose, that is, approximately 108 mg, would have been released. In contrast, after a single dose of fulvestrant 250 mg, only about 17% of the dose is released in the first 7 days, i.e., approximately 43 mg, whereas after multiple doses and at steady state the estimated release over one week is approximately 63 mg. Therefore, the exposure was roughly twice that achieved by the current fulvestrant regimen at steady state for both observed $C_{max}$ and estimated AUC over a comparable interval ($AUC_{0\text{-}7days}$), and similarly for the lowest observed concentrations over the first five days of dosing.

In this regard, a more profound suppression of proliferation was seen and a further reduction in ER/PgR and Ki67 expression (a predictor of clinical efficacy) may be possible with administration of a higher dose of fulvestrant, e.g., the dose used in this proposed trial 9238IL/0064. A mean $C_{max}$ (149 ng/ml) has already been observed for about 1 hour in the fulvestrant IV studies with no significant adverse events reported (Trial 0038). Although exposure to this concentration was brief, these data give confidence that increasing $C_{max}$ by increasing the fulvestrant dose is likely to be safe.

Pharmacokinetic modelling predicts that the administration of a dose of 500 mg monthly, with an additional 500 mg at day 14 of the first month only, will decrease the time to achieve steady-state levels. Phase III pharmacokinetic (PK) sampling data has demonstrated that a 250 mg dose administered monthly requires approximately 3-6 months before steady-state

drug concentrations ($C_{ss}$) are reached (Figure E7). Early achievement of high fulvestrant plasma concentrations may further improve the early progression rate.

For trial 0064, the expected mean peak plasma concentration ($C_{max}$) is approximately 27 ng/mL, around day 18 after the second fulvestrant administration on day 14. Over the next 10 months, $C_{max}$ will be expected in the range of 26 – 28 ng/mL. The trough plasma concentrations at steady state are expected to be approximately 15 ng/mL compared to approximately 7 ng/mL for the 250 mg monthly injection.

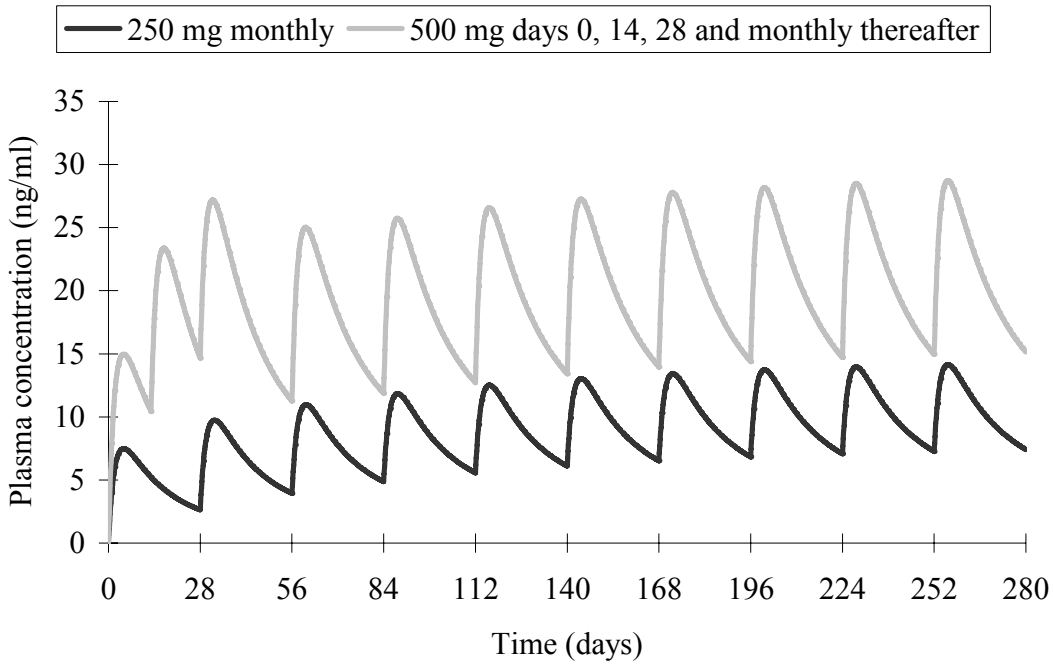
The predicted exposure during the first month of dosing the 500 mg regimen is 1.5 fold higher than the steady state exposure (approximately 10,800 ng·h/mL: vs 7245ng·h/mL) achieved with the standard monthly administration of the 250 mg intramuscular dose.

In addition, volunteers and patients have been previously exposed to plasma $C_{max}$ - concentrations up to 26 ng/mL using the short-acting im formulation (Trial 0029). With the intravenous formulation, mean maximum plasma concentrations ranged from 114 ng/mL - 166 ng/mL (Trial 0038 – Trial 0012) without any tolerability concerns.

It will thus be possible in this study to explore if the early achievement of higher concentrations than delivered by 250 mg monthly administration can improve efficacy measures. Due to the range of plasma concentrations previously encountered in other studies and an anticipated exposure change of only 1.5 fold over the first month, it is not anticipated that additional safety issues will develop with the use of a higher dose regimen in relation to the fulvestrant.

Figure 7 represents the mean parameters taken from the population PK analysis of the studies 9238IL/0020 and 9238IL/0021 (fulvestrant 250 mg administered every 28 days) and simulated in a PK model designed to predict the behaviour of the higher dose regimen used in this trial (fulvestrant 500 mg day 0, 500 mg days 14 and 28 and then every 28 days). Data is also shown for the simulated profiles for the 250 mg monthly formulation.

**Figure 7** **Predicted plasma concentrations for the 250 mg monthly administration and the 500 mg administration on days 0, 14, 28 and then monthly.**



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**Clinical Study Protocol: Appendix F**

| | |
|---|---|
| Drug Substance | ZD9238 (Fulvestrant) |
| Study Code | D6997C00002 (9238IL/0064) |
| Appendix Edition Number | 1 |
| Appendix Date | |

# Appendix F
# Pharmacogenetics

# PHARMACOGENETICS SYNOPSIS

## A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy



The genetic research described in this appendix will be submitted for regulatory/ethical approval and implemented with the clinical study protocol. All sections of the clinical study protocol apply to the genetics research described in this appendix. This appendix details additional procedures and considerations for inclusion of patients in the genetic component of the study.

### Study centre(s) and number of patients planned for genetic sampling

The Pharmacogenetics Part of the study will be conducted in as many centres as possible that participate in the main study.

### Objectives

Genes that may be investigated include:

- The oestrogen receptor gene and other genes in oestrogen mediated pathways

### Study design

Patients participating in the main study (D6997C00002 (9238IL/0064)) will be invited to contribute a single 9 mL blood sample for extraction of DNA for potential genetic analysis. Patients' participation in this genetic component is voluntary and any patient's decision not to participate will not exclude them from the main D6997C00002 (9238IL/0064) clinical study. Refusal to participate will involve no penalty or loss of benefits to which the patient would otherwise be entitled.

### Target population

Participants of study D6997C00002 (9238IL/0064).

## Statistical methods

The number of patients who will agree to participate in the genetic component of the study is unknown. It is therefore not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS FOR PHARMACOGENETICS

| Abbreviation or special term | Explanation |
|---|---|
| °C | Degrees Celsius |
| CGG | Clinical genotyping group |
| CRF | Case record form |
| CSR | Clinical study report |
| DGG | Development genetics group |
| DNA | Deoxyribonucleic acid |
| EDTA | Ethylenediamine tetra-acetic acid |
| LIMS | Laboratory information management system |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| SNP | Single nucleotide polymorphism |
| mL | Millilitre |
| UK | United Kingdom |

# 1. BACKGROUND TO PHARMACOGENETICS

Genetic variation within a population can contribute to inter-individual differences in drug response (where the term "response" is used broadly to include drug disposition, safety, efficacy and tolerability), as well as acting as markers for disease susceptibility and prognosis. Characterisation of genetic variation may help clarify the biology of drug action and elucidate processes that may influence safety and tolerability of a drug or class of drugs (Marchall, 1997).

With the increasing understanding of genes and their variations (polymorphisms), there is an increasing understanding of how these may impact drug response (the field of "pharmacogenetics"). Genetic variation in drug metabolising enzymes has been extensively studied and has been shown to be of clinical significance for a number of drugs (Tucker, 1994). For a number of these metabolising enzymes, particularly the cytochrome P450 isoenzymes, the genetic basis for altered activity is already well understood. This work is being expanded into other genes whose products are important in the absorption, distribution, metabolism and excretion of drugs, such as the drug transporter proteins. Whilst there are many factors affecting the pharmacokinetic profile of a given drug, genetic variation can be an important determinant and genotyping – to determine genetic variability - may allow for more rational dosage and safety predictions in patients.

Variations in genes that encode the molecular target of a drug, and genes involved in the signalling pathways related to that target are also candidates for influencing variability in therapeutic response. In comparison to the drug metabolising enzymes these genes, and the variations within them, are generally less well characterised and understood at the present time, although some relevant examples are beginning to emerge (Evans & Relling, 1999). In the future, however, it is likely that more information will become available on genes that are important in determining disease susceptibility, prognosis and therapeutic efficacy. In this respect it is of immense benefit to archive samples with appropriate informed consent for future analysis.

AstraZeneca plan to include investigations into genetic variations and their effect on drug response as part of the drug development program for all projects where it is considered to be appropriate. By using this information, the aim is to better understand the impact of genetic variation and how it can be utilised to bring better drugs to the market.

To achieve this goal a systematic collection of deoxyribonucleic acid (DNA) for genetic analysis (derived from blood samples taken from consenting study patients) will be implemented across a broad range of relevant clinical studies. The ability to acquire appropriate consent to collect blood samples to establish an archive and allow future meta-analysis of data derived from a number of studies for fulvestrant is of the utmost important. This study forms part of this strategy.

## 1.1 Rationale for pharmacogenetics

AstraZeneca intends to apply pharmacogenetics to the fulvestrant clinical development programme to explore how genetic variations may affect the clinical parameters associated with fulvestrant.

The benefits of being able to explore associations between genes and clinical outcomes within the fulvestrant programme are potentially many and include:

- Identification of determinants of pharmacokinetic profile of, and pharmacodynamic response to fulvestrant.
- The potential ability to identify individuals who may respond optimally to fulvestrant or a specific dose of fulvestrant

# 2. PHARMACOGENETIC OBJECTIVES

Genes that may be investigated include:

- The oestrogen receptor gene and other genes in oestrogen mediated pathways

In addition to the above named genes which we believe may influence therapeutic response to fulvestrant, it is likely that additional information on other genes important for this drug and for breast cancer for which the drug is being developed will become available in the future. It is, therefore important to retain the possibility of investigating additional genes in the context of fulvestrant clinical study D6997C00002 (9238IL/0064).

The term “response” is used broadly to include disposition, efficacy, safety and tolerability. This archive will be derived from patients participating in a variety of fulvestrant clinical studies.

**It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to fulvestrant, under study within the current study protocol. No other testing will ever be performed on the samples.**

# 3. PHARMACOGENETICS PLAN AND PROCEDURES

## 3.1 Pharmacogenetics plan

This appendix to the Clinical Study Protocol has been subjected to peer review according to AstraZeneca standard procedures.

The patient will be asked to participate in the genetic component at the screening visit. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 1 or at any visit until the patient leaves the study.

## 3.2 Selection of pharmacogenetics population

### 3.2.1 Study selection record

Patients will be asked to participate in the genetic research. Participation in this genetic component of the clinical study is voluntary and if a patient declines to participate in the genetic 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 the main body of the clinical study protocol.

### 3.2.2 Inclusion criteria

For inclusion in the genetic component to the study, patients must fulfil all of the inclusion criteria described in the main body of the study protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

### 3.2.3 Exclusion criteria

Exclusion from the genetic component of the study may be for any of the exclusion criteria specified in the main body of the study protocol or any of the following:

- Previous bone marrow transplant
- Patients who have had a blood transfusion in the last 120 days prior to the date of sampling for genetic research

### 3.2.4 Discontinuation of patients from the genetic component of the study

#### 3.2.4.1 Criteria for discontinuation

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

- withdrawal of consent to the genetics aspects of the study. Patients may withdraw from the genetic research component of the study at any time, independent of any decision concerning participation in other aspects of the clinical study described in the main body of the Clinical Study Protocol. Voluntary discontinuation will not prejudice further treatment.

#### 3.2.4.2 Procedures for discontinuation

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

- agrees to the genetic sample and any DNA extracted from the sample being kept for genetic analyses in the future
- withdraws consent for the sample to be kept for genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA

extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that DNA analysis 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 sample taken for genetic analyses. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

In the case of any patient withdrawing consent for genetic research, the investigator must notify the AstraZeneca monitor using the "Withdrawal of Consent Form" (to be supplied). Requests for sample destruction should be forwarded to the head of the Clinical Genotyping Group along with copies of the relevant documentation detailing study protocol number, centre number and patient enrolment code. The clinical study team and investigator will receive written confirmation from the Clinical Genotyping Group that the genetic sample has been destroyed.

# 4. GENETIC MEASUREMENTS AND CO-VARIABLES

## 4.1 Summary of genetics objectives and analysis

The purpose of the genetic component of the study is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors, which may influence the disposition, efficacy, safety and tolerability to fulvestrant and/or susceptibility to or prognosis of breast cancer under investigation in this study. The results of the genetic analyses will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on fulvestrant to generate hypotheses to be tested in future studies.

## 4.2 Collection of samples for genetic testing

Patients will provide a blood sample as per the inclusion criteria and visit schedule.

A single venous blood sample (9 mL) will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of five times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the CRF.

Genotype is a stable parameter, therefore if for any reason the blood sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

### 4.2.1 Sample processing and shipping

Blood samples will be shipped at ambient temperature from study centres to the main central laboratory where they should be stored at –80°C. Batches of samples will be sent to the DNA extraction laboratory at six month intervals.

Where possible, blood samples should be shipped in batches and shipment will be coordinated with the receiving site to ensure that samples arrive within working hours, on normal working days. A requisition sheet, detailing the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection, should accompany the shipment.

### 4.2.2 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labelled with the study number and patient number. Only the investigator will be able to link the blood sample to the individual patient. The sample and data will not be labelled with a personal identifier. The link between the patient enrolment/randomisation code and the DNA number will be maintained.

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca, Alderley Park, UK. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. Access to the link file will require written authorisation from the Clinical Development Team Leader.

**All DNA samples will be stored under secure conditions with restricted access at AstraZeneca. DNA samples will be retained for 15 years after completion of the study. The blood, DNA samples or data derived from the samples may be made available to groups or organisations working with AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law.**

# 5. DATA MANAGEMENT OF GENETICS COMPONENTS

In the case of genotypic data, only the date the patient gave consent to participation in the genetic component of the study and the date the blood sample was taken from the patient will be recorded in the paper CRF and database. The genotypic data will not be merged with the clinical dataset collected from the patient population for statistical analysis.

The genotypic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate to the clinical database. Some or all of the clinical study dataset may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

## 5.1 Reporting of genotypic results

Results from any genetic research performed will be reported separately from the clinical trial report. AstraZeneca will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient's DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients who will agree to participate in the genetic component of this study is unknown. It is therefore not possible to establish whether a statistically relevant number of patients will consent to provide sufficient data to be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

# 7. STUDY MANAGEMENT

## 7.1 Monitoring

Before first patient entry into the study, a representative of AstraZeneca will visit the investigational study site. In addition to the requirements described in the main body of the clinical study protocol the genetic component of the study will be discussed.

During the study, a representative of AstraZeneca will have regular contacts with the investigational site. One of the purposes of these visits will be to perform source verification

of the genetic consent of participating patients and to ensure that the investigational team are adhering to the specific requirements of the genetic aspects of the study.

## 7.2 Training of staff

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic testing with a representative of AstraZeneca. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' sample will also be made clear.

## 7.3 Changes to the protocol

Any changes to the pharmacogenetic research will comply with the principles described in Section 7.4 of the main body of the protocol.

## 7.4 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail. Specific reference to the genetic requirements will be included in the study agreement(s).

# 8. ETHICS

## 8.1 Ethics review

In addition to documenting IRB/IEC approval of the clinical study, where there is a genetic component to the study, approval must be obtained for the genetic part of the study and the genetic informed consent form from the IRB or IEC. It must be clearly stated in the approval that the genetic component of the study is approved. The investigator must submit written approval to AstraZeneca before any patient participates in the genetic component of the study.

## 8.2 Ethical conduct of the study

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

For studies including genetic analysis special precautions are taken as described in section 4.2.2 of this Appendix.

## 8.3 Informed consent

The pharmacogenetic component of this study is optional and the patient may participate in other components of the study without participating in the pharmacogenetic component. To

participate in the pharmacogenetic component of the study the patient must sign and date both the consent form for the non-genetic components of the study and the pharmacogenetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the genetic aspect of the study at any time.

## 8.4 Patient data protection

All data protection and confidentiality principles, described in the main body of the clinical study protocol, are applied to the genetic research.

Reference to participation in the genetic component of the study should not be recorded into the patients' general medical records. All notes should be kept within the clinical study records.

Due to the exploratory nature of the genetic research in this study, there will be no routine communication of results to patients. AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient, however, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patients personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patients' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

# 9. REFERENCES

Marchall A. Getting the right drug into the right patient. Nature Biotechnology 1997;15: 1249-1252.

Tucker G.T. Clinical implications of genetic polymorphism in drug metabolism. J Pharm Pharmacol 1994;46 (suppl.1) :417-434.

Evans W.E., Relling M.V. Pharmacogenomics: Translating functional genomics into rational therapeutics. Science 1999;286: 487-491.

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**Clinical Study Protocol: Appendix G**

| | |
|---|---|
| Drug Substance | ZD9238 (Fulvestrant) |
| Study Code | D6997C00002 (9238IL/0064) |
| Appendix Edition Number | 1 |
| Appendix Date | |

# Appendix G
# FACT-B Quality of Life Questionnaire

# FACT-B (Version 4)



Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**



| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |



| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

# FACT-B (Version 4)



**By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**



| | **EMOTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |



| | **FUNCTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

# FACT-B (Version 4)



**By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

| | **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| B1 | I have been short of breath | 0 | 1 | 2 | 3 | 4 |
| B2 | I am self-conscious about the way I dress | 0 | 1 | 2 | 3 | 4 |
| B3 | One or both of my arms are swollen or tender | 0 | 1 | 2 | 3 | 4 |
| B4 | I feel sexually attractive | 0 | 1 | 2 | 3 | 4 |
| B5 | I am bothered by hair loss | 0 | 1 | 2 | 3 | 4 |
| B6 | I worry that other members of my family might someday get the same illness I have | 0 | 1 | 2 | 3 | 4 |
| B7 | I worry about the effect of stress on my illness | 0 | 1 | 2 | 3 | 4 |
| B8 | I am bothered by a change in weight | 0 | 1 | 2 | 3 | 4 |
| B9 | I am able to feel like a woman | 0 | 1 | 2 | 3 | 4 |
| P2 | I have certain parts of my body where I experience significant pain | 0 | 1 | 2 | 3 | 4 |