Revised Clinical Study Protocol	
Drug Substance	Fulvestrant
Study Code	D699BC00001
Edition Number	6
Date	17 December 2021

A Randomised, Double-blind, Parallel-group, Multicentre, Phase III Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Anastrozole (ARIMIDEX™) 1 mg as Hormonal Treatment for Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer Who Have Not Previously Been Treated With Any Hormonal Therapy (FALCON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
001	05 December 2012	001 - US	14 January 2013
002	1 December 2017		
003	17 December 2021		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
001	27 June 2012		
002	14 January 2013		
003	18 January 2018		

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VERSION HISTORY

Version 6.0, 17 December 2021 (Global CSP Amendment 003)

Changes to the protocol are summarised below

Change of final overall survival (OS) analysis trigger from when 75% of patients have died to: when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled

The final OS analysis in the FALCON study will be changed from the currently-planned trigger of when 75% of patients have died to: when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled. A 7-day window has been established for collection of these data, and it has been added that public websites can be searched. The proposal is based on:

- High uncertainty around when 75% of patients will have died. Newly proposed final OS analysis trigger is expected to occur in July 2022. With a minimum follow up period of 8 years and at least 65% of patients will have had the event, survival curves should be robustly characterised.

- With continuing evolution in the standard of care, an extended follow-up for OS analysis may not be clinically relevant. The treatment paradigms and current clinical guidelines including the National Comprehensive Cancer Network (NCCN Guidelines Breast Cancer 2021) have evolved to recommend the combination regimens of cyclin-D kinase 4/6 inhibitors plus endocrine agent (fulvestrant/aromatase inhibitors) as category I preferred treatment options over monotherapy.

All relevant sections of the protocol have been updated to reflect these changes.
Sections updated: Protocol Synopsis, Sections 3.1, 5.6, 6.1, 6.2.2.2, 6.4.4, 10, 12.2.1, and 12.2.4. The statistical analysis detailed in Section 12.2.1 has been updated to reflect this change.

Also, references to 'second data cut-off' have been changed to 'final data cut-off'.

Supply of investigational product after final database lock

Updated with details of provision of fulvestrant and anastrozole being supplied as a continued access phase after final database lock.

All relevant sections of the protocol have been updated to reflect these changes.
Sections updated: Protocol Synopsis, Sections 3.1, 5.5.1, and 9.5.

Check of Concomitant Medication During Survival Follow-up Phase

Concomitant medication continues to be checked during the survival follow-up phase; consequently this has been added to Table 2 in Section 3.1 and is mentioned in Section 6.2.2.2.

COVID-19

Noted in Section 5.6 that COVID-19 vaccination with authorised vaccines is permitted at the discretion of the investigator.

Added text to Section 13.2.1 to note that summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated.

SAE Reporting

To more accurately reflect the SAE reporting process, the wording has been changed to say that SAEs will be reported (not recorded) on a paper-based SAE form, and it is clarified that the form will be submitted as per instructions on the form.

Sections updated: Sections 6.1, 6.2.2.2, 6.4.3, and 6.4.4.

Study Timetable

To reflect the progress of the study, study timetable details have been updated in the Protocol Synopsis and in Section 9.5.

Change to CRO Name

Throughout, references to ‘Quintiles’ have been changed to ‘IQVIA’

Other minor corrections/updates were made throughout the document.

Version 5.0, 18 January 2018 (Correction of the editorial mistake in Revised CSP version 4.0)

Changes to the protocol are summarised below

Sections affected:

Appendix G :

Questionnaires, which due to the editorial mistake, were not included in Appendix G (edition 1.0 dated 19 Apr 2012) of the Revised CSP version 4.0 dated 01 Dec 2017 have been added in the corrected Appendix G of the Revised CSP version 5.0 dated 18 Jan 2018.

Version 4.0, 1 December 2017 (Global CSP Amendment 002)

Changes to the protocol are summarised below

Delay of final overall survival (OS) analysis to 75% maturity

The final OS analysis in the FALCON study will be delayed from the currently-planned 50% maturity (approximately 231 events) to 75% (approximately 347 events). This proposal is based on:

- the observation that in previous fulvestrant studies, the OS curves split relatively late then maintain a clear treatment difference for the remainder of the study, suggesting that a later, more mature analysis of FALCON OS is more likely to demonstrate a difference between the treatment groups, if one exists
- the unique mechanism of action of fulvestrant, which may explain the late separation of the OS curves
- the fact that a delayed final analysis of OS will include a greater number of events, which will improve the statistical power to detect a difference between the treatment arms.

All relevant sections of the protocol have been updated to reflect these changes. Sections updated: Protocol Synopsis, Section 3.1, 5.6, 6.2.2.2, 10, 12.2.1, 12.2.4.

Section 5.5.1:

Updated to describe IP supply in the post OS analysis phase.

Section 6.1, 6.2, 6.4.3 and 6.4.4:

Updated to explain that SAEs will be recorded on a paper-based SAE report form in the post-OS analysis period

Version 3, 14 January 2013 (Local CSP Amendment 001, with Global Administrative Changes)
Version 3 of the CSP comprised local Amendment 001 along with administrative changes and, which was developed under a previous process where the changes were documented in a separate changes document and are not listed here.
Version 2, 5 December 2012 (Global CSP Amendment 001)
Version 2 of the CSP was developed under a previous process where the changes were documented in a separate changes document and are not listed here.
Version 1, 1 May 2012
Initial creation

PROTOCOL SYNOPSIS

A Randomised, Double-blind, Parallel-group, Multicentre, Phase III Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Anastrozole (ARIMIDEX™) 1 mg as Hormonal Treatment for Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer Who Have Not Previously Been Treated With Any Hormonal Therapy (FALCON)

International Co-ordinating Investigators

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Study centres and number of patients planned

This international randomised study will be conducted in approximately 450 postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not previously been treated with any hormonal therapy. Approximately 180 to 220 international centres are planned in Asia, Europe, North America, South America and South Africa. It is estimated that each centre will recruit between 2 to 20 patients over approximately a 27-month period.

Study period		Phase of development
Date of first patient enrolled	17 Oct 2012	III
Date of last patient enrolled	11 Jul 2014	
Date of data cut-off for primary analysis of progression-free survival	11 Apr 2016	
Estimated date of data cut-off for when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled	Q3 2022	

Objectives

Primary:

To demonstrate the superior progression-free survival (PFS) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

Secondary:

1. To compare the overall survival (OS) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

2. To compare the objective response rate (ORR), duration of response (DoR) and the expected duration of response (EDoR) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

3. To compare the clinical benefit rate (CBR), the duration of clinical benefit (DoCB) and the expected duration of clinical benefit (EDoCB) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

4. To compare the quality of life (QoL) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

5. To compare the safety and tolerability of fulvestrant 500 mg treatment versus that of anastrozole 1 mg treatment.

Exploratory:

To explore how variations in tumour biomarkers (DNA, RNA and/or protein based) may be related to factors that may influence development of cancer and/or study treatment response and resistance.

Study design

This is a randomised, double-blind, double-dummy, international, multicentre study comparing the efficacy and tolerability of fulvestrant with anastrozole. Eligible patients will

be randomised 1:1 to receive fulvestrant 500 mg or anastrozole 1 mg. Patients will be stratified at randomisation based on whether (1) they have locally advanced or metastatic breast cancer (2) they have received prior chemotherapy for locally advanced or metastatic breast cancer or not and (3) they have measurable or non-measurable disease.

The primary analysis will be performed when approximately 306 events have occurred (defined as objective disease progression, surgery or radiotherapy to manage worsening of disease, or death by any cause in the absence of progression). Upon objective disease progression, patients will enter the survival follow-up phase. After the data cut-off for the primary analysis, all the remaining patients, regardless of whether they are still receiving randomised treatment, will enter the survival follow-up phase and will otherwise be managed as per standard clinical practice. A survival analysis will be performed at the same time as the primary analysis and again when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled. After this point, data collection will cease for this study, the study database will close and the patient's treatment will be unblinded. The end of the study is defined as the last visit of the last patient, occurring when the last patient has discontinued study therapy.

Following the final survival analysis, the patient’s treatment will be unblinded. Patients are permitted to continue to receive open-label study treatment beyond the closure of the database as a continued access phase if, in the opinion of the investigator, they are continuing to receive benefit from treatment with fulvestrant or anastrozole and cannot access appropriate treatment outside of the clinical study protocol. Placebo treatment will be discontinued at this point. During this period (ie, after the final OS analysis), there will be no further survival follow-up for the patient.

Target patient population

Postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer (confirmed by histology), who have not previously been treated with any hormonal therapy, have a World Health Organisation (WHO) performance status of 0, 1 or 2 and at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline and is suitable for repeated assessment according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) guidelines. Patients may have received one line of cytotoxic chemotherapy as previous treatment of breast cancer prior to enrolment but there must be evidence of progressive disease at this time if the chemotherapy was given for the metastatic or locally advanced disease.

Investigational product, dosage and mode of administration

Fulvestrant 500 mg will be administered as two 5 mL intramuscular injections, one in each buttock, on Days 0, 14 (±3), 28 (±3) and every 28 (±3) days thereafter. Placebo will also be given to match the anastrozole administration schedule.

Comparator, dosage and mode of administration

The comparator, anastrozole will be administered orally as a single daily tablet at a dose of 1 mg/day. Placebo will also be given to match the fulvestrant administration schedule.

Duration of treatment

Randomised treatment will continue until objective disease progression unless any of the other criteria for treatment discontinuation are met.

Disease progression will be assessed locally by each investigator according to RECIST 1.1.

After objective disease progression, patients will enter the survival follow-up phase. In order to facilitate a decision on the subsequent treatment options, investigators may request to be unblinded to treatment allocation, once randomised treatment has been discontinued, and progression has been formally documented in the electronic case report form (eCRF).

After the data cut-off for the primary analysis, all the remaining patients, regardless of whether they continue to receive randomised treatment, will enter the survival follow-up phase of the study, and will otherwise be managed as per standard clinical practice.

Following the final survival analysis, patients are permitted to continue to receive open-label study treatment beyond the closure of the database as a continued access phase if, in the opinion of the investigator, they are continuing to receive benefit from treatment with fulvestrant or anastrozole and cannot access appropriate treatment outside of the clinical study protocol. Placebo treatment will be discontinued at this point. Alternative supply options will be discussed and may be implemented if they become available.

Outcome variable(s):

- Primary outcome variable
  - Progression-free survival
- Secondary outcome variables
  - Overall survival (OS) (time from randomisation to death from any cause)
  - Objective response (OR) (= complete response [CR] + partial response [PR] defined by RECIST 1.1 criteria)
  - Clinical benefit (= CR + PR + {stable disease [SD] ≥24 weeks} defined by RECIST 1.1 criteria)
  - Duration of response (DoR) (defined for patients with OR only, as the number of days from first response to date of progressive disease [PD], as defined by RECIST 1.1, or death)

- Duration of clinical benefit (DoCB) (defined for patients with CB only, as the time in days from date of randomisation until date of PD as defined by RECIST 1.1 or death)

- Expected duration of response (EDoR) (from first response) (EDoR for patients who had OR assuming a log-normal distribution for the duration, multiplied by the proportion of patients who had OR)

- Expected duration of clinical benefit (EDoCB) (EDoCB for patients who had CB assuming a log-normal distribution for the duration, multiplied by the proportion of patients who had CB)

- Trial Outcome Index (TOI) derived from the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) questionnaire, Total FACT-B score and patients' utility scores from the EQ-5D™ (EuroQol Group) questionnaire

- Frequency and severity of adverse events (AEs) as assessed by Common Toxicity Criteria (CTC) grade (Version 4.0), pre-defined AEs of interest (joint disorders and back pain), laboratory assessments, electrocardiogram (ECG), physical examination (including WHO performance status), vital signs (including blood pressure and heart rate)

- Exploratory

  - to investigate biomarkers in tumour samples potentially using a number of different analytical platforms, eg, tumour-specific sequence changes.

Statistical methods

The primary statistical analysis will compare the PFS between fulvestrant 500 mg versus anastrozole 1 mg using the stratified log-rank test, at the 2-sided 5% significance level. This analysis will be performed on the Intention to Treat population. Results will be presented in terms of an estimate of the hazard ratio (HR) (fulvestrant 500 mg: anastrozole 1 mg), associated confidence interval (CI) and p-value. A HR less than 1 would indicate that, on average, PFS is improved on fulvestrant 500 mg when compared with anastrozole 1 mg. Secondary analyses will examine OS, ORR, CBR, DoR, EDoR, DoCB, EDoCB, and patient-reported outcomes by use of FACT-B and EQ-5D questionnaires. Analysis of OS will be done using the stratified log-rank test, similarly to the analysis of PFS. ORR and CBR will be analysed using a logistic regression model and examination of the odds ratio of the 2 treatment groups. EDoR and EDoCB will be estimated using the methodology described by Ellis et al 2008. For the health-related QoL endpoints (FACT-B total score and TOI), a time to deterioration analysis will be performed. EQ-5D will be summarised only.

A multiple-testing procedure with an alpha-exhausting recycling strategy (Burman et al 2009) will be used in order to control strongly the Type I error at the 2-sided 5% significance level for the primary and key secondary endpoints.

AEs will be summarised by preferred term and system organ class (using the Medical Dictionary for Regulatory Activities [MedDRA]). Summaries of AEs by causality and CTC grade will also be presented. Fisher's exact test will be used in order to compare the incidence of pre-defined AEs of interest (joint disorders and back pain) between the two treatment groups. All other safety variables will also be summarised.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
AI	Aromatase inhibitor
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCS	Breast Cancer Subscale
CBR	Clinical Benefit Rate
CI	Confidence Interval
CONFIRM	Comparison of FASLODEX in Recurrent or Metastatic Breast Cancer (Study D6997C00002)
CR	Complete Response
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria (National Institutes of Health, National Cancer Institute)
CTCAE	Common Terminology Criteria for Adverse Event
DoCB	Duration of Clinical Benefit
DoR	Duration of Response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDoCB	Expected Duration of Clinical Benefit
EDoR	Expected Duration of Response
ER	Oestrogen receptor
EU	European Union
EWB	Emotional well-being
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-G	Functional Assessment of Cancer Therapy – General

Abbreviation or special term	Explanation
FALCON	Fulvestrant and anastrozole compared in hormonal therapy naïve advanced breast cancer (Study D699BC00001)
FIRST	Fulvestrant first-line Study comparing endocrine Treatments (Study D6995C00006)
FISH	Fluorescence in situ hybridisation
FWB	Functional Well-being
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard ratio
HRQoL	Health-related Quality of Life
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
INR	International Normalised Ratio
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.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention to Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MedID	Medication Identification (known as KitID in IVRS)
MRI	Magnetic Resonance Imaging
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NTL	Non-target Lesion

Abbreviation or special term	Explanation
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease
PET	Paraffin-embedded tissue
PFS	Progression-free Survival
PgR	Progesterone Receptor
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	Principal Investigator
PR	Partial Response
PRO	Patient Reported Outcome
PWB	Physical Well-being
QoL	Quality of Life
RECIST 1.1	Response Evaluation Criteria In Solid Tumours, Version 1.1
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical analysis plan
SD	Stable Disease
SERM	Selective oestrogen receptor modulator
SWB	Social well-being
TL	Target lesion
TOI	Trial Outcome Index
TTP	Time to Progression
ULRR	Upper limit of reference range
USA	United States of America
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

Investigators should be familiar with the current fulvestrant (ZD9238) Investigator's Brochure (IB).

1.1 Background

Breast cancer is a common disease with significant morbidity and mortality. Approximately 30% of women diagnosed with breast cancer die of the disease. Tumours that show oestrogen and/or progesterone receptors (ER or PgR) (hormone receptor positive disease) are suitable for hormonal therapy, which is generally less toxic than chemotherapy. Interventions are possible at all stages of the disease: prevention in women with high risk, therapy adjuvant to surgery, and first and subsequent lines of therapy for advanced disease. Early breast cancer is potentially curable (by surgery often combined with adjuvant therapy), while advanced disease is beyond the scope of curative surgery and is generally fatal.

Unmet needs for patients with advanced disease include higher response rates, prolonged duration of disease control, relief of symptoms, improvement in quality of life (QoL) and minimal toxicity associated with treatment. Over the past decade, the standard of care for hormone-receptor positive breast cancer has changed, with aromatase inhibitors (AIs) largely replacing anti-oestrogens (selective oestrogen receptor modulators [SERMs]) for adjuvant therapy. Sequential hormonal therapies are subsequently used in the advanced disease setting, progressing from non-steroidal AIs such as anastrozole (ARIMIDEX™) or letrozole (FEMARA®, Novartis Pharmaceuticals Corporation), to steroidal AIs such as exemestane (AROMASIN®, Pfizer Ltd) and then to fulvestrant (FASLODEX™)[1].

Fulvestrant is an oestrogen receptor antagonist with no known agonist activity, administered as a monthly intramuscular injection of a depot formulation. It binds the ER, renders it transcriptionally inactive and, because the fulvestrant-receptor complex is unstable, results in accelerated degradation of the receptor protein. Fulvestrant's pre-clinical and clinical characteristics are generally well established.

Studies in which the fulvestrant 250 mg dose regimen was compared to AIs or other SERMs in patients with hormone-receptor positive advanced breast cancer, have shown generally comparable results in terms of progression-free survival (PFS)/time to progression (TTP) and overall survival (OS) (Howell et al 2002, Howell et al 2004, Osborne et al 2002, Chia et al 2008). These studies were either in patients who had not previously received hormonal therapy for advanced disease, or in patients progressing after prior hormonal therapy.

The CONFIRM study (Study D6997C00002) was a randomised, double-blind, Phase III study to compare 2 dose levels of fulvestrant (500 mg versus 250 mg) in postmenopausal women with ER-positive (ER +ve) advanced breast cancer who had either relapsed whilst on adjuvant

[1] FASLODEX™ and ARIMIDEX™ are trademarks of the AstraZeneca group of companies.

endocrine therapy, or progressed whilst on first-line endocrine therapy for advanced disease (Di Leo et al 2010). The observation that the fulvestrant 500 mg dose regimen showed an efficacy advantage over the 250 mg dose regimen in this potentially less responsive patient population is encouraging for the effectiveness of the higher dose in hormonal therapy-naïve patients.

Further evidence that the fulvestrant 500 mg dose regimen may provide a clinical advantage over AIs was provided by the FIRST study (Study D6995C00006). This was a Phase II, randomised, open-label study of fulvestrant 500 mg versus anastrozole 1 mg in 205 women with advanced disease previously untreated with hormonal therapy or at least a year after completing adjuvant therapy. There were 2 time points for analysis of data from the FIRST study: a primary analysis (6 months after the last patient was randomly assigned) and a follow-up analysis (when approximately 69% of patients had progressed). Investigator assessment of radiographic scans was used for the main efficacy analyses.

At the time of the primary analysis, the primary response variable, clinical benefit rate (CBR), showed a numerical advantage for fulvestrant over anastrozole (72.5% versus 67.0%), but did not reach statistical significance (odds ratio=1.302; 95% confidence interval [CI]=0.717, 2.380; p=0.386). Despite the immaturity of the data at the primary analysis, TTP was significantly longer for fulvestrant versus anastrozole (hazard ratio [HR]=0.63; 95% CI=0.39, 1.00; p=0.0496; median TTP not reached for fulvestrant versus 12.5 months for anastrozole) (Robertson et al 2009). A post-hoc analysis of TTP using blinded independent review also showed a numerical benefit for fulvestrant over anastrozole (HR=0.79; 95% CI=0.45, 1.36).

A further assessment of TTP was performed at the follow-up analysis. The TTP endpoint of the FIRST follow-up analysis was composed of progression events confirmed via Response Evaluation Criteria in Solid Tumours (RECIST) assessment (for patients who progressed prior to the primary trial data cut-off) and progressive disease (PD) in the Investigator's opinion (for patients who progressed after the primary trial data cut-off). For patients who did not progress prior to the data cut-off for the primary analysis, TTP in the follow-up phase was calculated as the time from randomisation to progression, as per Investigator opinion. A statistically significant difference in favour of fulvestrant was seen corresponding to a 35% reduction in risk of progression (HR=0.66; 95% CI =0.47, 0.92; p=0.01), with median TTP being 10.3 months longer for fulvestrant than for anastrozole (23.4 versus 13.1 months, respectively) (Robertson et al 2010).

1.2 Research hypothesis

The hypothesis to be tested for the primary objective is that the efficacy of fulvestrant 500 mg is superior to that of anastrozole 1 mg by assessment of PFS.

1.3 Rationale for conducting this study

Data from the Phase II open-label study, FIRST, suggest an efficacy benefit for fulvestrant 500 mg compared with anastrozole as first-line endocrine therapy for patients with

hormone receptor-positive metastatic and/or locally advanced breast cancer (Robertson et al 2009, Robertson et al 2010).

This Phase III study (FALCON) is therefore intended to extend and confirm the clinical benefit of fulvestrant 500 mg compared with anastrozole 1 mg in approximately 450 postmenopausal women through the evaluation of the hypothesis that fulvestrant 500 mg per month will prove superior to anastrozole by the assessment of PFS. The proposed patient population (patients with advanced disease who have not received any previous hormonal therapy) reflects the majority (75%) of patients who were studied in FIRST.

1.4 Benefit/risk and ethical assessment

Fulvestrant at the original dose of 250 mg, has received marketing approval in all 72 countries where submitted for the treatment of postmenopausal women with ER +ve locally advanced or metastatic breast cancer whose breast cancer recurred or progressed on previous endocrine therapy. Fulvestrant, at a monthly dose of 250 mg, was well tolerated in clinical studies and the safety profile has been confirmed by analysis of post-marketing pharmacovigilance data. The CONFIRM study has since demonstrated that the fulvestrant 500 mg dose regimen has a clear clinically meaningful benefit over the fulvestrant 250 mg dose regimen, with a statistically significant prolongation of PFS and a 20% reduction in the risk of progressing for patients receiving the higher dose. A pooled analysis of safety data has shown that the risks associated with fulvestrant 500 mg are generally similar to those of fulvestrant 250 mg. Injection site reaction and hypersensitivity (predominantly pruritus) are the only adverse drug reactions for which there is evidence of an increased risk for fulvestrant 500 mg compared with fulvestrant 250 mg. This is consistent with the increased number of injections required for the fulvestrant 500 mg dose regimen compared to fulvestrant 250 mg.

In November 2009 variations were submitted in the European Union (EU), United States of America (USA) and Canada to update the recommended dose of fulvestrant, with 250 mg being replaced by 500 mg. In March 2010 the fulvestrant 500 mg dose was approved in the EU and approvals soon followed in Canada and the USA. The fulvestrant 500 mg dose is now approved in more than 60 markets worldwide. Fulvestrant was first approved as a new chemical entity in Japan in September 2011 at the 500 mg dose. Further worldwide submissions for the fulvestrant 500 mg dose are either ongoing or planned.

The safety profiles of fulvestrant and of anastrozole are well established. The very common adverse reactions associated with fulvestrant 500 mg are nausea, elevated liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatise [ALP]), asthenia and injection site reactions, while common reactions are urinary tract infections, hypersensitivity reactions, anorexia, headache, hot flushes, elevated bilirubin, vomiting, diarrhoea, and rash. For anastrozole, very common adverse reactions include rash, headache, hot flushes, nausea, arthralgia, joint stiffness, arthritis and asthenia, while common adverse reactions are anorexia, hypercholesterolaemia, somnolence, carpal tunnel syndrome, diarrhoea, vomiting, increases in ALP, ALT and AST, bone pain, myalgia, hair thinning, allergic reactions, vaginal dryness and vaginal bleeding. As anastrozole lowers circulating

oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture.

No significant differences were observed between the two treatment arms in the FIRST study for any of the individual pre-specified adverse events (AEs; endometrial dysplasia, gastrointestinal disturbances, hot flushes, ischaemia cardiovascular disorders, joint disorders, osteoporosis, thrombolic events, urinary tract infections, vaginitis and weight gain). A higher number of events describing joint disorders were observed in the fulvestrant 500 mg arm and although this difference was not statistically significant, these events are known to be associated with anastrozole and will be further investigated in the present study.

The improved efficacy, and similar safety, tolerability and health-related QoL (HRQoL) that fulvestrant 500 mg offers compared with fulvestrant 250 mg, indicate that there is an improved benefit-risk profile for fulvestrant 500 mg in postmenopausal women with advanced breast cancer who have recurred or progressed after previous endocrine therapy. Furthermore, the improvement for fulvestrant 500 mg compared with 250 mg was seen in all patient subgroups analysed.

The FIRST study has provided evidence that a fulvestrant 500 mg dose regimen may provide a clinical advantage over AIs in women with advanced disease previously untreated with hormonal therapy for at least a year after completing adjuvant therapy. Follow-up analysis indicated a statistically significant prolongation of the TTP with a 34% reduction in the risk of progressing for patients receiving the higher 500 mg dose (Robertson et al 2010).

The clinical benefit of fulvestrant 500 mg has been established; the results of this study will confirm whether it has a greater clinical benefit than anastrozole 1 mg in terms of PFS in the defined patient population.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to demonstrate the superior PFS of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

2.2 Secondary objectives

The secondary objectives of this study are:

1. To compare the OS of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

2. To compare the objective response rate (ORR), duration of response (DoR), and the expected duration of response (EDoR) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

3. To compare the CBR, the duration of clinical benefit (DoCB) and the expected duration of clinical benefit (EDoCB) of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

4. To compare the QoL of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

5. To compare the safety and tolerability of fulvestrant 500 mg treatment versus that of anastrozole 1 mg treatment.

2.3 Exploratory objectives

The exploratory objective of the study is to explore how variations in tumour biomarkers (DNA, RNA and/or protein based) may be related to factors that may influence development of cancer and/or study treatment response and resistance.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a randomised, double-blind, double-dummy, international, multicentre study comparing the efficacy and tolerability of fulvestrant (500 mg) with anastrozole (1 mg) in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer (confirmed by histology), who have not previously been treated with any hormonal therapy.

Patients will be assessed for eligibility for the study based on local laboratory results for hormone receptor status.

Approximately 450 women will be randomised 1:1 (fulvestrant: anastrozole). Patients will be stratified at randomisation based on whether (1) they have locally advanced or metastatic breast cancer (2) they have received prior chemotherapy for locally advanced or metastatic breast cancer or not and (3) they have measurable or non-measurable disease. To maintain blinding, patients randomised to fulvestrant will also receive placebo tablets to match anastrozole and patients randomised to anastrozole will also receive placebo injections to match fulvestrant. Patients will start study treatment on the day of randomisation (Day 0 [Visit 2]).

Study visits will occur at screening (Day -28 to -1), randomisation (Day 0), Day 14, Weeks 4, 8, 12, 16, 20, 24 and every 12 weeks thereafter (Table 1) until progression. Up to the data cut-off for the primary analysis, all randomised patients will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) every 12 weeks relative to the date of randomisation, until documented evidence of objective disease progression (regardless of

whether on study treatment or not). Patients with evidence of metastatic bone lesions at baseline must also have a bone scan/skeletal x-ray survey every 12 weeks.

Progression-free survival (PFS) will be determined based on tumour assessments performed locally by each investigator according to RECIST 1.1 (see Appendix D). Where surgery or radiotherapy is performed to manage worsening of disease, this will be captured as a progression event and documented in the electronic case report form (eCRF); these patients will continue to receive study medication and be scanned until imaging criteria for objective disease progression are met. To ensure comparability, identical imaging techniques must be used for the assessment of response at baseline and throughout the study. The single exception to this is where problems with global supplies of technetium-99m for bone scans may necessitate a switch to an alternative modality on prior discussion/agreement with the IQVIA Study Physician.

Treatment will continue until objective disease progression (see Section 6.3.3) unless any of the criteria for treatment discontinuation are met first (see Section 5.8). Upon discontinuation of study treatment or objective disease progression, patients will enter the survival follow-up phase. In addition, if surgery or radiotherapy is performed to manage worsening of disease this will be captured as a progression event. In order to facilitate decisions on subsequent treatment options, investigators may request to be unblinded to treatment allocation, once randomised treatment has been discontinued, and objective disease progression has been formally documented in the eCRF.

The primary analysis will be performed when approximately 306 progression events (see Section 6.3.3) have occurred. After the data cut-off for the primary analysis, all the remaining patients, regardless of whether they are still receiving randomised treatment, will enter the survival follow-up phase.

In the survival follow-up phase, study visits will be conducted in order to complete HRQoL assessments (at 3-monthly intervals prior to objective disease progression, at the treatment discontinuation visit, at 3-months post-progression, and thereafter at 6-monthly intervals post-progression until the data cut-off for the OS analysis), administer/dispense study medication (for patients still receiving randomised treatment), and to determine survival status. Further collection of data on objective disease progression will stop after the data cut-off for the primary analysis (ie, 12-weekly CT/MRI scans will no longer be recorded in the eCRF). During the survival phase of the study, patients will otherwise be managed according to standard clinical practice. Patients who enter the survival follow-up phase while still receiving randomised treatment may continue to receive treatment for as long as they receive clinical benefit (until criteria for discontinuation are met). Following confirmation of objective disease progression, follow-up may be conducted by telephone, and HRQoL questionnaires may be posted to patients for completion, if appropriate.

A survival analysis will be performed at the same time as the primary analysis and again when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled. After this point, data collection will cease for this study, the study database will close and the patient's treatment will be unblinded.

Patients are permitted to continue to receive open-label study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with fulvestrant or anastrozole and cannot access appropriate treatment outside of the clinical study protocol. Placebo treatment will be discontinued at this point.

After final database lock AstraZeneca will continue to supply fulvestrant and anastrozole as a continued access phase while the patient is benefiting, in the opinion of the investigator, but if the product development reaches a point where alternative options of supply become available these will be discussed with the investigator. Where an alternative supply route is determined to be the better option, including commercial products available in some regions, AstraZeneca will work with the investigator to transition patients to this alternative supply.

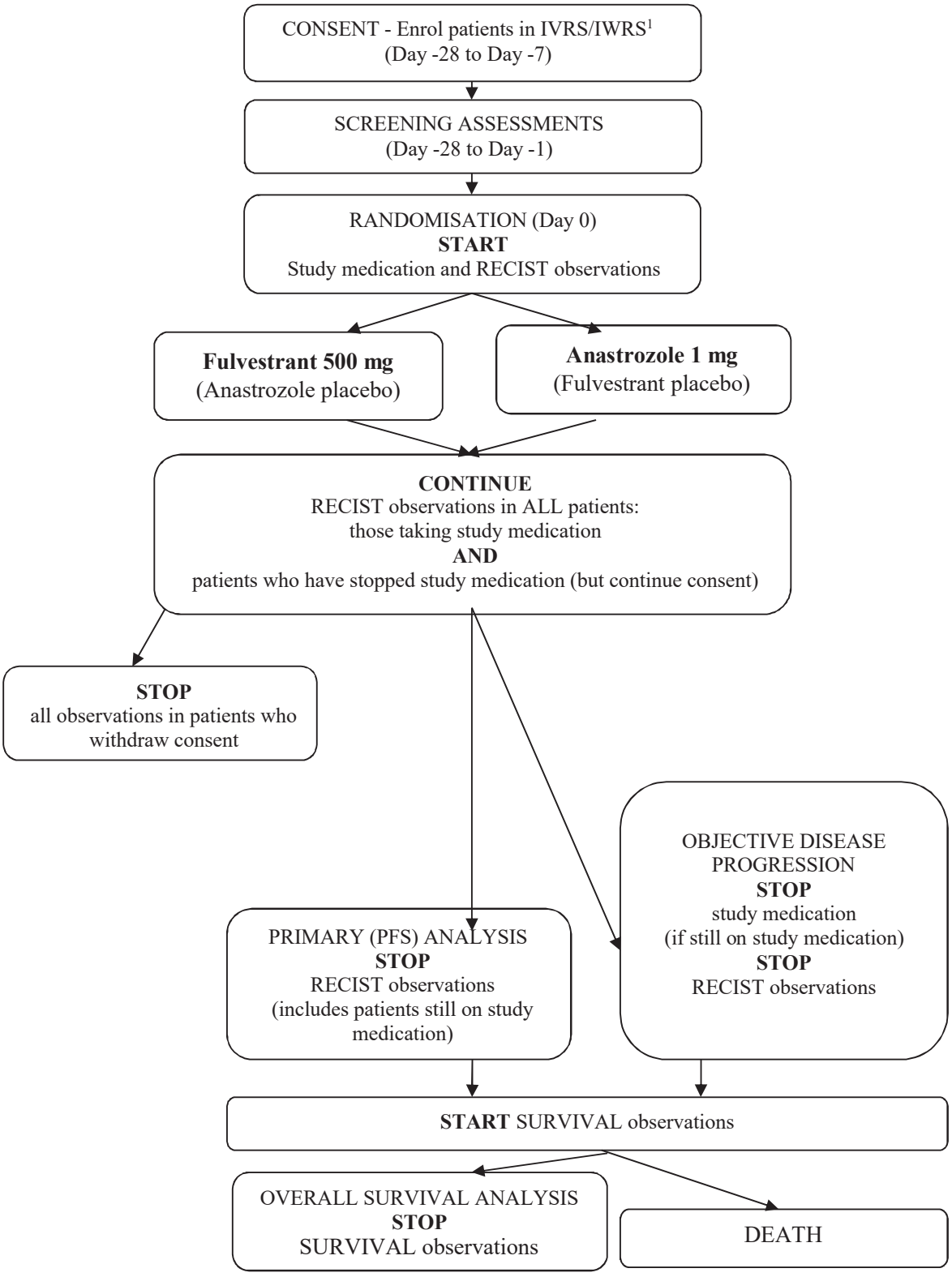
Safety will be monitored based on the frequency and severity of AEs, as assessed by Common Terminology Criteria (CTC) grade version 4.0, laboratory assessments, ECGs, physical examination (including World Health Organization [WHO] performance status) and vital signs (including blood pressure and heart rate).

An optional part of the study is the collection of archival and/or recent tumour samples (paraffin-embedded tissue [PET] block) if available, from either the primary tumour or a metastatic site for the purposes of biomarker analysis. In addition, patients who consent to participate in this biomarker research will also be asked if they are willing to provide a further optional tumour sample at progression, if, in the opinion of the investigator, the biopsy procedure does not pose additional significant risks to the patient. If a tumour sample is already available at the time of progression a further sample is not required. The main aim of this research is to identify patients most likely to benefit from fulvestrant (versus AIs), to explain non-responders and to study the changes associated with the development of resistance to these agents. Patients who do not consent to exploratory research on tumour samples may participate in all other aspects of the study. Details of the biomarker research are provided in Appendix H.

Approximately 180 to 220 international centres are planned in Asia, Europe, North America, South America and South Africa. It is expected that each centre will recruit between 2 to 20 patients over approximately a 27-month recruitment period.

The study flow chart is shown in Figure 1. The Study Plan for the primary analysis is presented in Table 1, and the Study Plan for the survival follow-up phase is presented in Table 2.

Figure 1 Study flow chart



[1]IVRS/IWRS = Interactive Voice Response System/Interactive Web Response System

Table 1 Study plan (for primary analysis)

Study plan	**Refer to Section:**	**Screening Phase**	**Treatment Phase**									**Treatment Discon-tinuation**
Visit number		**1**	**2 (Random -isation)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 onwards (every 12 weeks until progression)**	**99 (within 35 days of last injection)**
Visit window (days)				**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Week(s)		**-4 to 0 (Day -28 to -1)**	**0 (Day 0)**	**2 (Day 14)**	**4**	**8**	**12**	**16**	**20**	**24**	**36 and onwards**	
Informed consent	4.1, 5.2.1, 8.4	X										
Medical/surgical history	6.2.1	X										
Demography	6.2.1	X										
Inclusion/exclusion criteria	4	X	X									
Tumour characteristics	6.2.1	X										
Concomitant therapy	5.6, 6.2.1	X	X	X	X	X	X	X	X	X	X	X[a]
Electrocardiogram (ECG)	6.2.1, 6.4.7	X					X			X	X	X
Physical examination (including WHO Performance Status)	6.2.1, 6.4.6 Appendix F	X										
Vital signs	6.4.8		X		X	X	X	X	X	X	X	X
Height (Visit 2 only) and weight	6.4.6		X		X	X	X	X	X	X	X	X
Haematology/ clinical chemistry	6.2.1, 6.4.5, Table 3	X					X			X	X	X

Table 1 Study plan (for primary analysis)

Study plan	**Refer to Section:**	**Screening Phase**	**Treatment Phase**									**Treatment Discon-tinuation**
Visit number		**1**	**2 (Random -isation)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 onwards (every 12 weeks until progression)**	**99 (within 35 days of last injection)**
Visit window (days)				**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Week(s)		**-4 to 0 (Day -28 to -1)**	**0 (Day 0)**	**2 (Day 14)**	**4**	**8**	**12**	**16**	**20**	**24**	**36 and onwards**	
CT/MRI scan of the chest, abdomen and pelvis (RECIST 1.1)	6.2.1, 6.3.1, 6.3.3, Appendix D	X					X			X	X	X
Bone scan or skeletal x-ray survey[b] (RECIST 1.1)	6.2.1, 6.3.2, 6.3.3 Appendix D	X					X[b]			X[b]	X[b]	X[b]
Anastrozole (or matching placebo) dispensed	5.5		X				X			X	X	
Administration of fulvestrant (or matching placebo)	5.5.2		X	X	X	X	X	X	X	X	X Every 28 (±3) days after Visit 9	
Administration of anastrozole (or matching placebo)	5.5.2		←----------Continuous once daily dosing----------→									
Adverse events	6.2.1, 6.4	X	X	X	X	X	X	X	X	X	X	X[a]
Informed consent for tissue biomarker research	8.4.1	X										

Table 1 Study plan (for primary analysis)

Study plan	Refer to Section:	Screening Phase	Treatment Phase									Treatment Discon-tinuation
Visit number		**1**	**2 (Random -isation)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 onwards (every 12 weeks until progression)**	**99 (within 35 days of last injection)**
Visit window (days)				**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Week(s)		**-4 to 0 (Day -28 to -1)**	**0 (Day 0)**	**2 (Day 14)**	**4**	**8**	**12**	**16**	**20**	**24**	**36 and onwards**	
Optional tumour tissue sample for biomarker analysis (if available)	6.6.2, 7.2 Appendix H		X									X[C]
FACT-B questionnaire	6.5.1, 6.5.3 Appendix G		X				X			X	X	X
EQ-5D™ questionnaire	6.5.2, 6.5.3 Appendix G		X				X			X	X	X

a Details of AEs and concomitant therapy should be collected for up to 8 weeks after the last injection of fulvestrant (or matching placebo).

b Patients with metastatic bone lesions at baseline should have repeat bone scans or skeletal x-ray surveys every 12 weeks (±2 weeks) until progression (or until the data cut-off for the primary analysis, whichever occurs first). Patients who do not have metastatic bone lesions at baseline do not require follow-up bone scans or skeletal x-ray surveys unless a new lesion is suspected (clinically indicated).

c Only for consenting patients with disease progression who provided an optional tumour tissue sample at baseline, and for whom, in the opinion of the investigator, the biopsy procedure poses no additional significant risks.

Table 2 Study plan (survival follow-up phase)

Study plan	**Refer to Section:**	**PRIOR to Primary Analysis**	**AFTER Primary Analysis and Up To OS Analysis**			
		Patients have DISCONTINUED randomised treatment[a]	**Patients STILL ON randomised treatment**		**Patients have DISCONTINUED randomised treatment[a]**	
Weeks from last scheduled visit		**Every 12 weeks**	**Every 12 weeks**	**Treatment discontinuation**	**Week 12, 24, 48, 72 etc**	**Week 36, 60, 84 etc**
Visit number		**100, 101, 102 etc**	**200, 201, 202 etc**	**99 (within 35 days of last injection)**	**300, 301, 303, 305 etc**	**302, 304, 306 etc**
Visit window		**±2 weeks**	**±3 days**		**±2 weeks**	**±2 weeks**
CT/MRI scan of the chest, abdomen and pelvis (RECIST 1.1) until objective progression	6.3.1, 6.3.3 Appendix D	X				
Bone scan or skeletal x-ray survey[b] (RECIST 1.1) until objective progression (if indicated at baseline)	6.3.2, 6.3.3 Appendix D	X				
Serious adverse events (SAEs)	6.4.2, 6.4.4	X[c] (Up to 8 weeks after last injection only)	X	X	X[c,d] (Up to 8 weeks after last injection only)	
Concomitant therapy	5.6, 6.2.1	X[c] (Up to 8 weeks after last injection only)	X	X	X[c] (Up to 8 weeks after last injection only)	
Anastrozole (or matching placebo) dispensed	5.5		X			
Administration of fulvestrant (or matching placebo)	5.5.2		Every 28 (±3) days			

Table 2 Study plan (survival follow-up phase)

Study plan	Refer to Section:	PRIOR to Primary Analysis	AFTER Primary Analysis and Up To OS Analysis			
		Patients have DISCONTINUED randomised treatment[a]	Patients STILL ON randomised treatment		Patients have DISCONTINUED randomised treatment[a]	
Weeks from last scheduled visit		**Every 12 weeks**	**Every 12 weeks**	**Treatment discontinuation**	**Week 12, 24, 48, 72 etc**	**Week 36, 60, 84 etc**
Visit number		**100, 101, 102 etc**	**200, 201, 202 etc**	**99 (within 35 days of last injection)**	**300, 301, 303, 305 etc**	**302, 304, 306 etc**
Visit window		**±2 weeks**	**±3 days**		**±2 weeks**	**±2 weeks**
Administration of anastrozole (or matching placebo)	5.5.2		Continuous once daily dosing			
FACT-B questionnaire	6.5.1, 6.5.3, Appendix G	X[e]	X	X	X[e]	
EQ-5D™ questionnaire	6.5.2, 6.5.3, Appendix G	X[e]	X	X	X[e]	
Survival status	6.2.2.2	X	X	X	X	X
Best response to first subsequent breast cancer therapy and name, start and stop date of all subsequent breast cancer therapies	5.6	X	X		X	X

a Follow-up may be conducted by telephone, and FACT-B and EQ-5D questionnaires posted to patients for completion, if appropriate.
b Patients with metastatic bone lesions at baseline should have repeat bone scans or skeletal x-ray surveys every 12 weeks (±2 weeks) until progression (or until the data cut-off for the primary analysis, whichever occurs first). Patients who do not have metastatic bone lesions at baseline do not require follow-up bone scans or skeletal x-ray surveys unless a new lesion is suspected (clinically indicated).
c Details of SAEs and concomitant therapy should be collected for up to 8 weeks after the last injection of fulvestrant (or matching placebo).
d After the final analysis, SAEs are to be sent directly to AstraZeneca Patient Safety using a paper-based SAE report form, and for up until 8 weeks after the last injection of fulvestrant (or matching placebo).

e FACT-B and EQ-5D questionnaires should be administered at 3 months post objective disease progression, then at 6-monthly intervals.

3.2 Rationale for study design, doses and control groups

The population included in this study (ie, postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not been treated with any hormonal therapy and have received no more than one line of cytotoxic chemotherapy) reflects the majority (75%) of patients who participated in the FIRST study (Robertson et al 2009, Robertson et al 2010).

The randomised, double-blind design has been adopted to enable a robust comparison of the treatment groups. The double-blind, double-dummy administration of study medication has been selected to ensure rigorous comparison of the treatment effects in each arm that will include patient-reported outcomes. The comparator is anastrozole 1 mg, taken once daily.

The primary response variable, PFS, has been selected as it provides an objective measure of efficacy based on tumour size and is an established surrogate for clinical benefit. The secondary response variables of OS, ORR, CBR, DoR and DoCB are established variables in the assessment of cancer drugs. The variables eDoR and eDoCB represent a new and useful methodology that assesses data for all randomised patients for eDoCB, and all evaluable patients for eDoR, rather than just the data for responders. The collection of safety and tolerability data will allow the safety profiles of the 2 randomised treatments to be compared. HRQoL assessments provide a valuable source of additional information useful to both clinician and patient when making treatment decisions and the collection of best response to subsequent therapies will allow the outcome of subsequent therapies to be compared for each treatment group.

The dose regimens selected for this study are guided by the results of previous clinical trials, especially CONFIRM (Di Leo et al 2010) and FIRST.

The use of local, investigator review of scans to assess tumour response, rather than an independent central review, is consistent with the findings of a literature review of trials that used blinded independent central review, in which treatment efficacy was consistently estimated between local and central review despite relatively high discrepancy rates (Dodd et al 2008). The position is also consistent with the recommendations of the Pharmaceutical Research and Manufacturers of America (PhRMA)-sponsored PFS Independent Working Group (Amit et al 2011). It is not considered necessary to have an independent central review of CT/MRI scans in this study as it is considered to be sufficiently large, and adequately blinded, up to the point of objective disease progression, and the safety profiles of both hormonal agents at these doses are well established and similar. There is no expectation that toxicities during this study will inadvertently unblind the study.

To be eligible for this study, patients must have breast cancer that is ER/PgR positive and human epidermal growth factor receptor 2 (HER2) negative. Tumour samples will be analysed by local laboratories identified by principal investigators. Hormone and HER2 receptor status are standard and well recognised investigations. They are well established as predictive tests for appropriate tumour therapy and will be carried out in this trial by local laboratories.

4. PATIENT SELECTION CRITERIA

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

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

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

2. Histological confirmation of breast cancer.

3. Positive hormone receptor status (ER +ve and/or PgR +ve) of primary or metastatic tumour tissue based on local laboratory assessment.

4. Have EITHER

   – locally advanced disease not amenable to surgery or radiotherapy of curative intent. Patients may have had one line of cytotoxic chemotherapy, following which they must remain unsuitable for therapy of curative intent.

   OR

   – metastatic disease

   Patients may have received one line of cytotoxic chemotherapy as previous treatment of breast cancer but must show progressive disease prior to enrolment.

5. At least 1 lesion (measurable and/or non-measurable) that can be accurately assessed at baseline and is suitable for repeated assessment by CT, MRI or plain x-ray.

6. Postmenopausal woman, defined as a woman fulfilling any 1 of the following criteria (based on the NCCN definition of menopause [National Comprehensive Cancer Network 2008]):

   – Prior bilateral oophorectomy

   – Age ≥60 years

  - Age <60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle stimulating hormone and oestradiol in the postmenopausal range.

7. WHO performance status 0, 1 or 2.

For inclusion in the optional biomarker research component of this study, patients should fulfil the following criterion:

- Provision of informed consent for biomarker research.

If a patient declines to participate in the biomarker research, 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 to the main protocol.

4.2 Exclusion criteria

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

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 significantly compromised as a result of disease in the opinion of the investigator.

2. Prior systemic therapy for breast cancer other than one line of cytotoxic chemotherapy (the last dose of chemotherapy must have been received more than 28 days prior to randomisation).

3. Radiation therapy if not completed within 28 days prior to randomisation (with the exception of radiotherapy given for control of bone pain, which must be completed prior to the day of randomisation, see Section 5.6).

4. Herceptin-eligible (HER2 overexpression or gene amplification, ie, immunohistochemistry (IHC)3+ve or fluorescence in situ hybridisation (FISH)+ve, where appropriate).

5. Prior treatment with a non-approved or experimental drug for breast cancer.

6. Concomitant anticancer treatment (with the exception of bisphosphonates/denosumab, see Section 5.6).

7. Prior hormonal treatment for breast cancer.

8. Use of systemic oestrogen-containing hormone replacement therapy within the 6 months prior to randomisation.

9. Current or prior malignancy (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix) unless curatively treated with no evidence of disease within previous 5 years.

10. Any of the following laboratory values within 4 weeks of randomisation:

    – Platelets <100 × 109/L

    – Total bilirubin >1.5 × upper limit of reference range (ULRR) (Patients with confirmed Gilbert's syndrome may be included in the study)

    – ALT or AST >2.5 × ULRR if no demonstrable liver metastases or >5 × ULRR in presence of liver metastases.

11. History of:

    – bleeding diathesis (ie, disseminated intravascular coagulation, clotting factor deficiency) or

    – long-term anticoagulant therapy (although patients treated with anti-platelet therapy and low dose warfarin or other anticoagulant agents such as acenocoumarol are eligible providing they have an international normalised ratio [INR] of ≤1.6).

12. History of hypersensitivity to active or inactive excipients of FASLODEX™ or ARIMIDEX™ or castor oil.

13. Any severe concomitant condition which makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the study protocol, eg, uncontrolled cardiac disease or uncontrolled diabetes mellitus.

14. Previous randomisation in the present study.

15. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, its agents, and/or staff at the study site).

16. Participation in a clinical study and/or receipt of any investigational drug within 28 days prior to randomisation (participation in the survival follow-up period of a study is not an exclusion).

For procedures for withdrawal of incorrectly enrolled patients, see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

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

- Concomitant treatments listed in Section 5.6.

5.2 Patient enrolment and randomisation and initiation of investigational product

5.2.1 Procedures for enrolment

Patients will be assessed to ensure that they meet the eligibility criteria before being entered into the study (see Sections 4.1 and 4.2).

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. A separate informed consent must be obtained for patients who agree to participate in the optional biomarker research component of the study.

Informed consent and enrolment using the centralised Integrated Voice/Web Response System (IVRS/IWRS) must occur no more than 28 days before randomisation (ie, Day -28) and no later than on Day -7 (in order to ensure availability of study drug at site by Day 0).

The Principal Investigator (PI) or delegate will contact the IVRS/IWRS by telephone or using the web to register the patient when she is entered into the study, and will record a unique enrolment code (E-code) assigned to the patient by IVRS/IWRS in the patient medical records. The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (eg, the first patient screened at number 0001 would be assigned the E-code E0001001). This number is the patient's unique identifier and is used to identify the patient on the eCRF.

All screened patients are assigned an E-code and will be listed on the patient enrolment and identification log irrespective of whether or not they are subsequently randomised. If the patient is not randomised the IVRS/IWRS should be contacted to allow the termination of the patient in the system. If a patient withdraws from participation in the study, the patient E-code will not be reused.

5.2.2 Procedures for randomisation

Study treatment cannot be allocated until 7 days after the first patient at the site is registered in IVRS/IWRS. Patients will start study treatment on the day of randomisation (Day 0 [Visit 2]).

The biostatistics group within AstraZeneca or its representative is responsible for generating the randomisation scheme. The randomisation scheme will be produced by a computer software program that incorporates a standard procedure for generating random numbers. Patients will be stratified at randomisation based on whether (1) they have locally advanced or

metastatic breast cancer (2) whether they have received prior chemotherapy for locally advanced or metastatic breast cancer or not and (3) they have measurable or non-measurable disease.

Patient eligibility must be established before the patient is randomised through the IVRS/IWRS and drug is dispensed. Patients will be randomised strictly sequentially, as patients are eligible for randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the centralised IVRS/IWRS by telephone or using the web for the treatment allocation and dispensing of blinded treatment. Patients will be identified to the centralised IVRS/IWRS using patient E-code and date of birth (where local regulations allow collection of full date of birth).

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

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

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the Investigator should inform the IQVIA Study Physician immediately. The IQVIA Study Physician is to ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Study drug will be labelled using a unique Medication Identification (MedID) number, which is linked to the randomisation scheme. The active study drug and placebo for fulvestrant (pre-filled syringes) and anastrozole (tablets) will be identical and presented in the same packaging to ensure blinding of the study drug.

5.4.2 Methods for unblinding the study

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

The treatment code must not be broken unless requested by the Investigator once objective disease progression has been fully documented in the eCRF. The treatment code may also be broken in cases of unacceptable toxicity to the study treatment or in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The blind may also be broken if a patient withdraws consent and the appropriate management of the patient requires knowledge of the treatment randomisation. In this case, all data for the patient must be fully documented in the eCRF before the blind is broken.

When unblinding due to a medical emergency, the Investigator must document and report the action to AstraZeneca or its delegate, without revealing the treatment allocation.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product (IP) and that potentially require expedited reporting to regulatory authorities.

5.5 Treatments

5.5.1 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
Fulvestrant	2 × 250 mg/5 mL solution for intramuscular injection; 500 mg fulvestrant	AstraZeneca
Placebo to match fulvestrant	2 × 5 mL solution for intramuscular injection, 0 mg fulvestrant	AstraZeneca
Anastrozole	Tablet, 1 mg anastrozole	AstraZeneca
Placebo to match anastrozole	Tablet, 0 mg anastrozole	AstraZeneca

AstraZeneca Pharmaceuticals Investigational Products will pack, label, and supply the IP for this study via IVRS/IWRS. In the post-OS analysis phase (see Section 12.2.1), the IP will be supplied to sites manually outside of the IVRS/IWRS system. During the post-final OS analysis phase, drug dispensation and reconciliation will be handled by each site on each patient's visit.

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. Matching placebo will be supplied as a castor oil-based solution in clear neutral glass pre-filled syringes. Each syringe will contain 5 mL. Fulvestrant (and matching placebo) will be packed into cartons containing 2 syringes. Two syringes must be administered to receive the 500 mg dose regimen.

Anastrozole tablets (or placebo to match) will be supplied as film-coated tablets containing 1 mg of active substance. Tablets will be packed into bottles, each containing 112 tablets (3 months' supply).

Following the final survival analysis, patients are permitted to continue to receive open-label study treatment beyond the closure of the database as a continued access phase if, in the opinion of the investigator, they are continuing to receive benefit from treatment with fulvestrant or anastrozole, and cannot access appropriate treatment outside of the clinical study protocol. Placebo treatment will be discontinued at this point. During this period (ie, after the final OS analysis), there will be no further survival follow-up for the patient. If the product development reaches a point where alternative options of supply become available these will be discussed with the investigator. Where an alternative supply route is determined to be the better option, including commercial products available in some regions, AstraZeneca will work with the investigator to transition patients to this alternative supply.

5.5.2 Doses and treatment regimens

In order to support the double-blind, double-dummy design of this trial, each patient will receive both study treatments, one being placebo:

- Patients randomised to receive fulvestrant will also receive placebo to match the anastrozole schedule (tablets, once daily)

- Patients randomised to receive anastrozole will also receive placebo to match the fulvestrant schedule (injections on Days 0, 14 (±3), 28 (±3) and every 28 [±3] days thereafter).

Fulvestrant

Fulvestrant 500 mg (or matching placebo) will be administered as two 5 mL intramuscular injections, one in each buttock, at each visit on Days 0, 14 (±3), 28 (±3) and every 28 (±3) days thereafter until the patient permanently discontinues the treatment (refer to Section 5.8 for more details on discontinuation).

Each injection will be administered into the gluteus maximus muscle using an aseptic parenteral technique, and must be administered slowly over approximately 1 to 2 minutes. Following administration, the injection sites 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. Any severe local site reaction should be treated with appropriate medical intervention.

Dose reductions are not permitted.

For patients on warfarin or other anticoagulant agents such as acenocoumarol, refer to the precautions described in Section 5.6.

Anastrozole

Anastrozole (or matching placebo) will be taken orally as a single daily tablet at a dose of 1 mg/day from randomisation on Day 0 until the patient permanently discontinues the treatment (refer to Section 5.8 for more details on discontinuation). Anastrozole (or placebo to match) should be taken at the same time each day, swallowed whole with a drink of water. There are no food restrictions for the administration of anastrozole.

5.5.3 Labelling

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

The label will include at least the following information: study code, randomisation number, storage conditions and any other market specific requirements.

For fulvestrant packs, 2 labelled prefilled syringes will be packed into a single-dose carton.

For anastrozole packs, one labelled bottle containing 112 tablets (3 months' dosing) will be supplied.

All packs will be labelled and blinded according to the randomisation scheme.

5.5.4 Storage

All study drugs should be kept in a secure place. Fulvestrant must be stored in a refrigerator (2°C to 8°C) in the original packaging, to protect from light. Anastrozole must be stored below 30°C.

5.6 Concomitant and post-study treatment(s)

All prior treatments for cancer and all drugs given to, or taken by, the patient at entry, during the study and up to 8 weeks after the last injection of fulvestrant (or matching placebo) must be clearly documented on the appropriate eCRF page.

The following treatment restrictions apply:

- Patients who have received any prior systemic therapy for breast cancer other than one line of cytotoxic chemotherapy are ineligible for the study. The last dose of prior cytotoxic therapy must have been received more than 28 days prior to randomisation.

- No other non-approved or investigational agents for breast cancer are allowed concomitantly with study medication. In addition, given the relatively long elimination terminal half-life of fulvestrant, no investigational agent should be given concomitantly with study medication, or within 8 weeks of final administration of study medication to avoid any potential unknown drug-drug interactions.

- Radiotherapy given for control of bone pain must be completed prior to the day of randomisation.

- Patients requiring radiotherapy or surgery for breast cancer to manage worsening of disease after randomisation will be considered to have progressed. If radiation or surgery is performed for breast cancer for reasons other than objective disease progression, the patient will continue to receive study medication and be followed for objective disease progression.

- Bisphosphonate/denosumab therapy for the prevention of skeletal related events in patients with bone metastases must be started prior to randomisation.

- The use of herbal or traditional remedies should be discouraged while patients are on study treatment.

- Patients must not receive any other concurrent anticancer therapy, including investigational agents, while on study treatment (with the exception of bisphosphonate/denosumab therapy for the prevention of skeletal related events started prior to randomisation) (see Section 4.2, Exclusion Criterion 6).

- Sex hormone containing drugs such as hormone replacement therapy, progestational agents (megestrol acetate), dehydroepiandrosterone, other androgens (eg, oxandrolone) and SERMs (eg, raloxifene [Evista®]) are not permitted during the study. In cases where patients suffer severe menopausal symptoms, management with non-hormonal agents, eg, clonidine or venlafaxine, is recommended. In cases of atrophic vaginitis the use of non-hormonal vaginal moisturising or lubricating gels or creams is recommended. Use of oestrogen-containing vaginal creams or other topical preparations is not allowed on the study, but use of controlled-release vaginal rings (eg, Estring®) may be considered at the Investigator's discretion in severe cases or where all the other treatment possibilities have been exhausted and bearing in mind current advice on their use in combination with AIs.

- 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 into 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. Hormone antagonists and related agents (eg, soy isoflavones) are not allowed.

The following treatment restrictions relating to anti-coagulant therapy apply:

- Patients receiving long-term anti-coagulant therapy with warfarin or other anticoagulant agents such as acenocoumarol are ineligible for the study unless they are receiving a low dose and have an INR ≤1.6. The INR should be checked to ensure that it is ≤1.6 prior to each injection of fulvestrant (or matching placebo). If the INR is >1.6, the injections of fulvestrant (or matching placebo) 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 to 24 hours prior to each injection of fulvestrant (or matching placebo) and then resumed 12 to 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 or other anticoagulant agents such as acenocoumarol are required instead of LMWH, it should be recognised that the risk of intramuscular haemorrhage may be increased. In this situation, the dose of anticoagulant should be chosen according to the condition being treated and the INR should be monitored. The INR should be checked prior to each injection of fulvestrant (or matching placebo) and the injections should 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 (acetylsalicylic acid, ticlopidine, clopidogrel, 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 wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

COVID-19 vaccination with authorised vaccines is permitted at the discretion of the investigator.

Details of all subsequent breast cancer therapies received from the time of objective disease progression on randomised treatment, up to the date of data cut-off for the final OS analysis (when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled) must be collected (see Section 6.2.2.2).

5.7 Treatment compliance

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

Patients should be given clear instruction on how and when to take anastrozole or matching placebo tablets. Patients will be asked to return all unused and empty bottles containing anastrozole or matching placebo. Patients will be asked about compliance at each clinic visit and their tablet returns should be counted for compliance every 3 months at the time of each dispensing visit. Discrepancies between the number of tablets returned and the expected number of tablets returned should be discussed with the patient and the reasons for non-compliance documented. Patients judged to be non-compliant, may continue in the study, but should be counselled on the importance of taking their study medication as prescribed. If the patient is not compliant after counselling on the importance of taking study drug as instructed, the Investigator may withdraw the patient from study treatment.

Patients must continue with both parts of their blinded treatment (oral tablet plus injection); permanently discontinuing one blinded treatment whilst continuing the other is not permitted. Any interruptions in treatment must be documented on the appropriate eCRF.

5.7.1 Accountability

The study drug provided for this study must be used only as directed in the Clinical Study Protocol.

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

Investigational product will only be delivered to the centre when the required regulatory approvals have been obtained. Ethic committee approvals may also be required, depending on local regulations. It is the Investigator and/or institution's responsibility to establish a system for handling study treatment, so as to ensure that:

- Deliveries of products from AstraZeneca or their designee are correctly received by the Investigator or his or her designee;
- Such deliveries are properly documented.

The Investigator must maintain accurate records accounting for the receipt and for the disposition of the IP. It must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for.

Study site personnel will account for all received study drugs and return all unused study drugs to AstraZeneca, its representatives or to an authorised site following AstraZeneca approval to conduct destruction. Certificates of delivery and return should be signed. The destruction of IP will be done according to local requirements.

5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment. Patients will continue to be followed for objective disease progression and survival.
- AE
- Severe non-compliance to study protocol
- Incorrect enrolment and randomisation (see Section 5.3)
- Objective disease progression

- Patient lost to follow-up
- Any other reasons not listed above as per Investigator discretion (the reason must be adequately documented)

5.8.1 Procedures for discontinuation of a patient from investigational product and comparator

Study treatment will continue until objective disease progression (see Section 6.3.3), or other criteria for discontinuation are met (see Section 5.8). Patients must stop both treatments (active and placebo) upon discontinuation. A patient who discontinues study treatment prematurely will always be asked about the reason(s) for discontinuation and the presence of any AEs. Required assessments are detailed in the Study Plan (Table 1). Ongoing SAEs and AEs will be followed up (See Sections 6.4.3 and 6.4.4). The patient should return any leftover study drug.

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

5.9 Withdrawal from study

5.9.1 Randomised patients

Patients will be considered to have withdrawn from the study only due to the following reason:

- Patient decision (patient withdraws consent from participating in the study)
- Death
- Patient lost to follow-up (to declare a patient lost to follow-up, sites should make at least 3 attempts to reach out to the patient or the patient's family. The 3 attempts should be conducted at 3-month intervals)

Patients who choose to withdraw from the study should always be asked specifically whether they are withdrawing or continuing their consent for the optional biomarker research, and whether they would still allow contact for determination of survival follow-up. The Investigator/delegate should inform AstraZeneca of the withdrawal from these aspects of the study.

If a patient withdraws consent to survival follow-up, no further study procedures or follow-up assessments will be performed following withdrawal, and no further data will be collected with the exception of publically available death registry information where permitted locally (for patients whose termination reason is not death). The reason for withdrawal from the study should be recorded on the eCRF.

5.9.2 Screening failures

Screening failures are patients who do not fulfil the eligibility criteria for the study and are therefore not randomised. These patients should have their reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screening failures (not randomised patients).

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Inform Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in this Clinical Study Protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Patient-reported outcomes data (Functional Assessment of Cancer Therapy - Breast [FACT-B] and EQ-5D™) will be captured using paper questionnaires.

Note that in the period following the final OS analysis (when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled) (see Section 12.2.1), SAEs will be reported on a paper-based SAE form.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

The following screening procedures will be performed within 28 days prior to the first dose of study drug. Screening assessments may be performed over several days, if necessary, up to Day -1, as long as all results are available prior to randomisation.

- Recording of demographic data (date of birth, race, ethnic group)
- A standard medical and surgical history (including all previous, now resolved, significant medical conditions), date of diagnosis, extent of disease
- Recording of tumour characteristics
- Documentation of ER +ve and/or PgR +ve status and HER2 status (this can be based on an archival tumour sample, irrespective of age)

- Recording of concomitant medication (including details of previous anticancer therapy and prior use of hormone replacement therapy)
- 12-lead ECG
- Physical examination (including WHO performance status)
- A blood sample for standard clinical chemistry and haematology assessments
- Tumour assessment as per RECIST 1.1 (CT or MRI scan of the chest, abdomen and pelvis)
- For patients with locally advanced breast cancer, the reason that the patient's locally advanced breast cancer is not amenable to therapy of curative intent must be recorded in the eCRF.
- Bone scan or skeletal x-ray survey (nuclear medicine bone scan is preferred) as per RECIST 1.1. Patients who do not have metastatic bone lesions at baseline do not require follow-up bone scans or skeletal x-ray surveys.
- Recording of AEs.

6.2.2 Follow-up procedures

6.2.2.1 Discontinuation visit

The discontinuation visit should take place at the time of the last dose of study drug, or within 35 days of the last injection of study drug. Details of AEs and concomitant therapy should be followed-up for 8 weeks following the last injection.

Investigators should refer to the Study Plan (Table 1 and Table 2) for the list of procedures and assessments to be performed on discontinuation.

6.2.2.2 Survival follow-up phase

Patients who have progressed will enter the survival follow-up phase of the study, and otherwise be managed according to standard clinical practice.

At the time of the data cut-off for the primary analysis, patients who have not yet progressed will enter the survival follow-up phase of the study (see Table 2) and will continue to receive randomised treatment for as long as they obtain clinical benefit (until they meet the criteria for discontinuation).

Following discontinuation of randomised treatment, patients will be followed up for subsequent therapies, survival and QoL, unless they have withdrawn their consent. SAEs and details of concomitant medication should be collected for up to 8 weeks after the last injection of fulvestrant (or matching placebo).

After the data cut-off for the primary analysis, further data collection of objective disease progression will stop (ie, 12-weekly CT/MRI scans will no longer be recorded in the eCRF).

Patients will complete HRQoL assessments at 3-monthly intervals prior to objective disease progression, at the treatment discontinuation visit, at 3-months post-progression, and thereafter at 6-monthly intervals post-progression until the cut-off for the OS analysis. Following progression, patients should continue to have regular survival follow-up contacts every 12 (±2) weeks as detailed in the Study Plan (Table 2) until death or until the final survival analysis endpoint has been met, whichever occurs first. Details of the best response to the first breast cancer therapy subsequent to progression will be collected together with the drug name and start/stop dates of the first and all subsequent breast cancer therapies. Following confirmation of objective disease progression, follow-up may be conducted by telephone, and HRQoL questionnaires may be posted to patients for completion, if appropriate.

An additional survival contact will be made just after the time of the data cut-off for the primary analysis (ie, when approximately 306 PFS events have been observed), regardless of when the last survival contact was made. Another additional survival contact will be made around the time of the final data cut-off (when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled). This is to ensure that the survival information is as up to date as possible for the analysis of OS. The patient, patient's family, or the patient's current physician will be contacted for the latest survival information (unless the patient withdraws consent), and public websites searched, if appropriate.

For patients receiving open-label study treatment after the final data cut-off and OS analysis, SAEs will be reported on a paper-based SAE report form.

6.3 Efficacy

6.3.1 CT/MRI scans

Patients must have a baseline CT or MRI scan of the chest, abdomen and pelvis, performed within 4 weeks before the start of treatment, to assess the level of tumour burden.

The methods of assessment of tumour burden used at baseline (CT or MRI scans of the chest, abdomen and pelvis) must be used at each subsequent follow-up assessment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 12 (±2) weeks relative to randomisation, until objective disease progression as defined by RECIST 1.1 or until the data cut-off for the primary analysis. This includes patients who discontinue treatment prior to progression. If an unscheduled tumour assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the scheduled visits relative to baseline (ie, at 12 week [±2] week intervals).

6.3.2 Bone scan

Patients should have a baseline bone survey performed within 4 weeks before treatment. Patients with metastatic bone lesions at baseline should have repeat bone scans or skeletal x-ray surveys every 12 weeks (±2 weeks) until progression (or until the data cut-off for the primary analysis, whichever occurs first). Additional bone scans or skeletal x-ray surveys should be performed if clinically indicated. Bone lesions should be followed by the same methodology (the single exception to this is where problems with global supplies of technetium-99m for bone scans may necessitate a switch to an alternative modality - see Section 3.1). If an unscheduled tumour assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the scheduled visits relative to baseline (ie, at 12 week [±2] week intervals).

6.3.3 Tumour assessments

RECIST 1.1 criteria will be used to assess patient response to treatment, up to the data cut-off for the primary analysis. The RECIST 1.1 guidelines for measurable, non-measurable, target lesion (TL) and non-target lesions (NTLs) and the objective tumour response criteria (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]) are presented in Appendix D. In patients with non-measurable disease care must be taken to explicitly describe the finding which will qualify for progressive disease. To achieve unequivocal progression there must be an overall level of substantial worsening in non-target disease that is of a magnitude that the treating physician would feel it important to change therapy (Eisenhauer et al 2009).

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PD and Non CR/Non PD.

If the Investigator is in doubt as to whether progression has occurred, particularly with respect to NTL or the appearance of a new lesion, treatment should continue until the next scheduled assessment or sooner if clinically indicated and the patient's status should be reassessed. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. For patients with non-measurable disease only the increase in overall tumour burden based on the change in non-measurable disease should be comparable

to the increase that would be required to declare PD for measurable disease and merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Following progression, patients should continue to be followed up for survival every 12 (±2) weeks as outlined in the Study Plan.

In addition, patients requiring radiation or surgery to manage worsening of disease after randomisation will be considered to have progressed, but will continue to receive study medication and be scanned until imaging criteria for objective disease progression are met. Progression due to surgery or radiotherapy will be recorded in the eCRF.

6.4 Safety

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

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). 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.

Patients will be asked specifically about the presence or development of joint disorders (including pain and loss of movement in joints) and back pain at each visit or telephone contact.

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

6.4.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, treatment, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Prior to the data cut-off for the primary analysis non-serious AEs/SAEs will be collected from the time of signature of informed consent up until 8 weeks after the last injection of fulvestrant (or matching placebo).

During the survival follow-up phase only SAEs for patients still on randomised treatment will be recorded and reported. SAEs for these patients should be collected for up until 8 weeks after the last injection of fulvestrant (or matching placebo).

Following the survival follow-up phase, for those patients that remain on study treatment, SAEs will be recorded and reported directly into AstraZeneca Patient Safety for up until 8 weeks after the last injection of fulvestrant (or matching placebo). In the post-OS analysis period (see Section 12.2.1), SAEs will be reported on a paper-based SAE report form.

AEs will be graded according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.0.

Follow-up of unresolved adverse events

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

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE Grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP

- Outcome.

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE.

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Assessment of causality

The Investigator will assess causal relationship between IP and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

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

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

Adverse events based on signs and symptoms

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

Adverse events based on examinations and tests

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

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

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

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

Hy's Law

Cases where a patient shows an increase in AST **or** ALT **or** total bilirubin may need to be reported as SAEs, please refer to Appendix E 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law', for further instructions.

Disease progression

Objective disease progression is described in Section 6.3.3. Disease progression and events that are unequivocally due to disease progression should not be reported as AEs during the study.

Deaths

All deaths (both cancer-related and other) that occur during the study and within 8 weeks after the last dose of randomised treatment must be reported as follows:

- Death clearly resulting from unequivocal objective disease progression should be reported to the study monitor at the next monitoring visit and should be documented on the relevant eCRF but should not be reported as an AE or SAE.

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

In the event of death, the patient will be considered as having completed the study.

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for administration of study medication and have been identified after inclusion of the patient into this clinical 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.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF. For details of how SAEs are reported using WBDC, please refer to the study specific Safety Handling Plan. In the period following the final OS analysis (when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled) (see Section 12.2.1), SAEs will be reported on a paper-based SAE report form and submitted as per the instructions on the form.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** from when he or she becomes aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately, or **no later than 24 hours** from when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the IB for fulvestrant and the local approved labelling for the active comparator, anastrozole.

6.4.5 Laboratory safety assessment

Blood samples for determination of clinical chemistry and haematology, will be taken at the times indicated in the Study Plan (see Table 1).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator/delegate. The date, time of collection and results will be recorded on the appropriate eCRF.

The clinical chemistry and haematology will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. For blood volume see Section 7.1.

Table 3 lists the laboratory variables to be measured:

Table 3 Laboratory safety variables

Clinical Chemistry	Haematology
Alanine aminotransferase (ALT)	White blood cell count (total)
Aspartate aminotransaminase (AST)	Haemoglobin
Alkaline phosphatase	Absolute neutrophil count
Creatinine	Platelet count
Total bilirubin	INR (at Screening [Visit 1], and subsequently only when clinically indicated)

6.4.6 Physical examination

A complete physical examination will be performed at screening only and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities), and neurological systems.

Performance status will be assessed using the WHO criteria (refer to Appendix F) at screening to check eligibility criteria (see Section 4.1 for inclusion criteria).

Height (at first examination only) and weight will be recorded throughout the study. For timings of assessments refer to the Study Plan (Table 1).

6.4.7 ECG

Twelve-lead ECGs will be recorded throughout the study. For timings of assessments refer to the Study Plan (Table 1). The same method of assessment should be used throughout. ECGs

will be evaluated locally and the results recorded on the relevant eCRF page. Any clinically significant abnormal findings observed and recorded during the study will be recorded as AEs.

6.4.8 Vital signs

Vital signs (blood pressure and heart rate) will be measured throughout the study. For timings of assessments refer to the Study Plan (Table 1). Blood pressure and heart rate will be measured after the patient has been sitting for 5 minutes and before any blood sampling. Blood pressure obtained at Day 0 (Visit 2) will be considered the baseline. The measurement at Day 0 (Visit 2) must take place prior to the first dose of randomised treatment.

6.5 Patient reported outcomes (PRO)

Patient-reported outcomes, specifically HRQoL questionnaires, must be administered to all patients according to the schedules in Table 1 and Table 2. HRQoL questionnaires will continue to be administered to all patients (who have not withdrawn consent) at 3-monthly intervals prior to objective disease progression, at the treatment discontinuation visit, at 3-months post-progression, and thereafter at 6-monthly intervals post-progression up until the data cut off for the final OS analysis.

6.5.1 FACT-B

Functional Assessment of Cancer Therapy-Breast (FACT-B) was developed to measure the effect of breast cancer and its treatment on HRQoL (Brady et al 1997). It is a self-reported questionnaire, comprising 2 parts; Functional Assessment of Cancer Therapy-General (FACT-G) which is a generic questionnaire of 4 subscales (physical, emotional, social/family and functional well-being) which was developed for any tumour type, plus a 9-item breast cancer subscale specific to symptoms of breast cancer and its treatment.

6.5.2 EQ-5D™

The EQ-5D™ questionnaire is a standardised measure of health status, developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). The information can be converted into a single index value of health status, generally ranging from 0, representing a health state of being dead, to 1, representing a health state of full health. It consists of the EQ-5D™ descriptive system (comprising 5 dimensions – mobility, self-care, usual activities, pain/discomfort and anxiety/depression) plus an overall rating of health status measured on a visual analogue scale. For timings of assessments refer to the Study Plan (Table 1 and Table 2).

The EQ-5D™ health utility status questionnaire is provided in Appendix G.

6.5.3 Administration of HRQoL questionnaires

HRQoL questionnaires will be administered using paper questionnaires. The patient should complete the HRQoL questionnaires at the scheduled clinic visit at baseline, and throughout the study at the times specified in the Study Plan (Table 1 and Table 2). The patient should

also complete a questionnaire at their treatment discontinuation visit. If any scheduled HRQoL assessment is not completed the reason for non-completion should be recorded.

Each centre should allocate responsibility for HRQoL assessment to a specific individual (eg, a research nurse). The AstraZeneca designee will provide training for the relevant personnel in the administration of the questionnaires. Before patients are randomised, they must be informed of the rationale for the study and the study details, including the HRQoL questionnaires. 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 HRQoL data are 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 and health utility status. 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 HRQoL 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 or with any other centre staff.

Following completion, the nurse or appointed individual may quickly scan the questionnaire visually for completeness and should confirm verbally with the patient that the questionnaire has been completed fully. However, if appropriate, questionnaires may be posted to patients for completion following objective disease progression.

6.6 Biomarker research

6.6.1 Collection of tissue sections for biomarker research

Refer to Appendix H and the laboratory manual for details on exploratory biomarker sample collection, labelling, preparation, storage and shipment and for details of the type of testing that may be carried out on the tumour samples.

If no sample is available patients may still participate in the main part of the study.

6.6.2 Optional tumour tissue sample for biomarker research

Possible future analysis is likely to be performed retrospectively. The results may be pooled with biomarker data from other studies on fulvestrant or anastrozole to generate and/or validate emerging hypotheses.

Pre-treatment tumour samples (archival and/or recent) will be collected on randomisation to the study for patients who consent to participate in the optional biomarker research. In addition, patients who consent to participate in this biomarker research will also be asked if they are willing to provide an optional tumour sample at progression, if, in the opinion of the investigator, the biopsy procedure does not pose additional significant risks to the patient. If a tumour sample is already available at the time of progression a further sample is not required. This progression tumour sample will enable comparison studies to understand the molecular changes in the tumour that are associated with the development of resistance to either fulvestrant or anastrazole.

Tumour samples provided by the investigational site may either be in the form of a PET block or as 20 pre-cut slides. Tumour blocks or slides will be stored for potential retrospective analysis of biomarkers.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study will depend on the length of time the patient receives study drug. Table 4 is a guide to the approximate volume of blood that will be drawn from a patient who receives study treatment for 24 weeks. For schedule of required blood draws, see Table 1.

Table 4 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	3.5	3	10.5
	Haematology	2	3	6.0
Total				16.5

Note: Blood volumes required by different local laboratories may vary. The total volume shown in this table is the best estimate for a patient that will attend all scheduled visits and will have no retests during the first 24 weeks.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here. Samples analysed locally should be handled, stored and destroyed as per standard practice.

Unless repatriation is requested, biological samples for future research will be retained at the CCI or a named designated laboratory/storage facility for a maximum of 25 years following the completion of the CSR. The results from future analyses will be reported separately in a suitable scientific publication.

For details of the processing, handling and shipment of tumour samples for biomarker research see Appendix H and the laboratory manual.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

The PI at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed (or repatriated, if applicable), and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The PI:

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

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

8.3 Ethics and regulatory review

An Ethics Committee (EC) or Institutional Review Board (IRB) should approve the final Clinical Study Protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca or its representative before enrolment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca or its representative should approve any modifications to the ICF that are needed to meet local requirements.

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

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca or its representative will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

If the PI is responsible (depending on local regulations) for providing the ECs/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP, AstraZeneca or its representative will provide this information to the PI so that he/she can meet these reporting requirements.

8.4 Informed consent

The PI(s) at each centre will:

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

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

8.4.1 Biomarker research informed consent (tumour tissue sample only)

The pre-treatment tissue tumour sample for biomarker research is optional and the patient may participate in the main study without participating in the biomarker research. To participate in the biomarker research component of the study the patient must sign and date both the ICF for the main study (non-biomarker research components of the study) and the biomarker research component of the study. Patients who also consent to provide an additional (optional) tumour sample on progression must check the appropriate box indicating that they consent to provide this additional sample if it proves feasible to obtain such a sample at the time of progression (and if, in the opinion of the investigator, the biopsy procedure does not pose additional significant risks to the patient).

Copies of both signed and dated ICFs must be given to the patient and the original filed at the study centre. The PI(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the biomarker research aspect of the study at any time.

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

8.5 Changes to the protocol and informed consent form

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

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

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC are to approve the revised ICF before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca or its representative immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA OR DELEGATE

9.1 Pre-study activities

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

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca or its representative and the Investigator.

9.2 Training of study site personnel

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

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

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

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The PI at each centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca or its representative and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The study is expected to start in Quarter 2 or 3, 2012.

The end of the study is defined as the last visit of the last patient, occurring when the last patient has discontinued study therapy.

An initial data cut-off for the primary analysis of Progression Free Survival will occur following completion of the last patient assessment / visit contributing to this analysis. Data analysis will be performed and clinical study report written. A subsequent final data cut-off will be performed for the survival follow-up analysis and will occur following the last patient assessment/visit contributing to the OS analysis. At this time point, the clinical study database will close to new data, data analysis will be performed and a Clinical Study Addendum Report written. Patients are however permitted to continue to receive open-label study treatment beyond the closure of the database as a continued access phase if, in the opinion of the investigator, they are continuing to receive benefit from treatment with fulvestrant or anastrozole and cannot access appropriate treatment outside of the clinical study protocol. If the product development reaches a point where alternative options of the supply become available these will be discussed with the investigator. Where an alternative supply route is determined to be the better option, including commercial products available in some regions, AstraZeneca will work with the investigator to transition patients to this alternative supply. Placebo treatment will be discontinued at this point. For patients who do continue to receive study treatment beyond the time of this data cut-off, investigators will continue to report all SAEs to AstraZeneca Patient Safety up until 8 weeks after study treatment is discontinued, in accordance with Section 6.4.3 (Recording of Serious Adverse Events). Additionally, any SAE or non-serious AE that is ongoing at the time of this data cut-off must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

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

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by IQVIA.

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests, and assessments specified in the protocol into the WBDC system and according to the eCRF instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database. All entries and any changes performed will be tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be source data verified, reviewed, queried, and updated as needed. Data queries will be raised for inconsistent, impossible, or missing data.

When all data have been coded and validated, medically reviewed by AstraZeneca or its representative, and signed by the Investigator, the data will be frozen and then locked to

prevent further editing and a clean file will be declared. A copy of the eCRF will be archived at the study site when the study has been locked.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The study Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

The study database will be closed and the final survival analysis will be performed when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled.

Dictionary coding

Medical Coding will be performed using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and AstraZeneca Drug Dictionary. All coding will be performed by IQVIA.

Serious adverse event (SAE) reconciliation

SAE reconciliation reports will be produced and reconciled with Patient Safety Database and / or the Investigational Site.

Biomarker data

For biomarker samples (ie, tumour tissue samples), the original date of biopsy (historical tumour/re-biopsy tissue samples) and details regarding sample tracking will be recorded in the CRF and database.

Management of external data

AstraZeneca or its representative determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database. AstraZeneca or its representative will ensure that other data collection tools (eg, IVRS/IWRS) will be tested/validated as needed. External data reconciliation will be done with the clinical database as applicable.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variables

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST 1.1 (see Appendix D).

At each visit, patients will be programmatically assigned a RECIST visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments.

If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Progression-free survival (PFS)

Progression-free survival is defined as the time from randomisation until objective disease progression as defined by RECIST 1.1, or death (by any cause in the absence of progression). Where surgery or radiotherapy is performed to manage worsening of disease, this will be captured as a progression event and documented in the eCRF; these patients will continue to receive study medication and be scanned until imaging criteria for objective disease progression are met. The PFS time will always be derived based on scan/assessment dates, not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression

- When censoring a patient for PFS, the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment.

Patients who have not progressed or died at the time of the cut-off for the primary statistical analysis will be censored at the time of their last evaluable RECIST assessment. Patients who progress or die after 2 or more missed visits, will be censored at the time of the latest evaluable RECIST' assessment prior to the missed visits. If a patient has no RECIST follow-up assessments or has no evaluable baseline assessment and is still alive at the time of the analysis cut-off with no surgery or radiotherapy to manage worsening of disease, then they will be censored at 0 days for PFS. Symptomatic deterioration will not be regarded as a progression event.

If a patient discontinues treatment prior to objective disease progression and/or receives a subsequent therapy prior to progression then the patient will continue to be followed until evidence of objective disease progression (until the data cut-off for the primary analysis) as defined by RECIST 1.1 and their PFS time will be derived as defined above.

Overall survival (OS)

OS is defined as the time from randomisation until death by any cause.

Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

Objective response rate (ORR)

A patient is defined as having objective response (OR) if they have a visit response of CR or PR at some point during the study, prior to disease progression. Objective Response Rate (ORR) is defined as the percentage of patients who have OR during the study. The denominator in the calculation of the ORR for each treatment group will be the number of patients in the Intention to Treat [ITT] population with measurable disease at baseline.

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10 mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared with baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

Duration of response (DoR)

DoR is defined only for patients who had OR, as the number of days from the date of first documentation of response (CR/PR) until the date of disease progression (see Section 6.3.3).

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

Expected duration of response (EDoR)

The EDoR will be estimated using the formula EDoR $= pE_{f_p}(x)$,where $x$is the duration of response (DoR) as defined earlier for responders, p is the proportion of responders and $E_{f_p}(x)$ is the mean duration of response for responders. The estimation can be completed by using the maximum likelihood estimates of p and $E_{f_p}(x)$, as described by Ellis (Ellis et al 2008). The log normal distribution will be used for the duration of response and this assumption will be checked for appropriateness.

Clinical benefit rate (CBR)

A patient is defined as having clinical benefit (CB) if they have a visit response of CR or PR or stable disease (SD) for at least 24 weeks. The clinical benefit rate (CBR) is defined as the proportion of patients who have CB for a minimum of 154 days (ie, 22 weeks with allowance for a 2-week visit window). The number of patients per treatment group in the ITT population will be used as the denominator in the calculation of the CBR.

Duration of clinical benefit (DoCB)

DoCB is defined only for patients who had clinical benefit, as the time in days from date of randomisation until the date of disease progression (see Section 6.3.3).

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

Expected duration of clinical benefit (EDoCB)

The EDoCB will be calculated using the same approach as described above for EDoR, with x being the duration of clinical benefit (DoCB) as defined earlier for patients with clinical benefit, p the proportion of patients with clinical benefit and $E_{f_p}(x)$ the mean duration of clinical benefit for patients with clinical benefit.

11.2 Calculation or derivation of safety variables

In addition to the safety variables mentioned in Section 6.4, the following will also be derived.

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuations of IP due to AEs (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 FACT-B

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 et al 1997).

The following measure will also be derived from the FACT-B:

- The total FACT-B score comprising the sum of the scores from all the subscales; PWB, FWB, Social/family well-being (SWB), Emotional well-being (EWB), BCS.

11.3.1.1 Items to be reversed

- Each question in the FACT-B questionnaires has a choice of 5 responses, "Not at all", "A little bit", "Somewhat", "Quite a bit" and "Very much". The scores range from 0 ("Not at all") to 4 ("Very much") for positively phrased questions.

Negatively phrased questions have a reverse scoring, from 0 ("Very much") to 4 ("Not at all"). This results in a consistent approach, where higher scores indicate a better quality of life.

- Note, questions that are reversed (via subtraction of the response from 4) are: GP1-7, GE1, GE3-6, B1-3 and B5-B8. The response to item P2 'I have certain parts of my body where I experience pain' will not be included in the BCS total score, or any of the other derived quality of life scores since this item is not currently scored within the Functional Assessment of Chronic Illness Therapy (FACIT) scoring guidelines (version 4).

11.3.1.2 Missing data

- As per the FACIT scoring guidelines, more than 80% of questions in a questionnaire must be completed for the questionnaire to be evaluable. If 80% or less of questions are completed, the questionnaire is not evaluable, and the data will be listed, but not included in any summaries or analyses.

- For each domain (PWB, SWB, EWB, FWB and BCS) if more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc), the domain score can be prorated within each domain. This is done by multiplying the sum of the domain scores by the number of items in the domain, then dividing by the number of items actually answered. This can be done by using the formula below:

- **Prorated subscale score** = [Sum of item scores] × [N of items in domain] ÷ [N of items answered]

- If at least 50% of the domain items are missing, that domain will be treated as missing and thus non-evaluable. The total score for each variable (FACT-B TOI and Total FACT-B) is then calculated as the sum of the un-weighted prorated scores. If a domain score is non evaluable, any HRQoL variable which these domains contribute to is also termed non-evaluable. For example, for the FACT-B TOI variable, if PWB is non-evaluable at a visit, the FACT-B TOI variable is also non-evaluable at this visit.

11.3.1.3 Visit responses

The last non-missing assessment before randomisation will be assigned to be the baseline assessment.

At each post-baseline visit, the following criteria as listed below in Table 5, will be used to assign a FACT-B TOI and FACT-B total score visit response.

Table 5 Summary of HRQoL visit responses

Score	Change from baseline	Visit Response
FACT-B TOI (0-92 score range)	≥ +6	Improved
	≤ -6 or "Patient too affected by symptoms of disease under investigation" is answered as the reason for not completing HRQoL at visit.	Worsened
	>-6 and < +6	No change
	Not calculable	Not evaluable[a]
FACT-B total score (0-144 score range)	≥ +8	Improved
	≤ -8 or "Patient too affected by symptoms of disease under investigation" is answered as the reason for not completing HRQoL at visit.	Worsened
	>-8 and < +8	No change
	Not calculable	Not evaluable[a]

[a] The visit response will be classified as Non-Evaluable if 'No' has been ticked to the Question "Questionnaire completed" and the reason is one of: 'Patient unwilling', 'Patient cannot understand instructions', 'Patient too sick, other than disease under investigation', 'Administrative failure to distribute questionnaire to Patient' or 'Other', or if missing data is such that a score cannot be calculated (see section above on missing data).

The criteria for worsening of HRQoL, as measured by FACT-B TOI and FACT-B total score are based on Eton et al 2004.

Note for some patients it will not be immediately possible to obtain a PRO visit score response for a particular subscale, for example:

- Patients with no baseline score for a particular subscale, or no baseline data at all
- Patients whose baseline subscale score is close to the maximum or minimum possible score to allow an increase or decrease of the specific size to be observed.
  - For patients whose baseline score is greater than the maximum possible score for that subscale minus the score needed to satisfy improvement, the best visit response possible will be "No Change"
  - For patients whose baseline score is less than the threshold needed for worsening (eg, a baseline FACT-B TOI < 6) all post-baseline visit responses will be considered not-calculable.

11.3.1.4 Time to deterioration of Health related Quality of Life

Time to deterioration of HRQoL as measured by FACT-B TOI will be defined as the interval from the date of randomisation to the first assessment of worsened without an improvement in the next 12 weeks in FACT-B TOI, or the date of death (by any cause in the absence of symptom deterioration). Time to deterioration as measured by FACT-B total score will be derived similarly.

A worsening is as described in Table 5, for example, for FACT-B TOI a decrease in score from baseline of greater than or equal to 6, or "Patient too affected by symptoms of disease under investigation" answered as the reason for not completing HRQoL at a post-baseline visit will constitute a deterioration. Improvement is also as defined within Table 5.

A deterioration followed by an improvement within 12 weeks means that this first deterioration cannot be used in determining the time to deterioration of symptoms. However, if a subsequent worsening is seen, with no improvement in the following 12 weeks, this second deterioration will be used to derive the time to deterioration.

Progression will not be considered as deterioration in symptoms.

Note, under the same principles applied to the primary outcome variable (PFS), time to deterioration will be derived regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to symptom deterioration. In addition, similar to the analysis of PFS, if a patient either meets the criteria for deterioration, or dies but at a time point this is greater than 2 or more missed RECIST assessments of the last evaluable HRQoL assessment, then the patient will be censored at the time of the latest evaluable HRQoL assessment.

A number of situations will lead to a patient's time to deterioration of HRQoL endpoints being censored. These are:

- Patients who have not met the criteria for symptom deterioration or died at the time of analysis will be censored at the time of the latest evaluable HRQoL assessment:
  - The censoring date will be the date of the last assessment that led to evaluable being assigned for the specific HRQoL variable (eg, it could be the case that FACT-B TOI was evaluable but FACT-B total score was not evaluable at a visit, and in this case FACT-B TOI and FACT-B total score would be censored at different time points).
- Patients with no evaluable baseline or post-baseline data will be censored at 0 days unless they die within 2 visits of baseline
- Patients whose baseline subscale score is close to the minimum possible

– For patients whose baseline score is less than the threshold needed for worsening (eg, a baseline FACT-B TOI of < 6), time to worsening will be censored at 0 days unless they die within 2 visits of baseline.

The time to deterioration of HRQoL will always be derived based on assessment dates not visit dates.

11.3.1.5 HRQoL compliance rates

Summary measures of overall compliance and compliance over time will be derived. These will be based upon:

- Received forms = number of FACT-B forms received back plus the number not received back where the reason was 'Patient too affected by symptoms of disease under investigation'
- Expected forms = number of patients still in the study at the specified assessment time excluding patients in countries with no available translation
- Evaluable forms = FACT-B forms with at least one subscale that can be determined; or where REVPRDI form is ticked 'Patient too affected by symptoms of disease under investigation'

Thus the overall compliance rate is defined as number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline FACT-B form.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable form at the time point (as defined above), divided by number of patients still expected to complete forms. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms.

Similar compliance rates will also be determined for TOI and FACT-B total score.

11.3.2 EQ-5D™

The EQ-5D™ descriptive system comprises 5 questions (see Appendix G) which generate possible health states which can be converted into a weighted health status index by applying scores from the appropriate available 'value sets'.

11.4 Calculation or derivation of exploratory biomarker variables

Analyses may be performed to investigate potential biomarkers that may help to define a more specific patient population that would benefit from fulvestrant or anastrozole. The results of such an analysis will be reported separately to the CSR.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The ITT population will include all randomised patients. Patients in the ITT population will be analysed according to the treatment they were randomised to, regardless of the treatment actually received. The ITT population will be used for the primary analysis for this study.

12.1.2 Safety analysis set

All patients who received at least one dose of randomised treatment will be included in the Safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the group corresponding to the actual treatment initially received (in case they receive the wrong treatment initially but subsequently receive the correct treatment).

12.2 Methods of statistical analyses

Table 6 summarises all formal statistical analyses planned for this study.

Table 6 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoint analysed	Analyses
Progression free survival (PFS)	Based on RECIST 1.1 data from Investigator assessment, surgery/radiotherapy for worsening of disease, or death from any cause: Stratified log-rank test (Primary analysis) *Sensitivity analyses:* Based on RECIST 1.1, or death from any cause Cox proportional hazards regression model Censoring at time of treatment discontinuation/subsequent therapy Analysis of midpoints to assess time evaluation bias Subgroup analyses
Overall survival	Stratified log-rank test
Objective response rate	Stratified logistic regression analysis
Clinical benefit response	Stratified logistic regression analysis
Expected duration of response	Analysis following method described by Ellis et al 2008
Expected duration of clinical benefit	Analysis following method described by Ellis et al 2008
Time to deterioration of HRQoL	Cox proportional hazards model of time to deterioration of FACT-B TOI Cox proportional hazards model of time to deterioration of FACT-B total score
Pre-specified AEs	Fisher's exact test analysis of joint disorders and back pain

12.2.1 General principles

All descriptive statistics will be presented by treatment group. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group.

Baseline will be the last assessment of the variable under consideration prior to first dose intake.

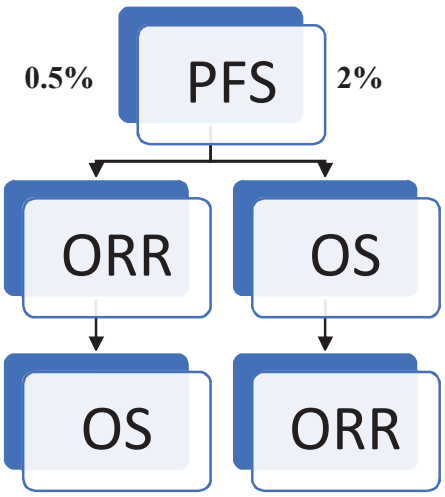
All data collected will be listed.

Efficacy data will be summarised and analysed on the ITT population. Safety data will be summarised and analysed on the safety population.

There are no planned co-primary analyses.

The key secondary endpoints of OS and ORR will be tested using a multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, the endpoints of OS and ORR will be tested in a pre-defined order as shown below. The secondary endpoints of CBR, EDoR, EDoCB, FACT-B and EQ-5D will not be included in this MTP.

Figure 2 Multiple testing procedure



The primary endpoint (PFS) is tested at a single time point when approximately 306 progression events have occurred. The secondary endpoints of OS and ORR will then be tested in the MTP using a weighted proportion of alpha (test mass; the total test mass equals alpha) and test mass that becomes available after each rejected hypothesis is recycled to secondary endpoints not yet rejected. This testing procedure stops when the entire test mass is allocated to non-rejected endpoints. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control the Type I error at 2.5% (1-sided), amongst the primary (PFS) and the key secondary (OS, ORR) endpoints.

PFS and ORR will be analysed at one time point only. However, OS will be analysed on 2 occasions; at the time of the primary analysis and again when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled. The available alpha will be controlled amongst the 2 OS analyses. Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach will be used for the interim analysis where the significance level applied at the interim is dependent upon the proportion of information available.

For the final OS analysis, Haybittle-Peto alpha adjustment will be used to account for the actual proportion of information available at the interim analysis and alpha already spent. MTP is illustrated below:

- 2% alpha was available for OS overall.

- At the time of the primary analysis in 2016, 142 deaths had been observed and the final OS analysis was planned to take place when 50% of patients had died (approximately 231 events) as per the original study protocol. Therefore, 142/231 = 0.6147 of the full death information was assumed to be available and 0.301% one-sided significance level was used as per Lan DeMets spending function.

- The final OS analysis trigger has changed since the primary analysis in 2016 and as per the latest update, the final OS will be triggered when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled. Using the steps below, 1.845% one-sided alpha is available for the final OS analysis:

  – 0.301% of alpha has already been spent at the time of the primary analysis

  – approximately 310 death events are estimated to occur at the time of the final OS analysis in July 2022

  – recalculated proportion of the information available at the time of the primary PFS analysis is 142/310 = 0.46

  – using Haybittle-Peto to account for the recalculated proportion of information available at the primary analysis and alpha already spent, 1.845% one-sided alpha is available for the final OS

Patient disposition will be summarised for all patients. A summary of the important protocol deviations will be produced. Demography will be summarised on the ITT population. Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the statistical analysis plan (SAP).

12.2.2 Efficacy

12.2.2.1 Progression-free survival (PFS)

The primary statistical analysis will compare the PFS between fulvestrant 500 mg versus anastrozole 1 mg using the stratified log-rank test using the Breslow method to handle ties (Breslow, 1974). The HR and its CI can be estimated from the log-rank as follows (Berry et al 1991, Collett, 2003, Sellke and Siegmund 1983):

$HR = \exp(U/V)$

95% CI for $HR = (\exp\{U/V - 1.96/\sqrt{V}\}, \exp\{U/V + 1.96/\sqrt{V}\})$

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki}, -e_{1ki})$ is the stratified log-rank test statistic obtained from the SAS LIFETEST procedure, $\sqrt{V} = \sqrt{\sum_k V_k}$, is its standard deviation, k denotes the stratum and d_{1ki} and e_{1ki} are the observed and expected events in group 1, stratum k.

Results will be presented in terms of an estimate of the HR (fulvestrant 500 mg: anastrozole 1 mg), associated CI and p-value. A HR less than 1 would indicate that, on average, PFS is improved on fulvestrant 500 mg when compared with anastrozole 1 mg.

The decision as to whether or not the primary study objective has been achieved will be made upon the superiority test for PFS using the log-rank test in ITT population, at the 5% (2-sided) significance level.

The number of events at the time of analysis, as well as point estimates of the median, lower and upper quartile for PFS (when feasible to do so) will be presented for each treatment group and PFS will be displayed graphically using Kaplan-Meier plots.

Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be as a result of treatment-by-covariate interactions, which will be investigated.

Sensitivity analyses

A sensitivity analysis using Cox Proportional Hazards regression will also be performed, with treatment and relevant baseline prognostic covariates included in the model. The Efron method will be used to handle ties (Efron, 1977). The covariates to be included are ER +ve and PgR +ve at baseline (no/yes), metastatic disease at baseline (no/yes), use of bisphosphonates as concomitant medication at baseline (yes versus no), measurable disease at baseline (yes versus no), prior chemotherapy for locally advanced or metastatic breast cancer (yes versus no) and geographic region (geographic split to be defined in SAP) and prior systemic oestrogen-containing hormone replacement therapy (no/yes). This analysis will be performed on the ITT population.

A global interaction test will be performed to test if overall the treatment benefit was consistent across the covariates. This will be done by fitting a model with treatment and the 3 stratification factors and comparing that with the model with treatment, the 3 factors and the factor by treatment interactions. If the fit of the model is not significantly improved (at the 10% level) then it will be concluded that overall the treatment effect is consistent across the covariates.

This test will be conducted by taking the difference in the log likelihood between the model containing all the covariates and 2-way interactions and the model without these interactions. The difference will be multiplied by -2 (ie, minus 2) and this statistic has a chi-squared distribution with degrees of freedom equal to the difference in the number of parameters between the two models.

If the global interaction test is significant, for each of the covariates listed above the covariate by treatment interaction will also be assessed individually and if the p-value for this is not significant (at the 10% level) then the treatment effect will be assumed to be consistent across the values of this covariate. These tests will be carried out in the same way as the global interaction test. Treatment effect may be investigated in groups as defined by these covariates to locate the source and nature of any interactions or if that would aid interpretation of the trial results.

A sensitivity analysis will be performed whereby patients are censored at the time they discontinue treatment and/or receive subsequent therapies prior to documented disease progression.

A sensitivity analysis will be performed based on RECIST 1.1, or death from any cause.

In order to assess evaluation-time bias, the primary PFS analysis will be repeated, but based on the midpoint of the time between progression detected and the previous visit. To support this analysis, the mean of patient-level average inter-assessment times will be tabulated for each treatment.

Subgroup analysis

Analysis of the following subgroups as defined by the 7 covariates will be performed, if numbers permit, for the ITT population:

- ER +ve and PgR +ve at baseline (no/yes)
- Metastatic disease at baseline (no/yes)
- Used bisphosphonates as concomitant medication at baseline (no/yes)
- Measurable disease at baseline (no/yes)
- Prior chemotherapy for locally advanced or metastatic breast cancer (yes versus no)
- Geographic region (geographic split to be defined in the SAP)
- Prior systemic oestrogen-containing hormone replacement therapy (no/yes)

The subgroup analyses will be performed on the primary endpoint PFS only using the stratified log-rank test. For each subgroup, the number and percentage of events at the time of analysis and the median PFS will be presented. In addition, the HR and 95% CI for the

treatment group comparison will be presented and the data will be displayed graphically using a Kaplan-Meier plot for each subgroup.

A forest plot will be produced for PFS showing the hazard ratio with associated 95% CIs of each subgroup.

12.2.2.2 Objective response rate (ORR)

A summary of ORR will be presented by treatment group. In addition, ORR will be analysed using a logistic regression model including the 3 stratification factors. The results will be expressed in terms of the odds ratio and its associated CI and p-value. The p-value will be based on twice the change in log-likelihood resulting from the addition of treatment factor to a model that contains the factors. CIs will be profile likelihood intervals (eg, using option LRCI in SAS PROC GENMOD).

12.2.2.3 Overall survival (OS)

OS will be compared between fulvestrant 500 mg and anastrozole 1 mg using the stratified log-rank test. Results will be presented in terms of an estimate of the HR (fulvestrant 500 mg: anastrozole 1 mg), associated CI and p-value. HR and 95% CIs will be calculated using the same methodology as for PFS. A HR less than 1 would indicate that, on average, OS is improved on fulvestrant 500 mg when compared with anastrozole 1 mg.

The number of events at the time of analysis, as well as point estimates of the median, lower and upper quartile for OS (when feasible to do so) will be presented for each treatment group and OS will be displayed graphically using Kaplan-Meier plots.

12.2.2.4 Clinical benefit rate (CBR)

A summary of CBR will be presented by treatment group. In addition, CBR will be analysed using a logistic regression model including the 3 stratification factors. The results will be expressed in terms of the odds ratio and its associated CI and p-value. The p-value will be based on twice the change in log-likelihood resulting from the addition of treatment factor to a model that contains the 3 stratification factors. CIs will be profile likelihood intervals (eg, using option LRCI in SAS PROC GENMOD).

12.2.2.5 Duration of response (DoR)

DoR will be presented graphically per treatment group using Kaplan-Meier plots. Estimates of the median DoR for each treatment group and the corresponding 95% CI will also be presented.

12.2.2.6 Duration of clinical benefit (DoCB)

DoCB will be presented graphically per treatment group using Kaplan-Meier plots. Estimates of the median DoCB for each treatment group and the corresponding 95% CI will also be presented.

12.2.2.7 Expected duration of response (EDoR)

An analysis of EDoR will be performed by calculating the ratio of the EDoR of fulvestrant 500 mg to that of anastrozole 1 mg. The 95% CI will also be provided. By including all evaluable patients, this methodology allows an unbiased comparison of treatments for DoR (Ellis et al 2008).

12.2.2.8 Expected duration of clinical benefit (EDoCB)

An analysis of EDoCB will be performed by calculating the ratio of the EDoCB of fulvestrant 500 mg to that of anastrozole 1 mg. The 95% CI will also be provided. By including all randomised patients, this methodology allows an unbiased comparison of treatments for DoCB (Ellis et al 2008).

12.2.3 Tolerability and safety

12.2.3.1 Adverse events (AE)

AE data will be summarised using MedDRA by preferred term and system organ class. Summaries will be produced based upon number of patients and number of AEs. The number of patients who withdraw or die due to AEs will be summarised. AEs will also be summarised by maximum reported CTCAE grade and Investigator's causality assessment. A summary of the number of patients with a causally related AE will also be produced. The number of patients with a causally related AE with an outcome of death will be presented. A summary of all deaths and the primary cause of death will be produced. A summary of the key information for deaths will also be produced. SAEs and OAEs will be summarised.

The incidence of the pre-defined OAEs of interest (ie, joint disorders and back pain) will be compared between the two treatment groups using Fisher's exact test. The analysis will be done on the Safety population.

12.2.3.2 Health-related Quality of Life (HRQoL)

For each applicable visit, a summary of the FACT-B scores, and also the change from baseline scores, will be summarised and presented graphically. Specifically, the TOI, Total FACT-B, and the individual subscale scores will be summarised in this way.

The scores from other PRO assessments and their change from baseline will be summarised and presented graphically by visit.

The analysis of time to deterioration of TOI and FACT-B total score will be as outlined for the primary PFS analysis.

Change from baseline in all HRQoL subscale scores will be listed and summarised but no formal statistical analysis will be performed.

The EQ-5D™ data will be listed and summarised only.

12.2.3.3 Other assessments

Laboratory variables (haematology and clinical chemistry) will be summarised per time point and summaries of change from baseline will also be produced. Vital signs, ECG data withdrawals, exposure data, concomitant medications, previous medical and surgical history, weight, height and physical examination data will be listed and summarised by treatment group.

12.2.4 Interim analyses

No interim analysis of PFS will be performed.

There will be an interim analysis of OS at the time of the primary analysis of PFS. A further analysis of OS will occur when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2 and is based on the primary endpoint of PFS.

Approximately 450 patients will be randomised to achieve 306 progression events. If the true HR=0.69, this number of events will provide 90% power to demonstrate statistical significance at the 5% two-sided significance level. Assuming the median PFS on anastrozole is 13 months, a PFS HR of 0.69 corresponds to the median PFS of 18.8 months on fulvestrant 500 mg. The smallest treatment difference that would be statistically significant is PFS HR=0.80 (which translates to approximately a 3.3 month median difference, assuming proportional hazards and an exponential distribution).

12.4 Data monitoring committee

An Independent Data Monitoring Committee (IDMC) will not be used in this study. Safety data for both study medications are very extensive and are highly unlikely to be modified by the results of this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.**

In the event of a medical emergency the Investigator may contact the 24-hour IQVIA Medical Emergency Contact Centre PPD

13.2 Overdose

If an overdose occurs, routine supportive measures should be taken.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, ie, immediately, or **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

Only postmenopausal women are eligible to participate in this study. Pregnancy should be ruled out prior to study start in case of doubt.

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Clinical Study Protocol Appendix C	
Drug Substance	Fulvestrant
Study Code	D699BC00001
Edition Number	1.0
Date	19 April 2012

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Fulvestrant
Study Code	D699BC00001
Edition Number	1.0
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Appendix D
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CR	Complete response
CT	Computed Tomography
FDG-PET	Fluorodeoxyglucose (^{18}F) positron emission tomography
iv	intravenous
MRI	Magnetic Resonance Imaging
NA	Not applicable
NE	Not evaluable
NTL	Non-target lesion
PD	Progressive disease
RECIST 1.1	Response Evaluation Criteria In Solid Tumours, Version 1.1
SD	Stable disease
TL	Target lesion

1. INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria In Solid Tumours, (RECIST) Version 1.1 Guidelines (Eisenhauer et al 2009) for the FALCON study (Study D699BC00001) with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

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

At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computed tomography (CT), magnetic resonance imaging (MRI) and plain X-ray and is suitable for repeated assessment.

Measurable:

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

Non-measurable:

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

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

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

Special cases:

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

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

Target lesions:

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

Non-target lesions:

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

3. METHODS OF ASSESSMENT

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

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

Table 1: Summary of methods of assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination (for skin lesions only)	Clinical examination (for skin lesions only)
	X-ray, chest X-ray	X-ray, chest X-ray
		Ultrasound
		Bone scan[(a)]
		FDG-PET[(a)]

[a] Can be used if also assessed at baseline (as per Section 3.8 and 3.9)

3.1 CT and MRI

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

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

3.2 Clinical examination

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

3.3 X-ray

3.3.1 Chest X-ray

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

3.3.2 Plain X-ray

Plain X-ray may be used in this study as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

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

3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used in this study for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

Tumour markers will not be used in this study for tumour response assessments as per RECIST 1.1.

3.7 Cytology and histology

Histology will not be used in this study as part of the tumour response assessment as per RECIST 1.1.

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

3.8 Isotopic bone scan

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

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

3.9 FDG-PET scan

Fluorodeoxyglucose (^{18}F) positron emission tomography (FDG-PET) scans may be used in this study as a method for identifying new lesions (provided a baseline scan is available), according with the following algorithm: new lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

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

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments will be performed every 12 (±2) weeks after randomisation, until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

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

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

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

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

Table 2: Evaluation of target lesions

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

4.3 Non-target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be

recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3: Evaluation of non-target lesions

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

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. For patients with non-measurable disease only the increase in overall tumour burden based on the change in non-measurable disease should be comparable to the increase that would be required to declare PD for measurable disease and merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

4.4 New lesions

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

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

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

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans

confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

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

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

4.6 Evaluation of overall visit response

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

Table 4: Overall Visit Response

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

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

In addition, if not all TL measurements are recorded for a particular visit, but the sum of recorded TLs is sufficiently increased to result in a 20% increase, and an absolute increase of at least 5mm from nadir, even assuming that the non-recorded TLs have disappeared, then the overall visit response will be assigned to PD.

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

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

5.1 CT scan

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

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

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

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

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT

without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

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

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

5.2 MRI scan

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

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

5.3 FDG-PET scans

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

performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

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

6. REFERENCES

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

Clinical Study Protocol Appendix E	
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Appendix E
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix F	
Drug Substance	Fulvestrant
Study Code	D699BC00001
Edition Number	1.0
Date	19 April 2012

Appendix F
WHO Performance Status

WHO PERFORMANCE STATUS

Description	Status
Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia.	**0**
Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains subjects who are fully active, as in grade 0, but only with the aid of analgesics	**1**
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours	**2**
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	**3**
Completely disabled, unable to carry out any self-care and confined totally to bed or chair	**4**

Clinical Study Protocol – Addendum #1	
Drug Substance	Fulvestrant
Study Code	D699BC00001
Addendum Version	1
Date	23January 2018

Addendum #1 to the Revised CSP v 4,0 dated 01Dec2017

A Randomised, Double-blind, Parallel-group, Multicentre, Phase III Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Anastrozole (ARIMIDEX™) 1 mg as Hormonal Treatment for Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer Who Have Not Previously Been Treated With Any Hormonal Therapy (FALCON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 1, 23 January 2018 (Global Addendum #1 to the Revised CSP v 4,0 dated 01Dec2017)

Sections of the Revised CSP v 4,0 dated 01Dec2017 affected:

- Appendix G

Description of the update:

Due to an editorial mistake, Patient Reported Outcomes questionnaires (FACT-B and EQ-5D™), were not included in Appendix G (edition 1,0 dated 19 Apr 2012) of the revised CSP version 4,0 dated 01 Dec 2017.

To correct and document this omission an Addendum #1 has been developed.

The corrected Appendix G (edition 1,0 dated 19 Apr 2012) including Patient Reported Outcomes questionnaires (FACT-B and EQ-5D™) is attached to this document.

Attachement:

Appendix G (edition 1,0 dated 19 Apr 2012) Patient Reported Outcomes (FACT-B and EQ-5D™)

AstraZeneca

Clinical Study Protocol Appendix G	
Drug Substance	Fulvestrant
Study Code	D699BC00001
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Appendix G
Patient Reported Outcomes (FACT-B and EQ-5D™)

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to 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 mark 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)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	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)

Please circle or mark one number per line to indicate your response as it applies to the <u>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 pain	0	1	2	3	4

EQ - 5D

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

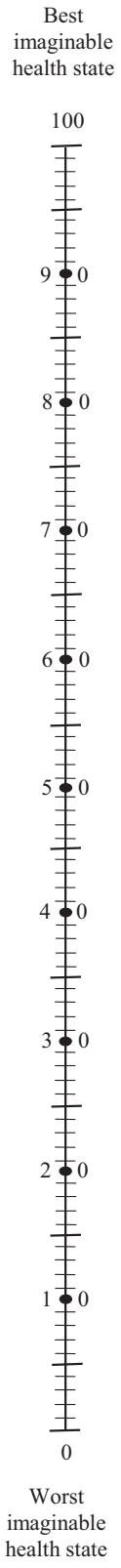
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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AstraZeneca

Clinical Study Protocol Appendix H	
Drug Substance	Fulvestrant
Study Code	D699BC00001
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Appendix H
Biomarker Research

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical study report
EC	Ethics Committee
ER	oestrogen receptor
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
PgR	progesterone receptor
PI3K	phosphoinositide 3-kinase
PTEN	phosphatase and tensin homolog

1. BACKGROUND

As part of the clinical drug development programmes for fulvestrant and anastrozole AstraZeneca is investigating variations in biomarker profiles and their relationship to drug effect and toxicity. These biomarkers may be derived from DNA, RNA, proteins and metabolites and potentially be predictive markers of response or potential toxicity. By generating this information, we aim to better understand the impact of variation between individuals and how this knowledge can be utilised to bring the right drugs to the right patient.

To achieve this goal a systematic collection of biological samples including those taken from patients' tumours will be undertaken where appropriate.

1.1 Rationale for research

AstraZeneca may perform biomarker research in the fulvestrant and anastrozole clinical development programmes to explore how variations in biomarkers (DNA, RNA and/or protein based) may be related to fulvestrant, anastrozole and other factors that may influence development of cancer.

Recent studies have demonstrated that it is possible to predict which patients are most likely to gain benefit from therapy via molecular profiling of the tumour (Paik et al 2004: Ring et al 2006). For example complex gene expression profiles derived from solid tumour samples can be translated into simple scores that predict which patients are most likely to benefit from treatment (Paik et al 2006). Non-heritable, tumour-specific alterations to DNA have also been linked to prognosis and to potential treatment benefit (Wu et al 2007, Yoshida et al 2007, Sunaga et al 2007, Massarelli et al 2007 and Beauclair et al 2007). Astrazeneca is committed to delivering the right drug to those patients most likely to gain clinical benefit. The ability to acquire appropriate consent to collect biological samples and perform exploratory analysis is of the utmost importance to the success of this initiative. Samples will be used to both support the development of fulvestrant and anastrozole and also new projects targeting the breast cancer disease area.

The benefits of being able to explore associations between biomarker variations and clinical outcomes within the fulvestrant and anastrozole programmes are potentially many; for example, the possibility to identify patients most likely to benefit from treatment, explain potential outliers, such as non-responders or to explain potential adverse reactions related to drug exposure.

2. RESEARCH OBJECTIVES

Biomarker technologies enable the measurement of many different molecules, such as DNA, RNA, proteins and metabolites, within a sample. The objective of this research is to explore how variations in tumour biomarkers (DNA, RNA and/or protein based) may be related to

factors that may influence development of cancer and/or study treatment response and resistance.

3. RESEARCH PLAN AND PROCEDURES

3.1 Research plan

In the study the following samples will be requested:

- Tumour sample(s) (archival and/or recently acquired formalin-fixed paraffin-embedded specimens)

3.2 Selection of biomarker research population

3.2.1 Study selection record

All patients who take part in the study will be asked to participate in this (optional) biomarker research.

3.2.2 Withdrawal of patients from this biomarker research

3.2.2.1 Procedures for withdrawal

Patients who withdraw from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this biomarker research. It must be established whether the patient:

- Agrees to the biomarker samples and any preparations derived from the sample being kept for research in the future

- Withdraws consent for the samples to be kept for biomarker research in the future and wishes the samples to be destroyed. If a patient withdraws consent to the use of donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for biomarker 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.

4. MEASUREMENTS AND CO-VARIABLES

4.1 Summary of objectives and analysis

The purpose of this research is to generate data for use in futher retrospective analyses. These analyses will explore factors, which may influence the disposition, efficacy, safety and

tolerability to fulvestrant or anastrozole and/or susceptibility to or prognosis of cancer. The results of this research may not form part of the clinical study report for the main study. The results may be pooled with data from other studies on fulvestrant or anastrozole to generate hypotheses to be tested in future studies.

4.2 Collection of samples for Biomarker research

AstraZeneca or its designee will act as the central laboratory for sample logistics and laboratory analysis. Details of sample collection, processing, shipping and storage are described in the Laboratory Manual.

The samples and data for analysis in this research will be coded and will not be labelled with any personal details. Each sample will be identified with the study number and patient enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient.

Where genetic analysis will be undertaken the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution for all samples 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 be 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 (or employee's of contract laboratories etc.) working with the DNA. No analysis of heritable genetic changes will be performed, only changes that have occurred somatically in the tumour and which may have a bearing on tumour response eg, mutations in the phosphoinositide 3-kinase (PI3K) gene or loss of phosphatase and tensin homolog (PTEN) may be analysed.

Samples taken previously, as part of routine care, will remain the property of the donating organisation.

4.2.1 Tumour samples

Collection of optional tumour sample for biomarker research

Pre-treatment tumour sample(s) (archival and/or recent) will be obtained only once consent has been given by the patient. The sample(s) may be analysed for a range of oncology biomarkers eg, oestrogen receptors (ER), progesterone receptors (PgR) and other exploratory factors thought to be associated with response and resistance to study treatment.

Patients who consent to participate in the biomarker study and allow the analysis of their pre-treatment tumour tissue for biomarkers will be asked if they consent to a second optional biopsy procedure, if, in the opinion of the investigator, the biopsy procedure does not pose additional significant risks to the patient. If a tumour sample is already available at the time of progression, a further sample is not required. This optional biopsy procedure is for

consideration in the event that the patient progresses while on the trial and has a lesion which is accessible by standard biopsy procedures at the time of progression. This biopsy tissue would be obtained after disease progression while on the trial would be collected for biomarker research on the exploratory factors thought to be associated with resistance to either fulvestrant or anastrazole.

The tumour samples (both the pre-treatment and the optional post-progression biopsy) will preferably be in the form of a formalin fixed paraffin embedded block. If this is not possible, 20 slides of freshly prepared unstained 5 micron sections from the tumour block/s may be provided. Further details on sample processing, handling and shipment are provided in the investigators Laboratory Manual.

4.3 Chain of custody of biological samples

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

The principal investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment and keeps documentation of receipt of arrival.

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

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

Samples retained for further use are registered in AstraZeneca bio bank or external laboratory provider systems during the entire life cycle. Unless repatriation is requested, samples will be stored for a maximum of 25 years from clinical study report completion after which they may be destroyed.

5. MANAGEMENT OF RESEARCH DATA

Some of the dataset from the main study may be duplicated within AstraZeneca for exploratory analyses in combination with the biomarker data. Neither the patient's name nor any other personal identifiers will be part of this dataset. Biomarker data may not be reported in the clinical study report (CSR). Only the date the patient gave consent to participation in the research and the date and time the biological sample(s) (if applicable) was taken from the patient will be recorded in the electronic case report form and database.

AstraZeneca will not provide biomarker research 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 samples 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 research 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 research and the number of whom will have any particular clinical outcome are 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 centre. The requirements described in the main study and this biomarker research will be discussed.

During the study, a representative of AstraZeneca will have regular contacts with the investigational centres. One of the purposes of these visits will be to perform source verification of the informed consent of participating patients and to ensure that the investigational team are adhering to the specific requirements of this biomarker research.

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 samples and biomarker research with a representative of AstraZeneca. The requirements for the collections of the patients' sample will also be made clear.

7.3 Study agreements

The principal investigator at each study centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this research. 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 requirements relating to this biomarker research will be included in the study agreement(s).

8. ETHICS

8.1 Ethics review

Ethics Committee (EC)/Institutional Review Board (IRB) approval of the study with this biomarker research must be obtained and documented from the relevant EC.

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 International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

8.3 Informed consent

To participate in the biomarker component of the study the patient must sign and date the main study consent form and the biomarker research consent form. Patients who also consent to provide an additional (optional) tumour sample on progression must check the appropriate box indicating that they consent to provide this additional sample. Copies of signed and dated consent forms must be given to the patient and the originals filed at the study centre in the investigator's study file. The principal investigator is responsible for ensuring that consent is given freely.

8.4 Patient data protection

All data protection and confidentiality principles, described in the main study protocol, are applicable to this biomarker research.

Due to the exploratory nature of this biomarker research, there will be no routine communication of results to patients. AstraZeneca will not provide individual 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.

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