Amended Clinical Study Protocol

Drug Substance	ZD4054
Study Code	D4320C00015
Edition Number	1
Date	[redacted]

A Phase III, Randomised, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of Once-daily Orally Administered ZD4054 10 mg in Non-metastatic Hormone-resistant Prostate Cancer Patients

Sponsor: [redacted]

AstraZeneca Research and Development site representative

[redacted] Date

[redacted]

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

[redacted]

PROTOCOL SYNOPSIS

A Phase III, Randomised, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of Once-daily Orally Administered ZD4054 10 mg in Non-metastatic Hormone-resistant Prostate Cancer Patients

Investigator

The international coordinating investigator(s) for this study are:

[redacted]

Study centre(s) and number of patients planned

This study will be conducted in approximately 400 hospital-based centres worldwide. The total number of patients planned to be entered into this study is 1500.

Study period		Phase of development
Date of first patient randomised	[redacted]	III
Estimated date of last patient completed	[redacted]	

Total study duration is approximately 4.5 years[redacted] This consists of approximately 18 months' (Japan and China approximately 24 months') recruitment and up to 3 years' follow-up for survival after the last patient is recruited.

[a] The end date given is an estimate of the time taken to reach 590 deaths, and is therefore dependent upon death rate and may vary.

Objectives

Table S1 Study objectives

Study objectives	Study variables
Primary objectives	**Primary outcome variables**
1. To determine the effect of ZD4054 on overall survival compared to placebo	Overall survival, defined as time to death (from randomisation) from any cause
2. To assess the effect of ZD4054 on progression free survival compared to placebo	Progression free survival defined as the time from randomisation until documentation of progressive metastatic disease Progression defined as any of: • One or more new bone lesions on bone scan (confirmed, if ≤3 lesions, by CT, MRI or x-ray) • Development of malignant visceral disease on CT/MRI • Death in absence of progression N.B. Local recurrence of disease resulting in urinary retention and loco-regional node involvement is not classified as progression
Secondary objectives:	**Secondary outcome variables:**
1. To investigate the tolerability and safety profile of ZD4054	Safety and tolerability in terms of incidence and severity of adverse events, vital signs, laboratory data, electrocardiogram (ECG) and physical examination findings
2. To investigate the effect of ZD4054 on time to prostate-specific antigen (PSA) progression compared to placebo	Time to PSA progression, defined as the time to the first PSA value ≥50% from baseline, seen in at least two consecutive PSA values
3. To assess the effects of ZD4054 on Health-related Quality of Life (HRQOL) compared to placebo	Functional well being (FWB) as recorded by the FWB domain of the FACT-P and the total FACT-P score
4. To investigate the effect of ZD4054 on time to symptomatic progression compared to placebo	Time to symptomatic progression, defined as time to pain requiring opiate analgesia due to metastatic disease
Exploratory objectives:	**Exploratory outcome variables:**
1. To assess the effects of ZD4054 on health status compared to placebo	Measured by EQ-5D (EuroQol-5 Dimension)
2. To assess the effects of ZD4054 on the plasma concentration of brain natriuretic peptide (BNP) and explore its utility to predict development of cardiac failure	Plasma concentration of BNP and incidence of cardiac failure

Table S1 Study objectives

Study objectives		Study variables
3.	To collect optional serum and plasma samples for investigation of exploratory biomarkers	Blood samples may be collected for exploratory biomarker research. Future analysis may aim to determine the effect of study treatments versus placebo on biomarkers, their correlation to disease progression / response to therapy or an improved understanding of disease progression
4.	To collect prostate cancer tissue (eg, from diagnostic samples and / or on study TURP or biopsies) from consenting patients and store for further investigation	Available tumour specimens may be collected for exploratory biomarker research. Future analysis may aim to determine the effect of biomarkers on clinical outcomes, including disease progression, and response to study treatments versus placebo
5.	To collect an optional pharmacogenetics sample from consenting patients. DNA will be extracted and stored for possible future analysis	Any genotyping would investigate genes believed to be involved in the response to ZD4054

Study design

This is a randomised, double-blind, parallel-group, multi-centre, 2-arm, Phase III study to assess the efficacy and safety of 10 mg ZD4054 in comparison with placebo, in patients with non-metastatic hormone-resistant prostate cancer. Randomisation will be 1:1, stratified by centre, and patients will be randomised to either ZD4054 or placebo.

Following the start of study therapy all patients may receive standard prostate cancer therapies in the form of:

- Regular follow-up
- Symptomatic therapy for urinary obstruction
- Castration therapy either surgical or medical, including luteinising hormone-releasing hormone analogue (LHRHa), megace, estradiol.

In addition, patients could receive other therapies including prednisolone, estramustine, ketoconazole at investigator's discretion without being considered treatment failures or having to stop study therapy. Chemotherapy may also be administered in addition to study therapy at investigator's discretion after objective progression if the patient is considered likely to derive benefit; though it should be noted that experience with ZD4054 in combination with chemotherapy is limited at the time of initiation of this study.

The following treatments are excluded from the allowed standard/palliative care:

- Any other experimental agent.

Target patient population

A total number of 1500 non-metastatic hormone-resistant prostate cancer patients who have rising serum prostate-specific antigen (PSA) levels despite medical or surgical castration.

Investigational product, dosage and mode of administration

Patients will be randomised 1:1 to receive 10 mg ZD4054, or placebo, given orally once daily in tablet form.

Comparator, dosage and mode of administration

Matched placebo given orally once daily in tablet form.

Duration of treatment

Patients may continue on randomised study treatment after disease progression unless or until another discontinuation criterion is met.

Statistical methods

Overall survival (OS) and progression free survival (PFS) are co-primary endpoints for this study. To preserve the study significance level at 5%, the significance level is set at 4% for OS and 1% for PFS. A total of 590 deaths are required. If the true hazard ratio for ZD4054 versus placebo is 0.75 then the study will have 90% power to demonstrate a statistically significant effect in OS at the 4% significance level. With a total of 1500 patients, a recruitment period of approximately 18 months (Japan and China approximately 24 months) from [redacted] and a median OS for the placebo group of approximately 47 months, it is estimated that 590 deaths will occur approximately 52 months after the first patient entered the study.

There will be 2 formal analyses for this study. OS and PFS will be analysed at the first analysis and OS will be analysed at the second analysis. To account for the 2 analyses of OS, the overall type I error rate of 0.04 will be split using the method proposed by Jennison and Turnbull (Jennison and Turnbull 2000). The significance level at first analysis will be set at 2.5%, and the significance level for the final analysis will subsequently be calculated to preserve the overall type I error rate of 0.04 based on the actual number of observed events at the first and final analyses. For instance, given that 410 events are observed at the first analysis and if 590 events are observed at the final analysis as planned, then the significance level for the final analysis will be 2.62%.

The first analysis will be carried out when 410 deaths have occurred and it is estimated that this will be around 37 months after first patient entered the study. At this point it is estimated that 690 progression events will have occurred. If the true hazard ratio for ZD4054 versus placebo is 0.75 then the study will have greater than 85% power to demonstrate a statistically significant difference in PFS at the 1% significance level. The median PFS is assumed to be around 24 months for the placebo group, based on results from a similar study with atrasentan (presented at ASCO 2007 Multidisciplinary Prostate Cancer Symposium).

[redacted]

The second analysis will be carried out when 590 deaths have occurred and it is estimated that this will be around 52 months after the first patient entered the study.

Overall survival is defined as the time to death from any cause from randomisation into the study. Patients who have not died at the time of the analysis will be censored using the last available assessment date.

Progression-free survival is defined as the time from randomisation to documentation of metastatic disease. Patients who have not had a progression event at the time of analysis will be censored using the last available assessment date.

Time to PSA progression is defined as the time from randomisation to the first PSA value, which is at least 50% higher than the baseline value, seen in at least 2 consecutive PSA values. Patients who have not had a PSA progression at the time of analysis will be censored using the last available assessment date.

Time to symptomatic progression is defined as time to pain requiring the use of opiates due to metastatic disease from randomisation. Patients who have not had a symptomatic progression at the time of analysis will be censored using the last available assessment date. For bone metastasis, metastatic disease must be confirmed by a bone scan and if ≤3 lesions are visible, they must be confirmed by CT, MRI or plain x-ray. For visceral metastasis, metastatic disease must be confirmed by CT or MRI scans. The pain must correlate with the location of the metastasis.

Time to death, progression-free survival, PSA progression and symptomatic progression will be analysed using the log-rank test.

For the FACT-P, raw data and change from baseline will be presented for each treatment group for the total score and each subscale.

For the assessment of tolerability and safety, incidence and severity of adverse events (Aes) (based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 [NCI CTCAE] grading), laboratory values, vital signs ECGs and physical exam will be summarised by dose group.

Demography and baseline data will be summarised by treatment group.

There are 3 analysis sets defined for this study. The intention-to-treat (ITT) population which comprises all randomised patients, the safety analysis set which comprises all randomised patients who received at least one dose of study medication and the quality of life analysis set, which comprises all randomised patients who have valid baseline quality of life data and at least one evaluable follow-up visit data.

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LIST OF SUPPLEMENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.7.1.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Assessment	An observation made on a variable involving a subjective judgement
AST	Aspartate aminotransferase
BAP (serum)	Serum bone specific alkaline phosphatase
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
°C	Degrees Celsius
CNS	Central nervous system
CrCl	Creatinine clearance
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computer tomography
CTX (serum)	C-terminal crosslinking telopeptide
CYP	Cytochrome P450 enzymes
DL	Decilitres
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DQF	Data query form
DUS	Disease Under Study
eCRF	Electronic case report form
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group

Abbreviation or special term	Explanation
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetate
EGF	Epithelial growth factor
EGFR	Epithelial growth factor receptor
EQ-5D	EuroQol-5 Dimension health status questionnaire
ET-1	Endothelin-1
ETA	Endothelin receptor subtype A
ETB	Endothelin receptor subtype B
FACT-P	Functional assessment of cancer therapy for prostate cancer
FWB	Functional well being domain of the FACT-P
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HPLC-MS-MS	High performance liquid chromatography – Mass spectrometry-Mass Spectrometry
HR	Heart rate
HRPC	Hormone-resistant prostate cancer
HRQOL	Health Related Quality of Life
IB	Investigator brochure
ICH	International Conference on Harmonisation
[redacted]	[redacted]
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IP	Investigational Product
IPS	Investigational product section
IRB	Institutional Review Board
ITT	Intention to treat
IVRS	Interactive voice response system
LDH	Lactate Dehydrogenase
LFT	Liver function test
LHRH	Luteinizing hormone-releasing hormone

[redacted]

Abbreviation or special term	**Explanation**
LHRHa	Luteinising hormone-releasing hormone analogue
LIMS	Laboratory Information Management System
LOQ	Limit of quantification
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
Measurement	An observation made on a variable using a measurement device
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Millilitre
mL/min	Millilitres per minute
MmHg	Millimetres of mercury
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
NC	Not calculable
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
ng/dL	Nanograms per decilitre
nmol/L	Nanomoles per litre
NMR	Nuclear magnetic resonance
NQ	Non quantifiable
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 4.7.1.1).
Outcome variable	A usually derived variable, specifically defined to be used in the analysis of a study objective
P	Plasma
PCRF	Paper Case Report Form
PCS	Prostate Cancer Symptom
PD	Pharmacodynamic
PFS	Progression Free Survival

Abbreviation or special term	Explanation
PGx	Pharmacogenetics
Principal Investigator	A person responsible for the conduct of a clinical study at a study site. Every study centre has a principal investigator.
PRN	As required
PRO	Patient reported outcomes
PSA	Prostate Specific Antigen
OS	Overall Survival
QTc	Corrected QT duration
SAE	Serious adverse event (see definition in Section 4.7.1.1).
SAP	Statistical analysis plan
SAS	Statistical analysis system
SDV	Source Document Verification
TURP	Transurethral resection and prostatectomy
U	Urine
ULN	Upper Limit of Normal
Variable	A characteristic of a property of a patient or healthy volunteer that may vary eg, from time to time or between patient or healthy volunteer
VAS	Visual analogue score
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White Blood Cell Count
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

The main purpose of this study is to assess the effect of ZD4054 on progression free survival (PFS) and Overall Survival (OS) compared to placebo (reflecting standard care alone) in men with non-metastatic hormone-resistant prostate cancer. Information about the pre-clinical and clinical studies to date for ZD4054 is covered in detail in the Investigator Brochure (IB). The IB is intended to facilitate the investigator's understanding of the compound for clinical studies in which the product is administered in tablet form.

1.1.1 Prostate cancer

Even though radiation therapy and radical prostatectomy provide excellent cancer control for men with prostate cancer, prostate-specific antigen (PSA) recurrence develops in up to 35% of patients within 10 years of their primary therapy (Freedland et al 2005, Hanks et al 2002). In a large retrospective study, the median time from biochemical recurrence to metastasis was 8 years and the time from metastasis to death, 5 years (Pound et al 1999). For men who go on to develop metastatic disease, PSA recurrence is clearly the first indication that the cancer has returned, and investigators are currently initiating therapy with rising PSA before metastases are evident. There is no standard therapy for men with a PSA-only recurrence; a number of therapies are presently being evaluated, along with watchful waiting. A major treatment modality used in these men is hormonal therapy consisting of either a luteinising hormone releasing hormone analogue (LHRHa) alone or in combination with an anti-androgen. Despite the ability of hormonal therapy to slow or reverse the PSA rise in these men, in the vast majority PSA does eventually start to rise and the prostate cancer becomes hormone-resistant prostate cancer (HRPC). Due to the large number of men living with prostate cancer today (230,000 new cases/year in the US and 30,000 new cases /year in the UK (Cancer Research UK, American Cancer Society), a large number of men advance into a state of HRPC.

1.1.2 Endothelin and endothelin receptors

Three endothelin isoforms have been characterised (ET-1, ET-2 and ET-3), and 2 receptors (ET_A and ET_B). ET-1, originally identified as a potent vasoconstrictor, has been implicated in various aspects of tumour progression, including proliferation, apoptosis, angiogenesis (Dawas et al 1999), bone remodelling in metastatic disease (Kozawa et al 2000), and modification of tumour blood flow (Chaplin et al 1998). The predominant actions of ET-1 appear to be mediated via the ET_A receptor (Levin 1995). There is also evidence suggesting that the ET_A receptor is involved in mediating nociceptive effects associated with ET-1 and in stimulating proliferation and differentiation of osteoblasts. ET_A-receptor blockade reduces the formation of bone metastases in vivo. There has been particular interest in the role of ET-1 in prostate cancer (reviewed by Nelson and Carducci 2000). Elevated levels of circulating ET-1 have been found in men with metastatic prostate cancer, as has over-expression of the ET_A receptor in prostate cancer cells and down-regulation of the ET_B receptor, which is thought to induce cell apoptosis and acts as a clearance mechanism for plasma ET-1 (Fukuroda et al

1994). The ideal profile proposed for an endothelin antagonist for use in the treatment of prostate cancer is a specific ET_A receptor antagonist which has no inhibitory activity at the ET_B receptor. This should block the cell proliferation and survival signals mediated by ET_A receptor, while allowing the beneficial ET_B receptor mediated tumour cell apoptosis and ET-1 clearance.

1.2 Rationale

This study will be conducted in men with non-metastatic prostate cancer that is resistant to hormonal therapy (HRPC) to evaluate the ability of ZD4054 to prolong OS and PFS. All patients entered into this study will have rising PSA despite medical or surgical castration. Currently, no standard therapy exists for men fitting this profile, and numerous therapies are currently being used in these patients, including watchful waiting. A recent study evaluating the natural history of men with non-metastatic HRPC demonstrated a median PFS of 30 months (Smith et al 2005).

Study D4320C00006 (4054IL/0006) was a Phase II study that compared 2 doses of ZD4054 versus placebo in men with metastatic HRPC. In the first analysis of the study, there was a reduction in the risk of progression for both ZD4054 10 mg and ZD4054 15 mg, however this did not reach statistical significance. The study also showed an improvement in survival for both doses of ZD4054 versus placebo (second analysis results: ZD4054 15 mg versus placebo HR = 0.65, 80% CI (0.49 to 0.86), p = 0.051; ZD4054 10 mg versus placebo HR = 0.55, 80% CI (0.41 to 0.73), p = 0.008). As this study demonstrated that ZD4054 has activity in patients with asymptomatic or mildly symptomatic metastatic HRPC, it is appropriate to assess the effects in a population of men with HRPC but no evidence of metastatic disease. Watchful waiting on a background of continued hormonal treatments is considered an appropriate therapy in non-metastatic hormone-resistant prostate cancer and therefore the comparator to ZD4054 in this study will be placebo on a background of standard prostate cancer therapies.

The most common site of metastasis in HRPC is bone, which often has significant symptomatic sequelae, such as severe pain or pathologic fractures. Therefore, increasing the survival time prior to the development of metastasis in these men will have a clear clinical benefit. In the study by Smith referenced above, the median PFS in men with baseline PSA >7.7 ng/mL was estimated to be <2.5 years, whereas median PFS was not reached by 3 years in men with PSA values <7.7 ng/mL. Therefore men with higher baseline PSAs at presentation had a faster time to progression. The patients randomised onto the Smith study had a median PFS of 13.8 with a 25^{th} percentile level of 5.6 ng/mL. Since the patient population will be derived from a similar pool of patients in this protocol, the range of PSA values should be similar to what was observed by Smith, and therefore no stratification based on PSA will be used for this study.

The collection of serum and tissues samples for exploratory biomarker work provides an opportunity to investigate as yet unidentified biomarkers that correlate to parameters such as response to therapy. Data generated in this study may also form part of a pooled analysis with other ZD4054 studies. Exploratory biomarker data will not be reported in the Clinical Study Report (CSR).

Collection of an optional blood sample for pharmacogenetics will allow for ZD4054 studies to explore how genetic variations may affect clinical parameters associated with ZD4054. Data generated in this study may also form part of a pooled analysis with other ZD4054 studies. Pharmacogenetics data will not be reported in the CSR.

2. STUDY OBJECTIVES

2.1 Primary objectives

The primary objectives of this study are:

1. To determine the effect of ZD4054 on overall survival (OS) compared to placebo, where overall survival is defined as time to death (from randomisation) from any cause

2. To assess the effect of ZD4054 on progression free survival (PFS) compared to placebo. PFS is defined as the time from randomisation until documentation of progressive metastatic disease, where progression is defined as any of:

   - One or more new bone lesions on bone scan (confirmed, if ≤3 lesions, by CT, MRI or x-ray)
   - Development of malignant visceral disease on CT/MRI
   - Death in absence of progression.

N.B. Local recurrence of disease resulting in urinary retention and loco-regional node involvement is not classified as progression.

2.2 Secondary objectives

The secondary objectives of the study are:

1. To investigate the tolerability and safety profile of ZD4054

   - Adverse events
   - Vital signs
   - Laboratory data
   - ECGs
   - Physical examination

2. To investigate the effect of ZD4054 on time to prostate-specific antigen (PSA) progression compared to placebo, where time to PSA progression is defined as the time to the first PSA value ≥50% from baseline seen in at least 2 consecutive PSA values

3. To assess the effects of ZD4054 on Health-related Quality of Life (HRQOL) compared to placebo

4. To investigate the effect of ZD4054 on time to symptomatic progression compared to placebo, defined as time to pain requiring opiate analgesia due to metastatic disease (where metastatic disease has been previously confirmed by bone scan or CT/MRI).

2.3 Exploratory objectives

The exploratory objectives of the study are:

1. To assess the effects of ZD4054 on health status compared to placebo, as measured by the EQ-5D (EuroQol-5 Dimension)

2. To assess the effects of ZD4054 on the plasma concentration of brain natriuretic peptide (BNP) and explore it's utility to predict development of cardiac failure

3. To collect optional serum and plasma samples for investigation of exploratory biomarkers. Blood samples may be collected for exploratory biomarker research. Future analysis may aim to determine the effect of study treatments versus placebo on biomarkers, their correlation to disease progression / response to therapy or an improved understanding of disease progression

4. To collect prostate cancer tissue (eg, from diagnostic biopsies and / or on study TURP or biopsies) from consenting patients and store for further investigation. Available tumour specimens may be collected for exploratory biomarker research. Future analysis may aim to determine the effect of biomarkers on clinical outcomes, including disease progression, and response to study treatments versus placebo

5. To collect an optional pharmacogenetics sample from consenting patients. DNA will be extracted and stored for possible future analysis. Any genotyping would investigate genes believed to be involved in the response to ZD4054.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

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

This is a randomised, double-blind, parallel-group, multi-centre, 2-arm, Phase III study to assess the efficacy and safety of 10 mg ZD4054 in comparison with placebo in non-metastatic patients with hormone-resistant prostate cancer. Randomisation will be 1:1, stratified by centre and patients will be randomised to either ZD4054 or placebo. Approximately 1500 non-metastatic hormone-resistant prostate cancer patients who have rising serum prostate-specific antigen levels despite medical or surgical castration will be recruited. They will be recruited into approximately 400 hospital-based centres globally.

Patients will receive 10 mg ZD4054 or placebo, given orally once daily (see Section 3.4) until a discontinuation criterion is met. After progression, survival status will be assessed every 6 months.

Following the start of the study, patients may receive standard prostate cancer therapies which may include any of the following: regular follow up; symptomatic therapy for pain control or urinary obstruction and castration therapy either surgical or medical, including luteinising hormone-releasing hormone analogue (LHRHa), megace, estradiol. In addition patients could receive other therapies including prednisolone, ketoconazole at the investigator's discretion without being considered treatment failures or having to stop ZD4054 or placebo therapy. Following disease progression, patients may continue on randomised study treatment unless or until another discontinuation criterion (outlined in Section 3.3.5.1) is met. Chemotherapy may also be administered in addition to study treatment at the investigator's discretion after objective progression if the patient is considered likely to derive benefit; though it should be noted that experience with ZD4054 in combination with chemotherapy is limited at the time of initiation of this study.

Patients will attend study visits and have assessment performed according to the schedule detailed in the Study Plan Table 1. All patients will undergo a bone scan and CT or MRI scan of the abdomen and pelvis (and additional regions where clinically indicated) at entry and then every 16 weeks until progression.

If a patient discontinues study therapy before a progression criteria is met, AEs will be collected for the first 28 days. The patient will be followed up every 16 weeks until progression, and thereafter every 6 months for survival and enquiry about onset of symptoms from metastases, until the final survival analysis is performed.

For patients who continue study therapy after progression, AEs will be continue to be collected along with other assessments every 6 months as per Study Plan Table 1. For patients

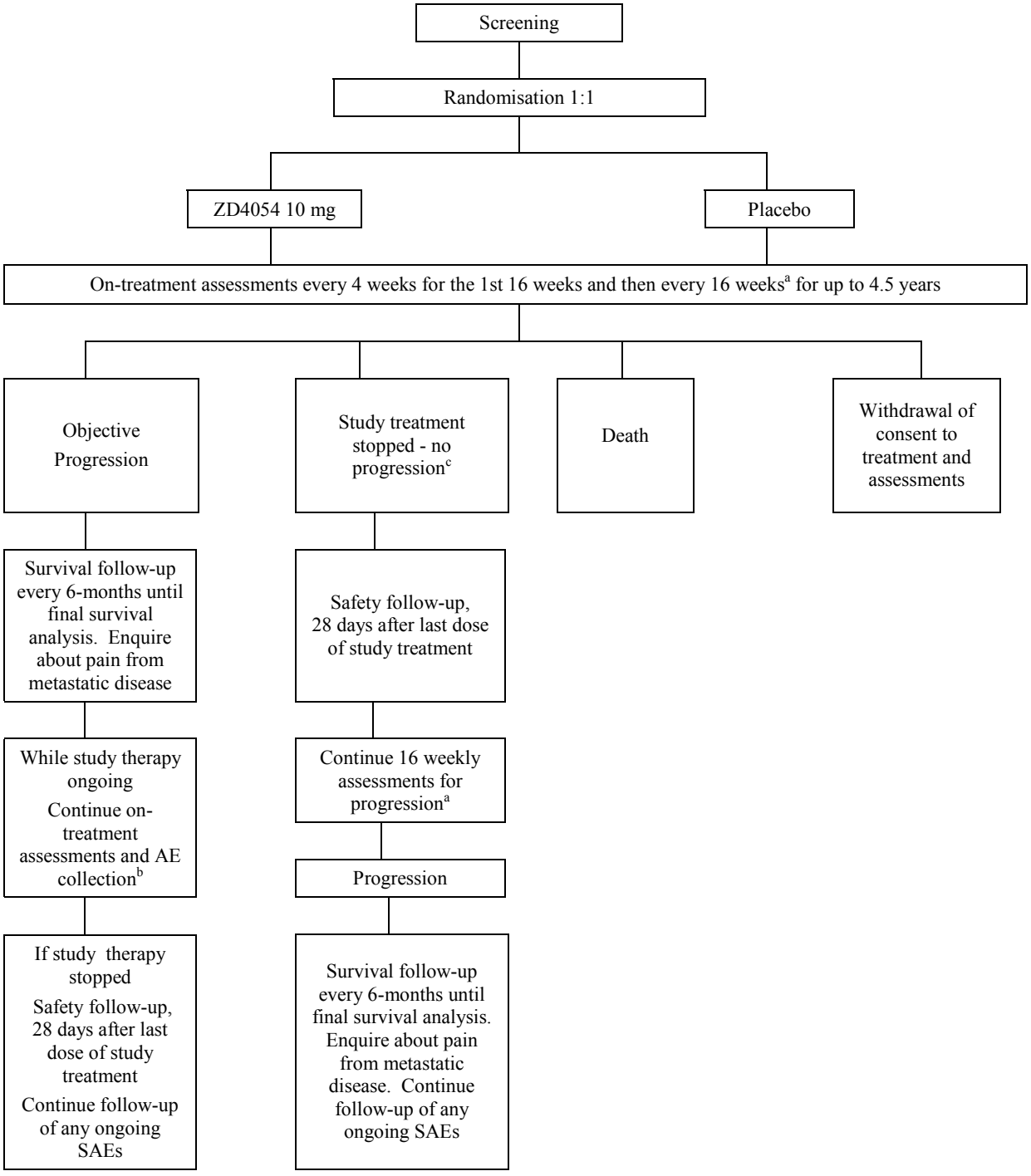
who subsequently stop study therapy, AEs will be continue to be collected for the first 28 days off study therapy.

Serum and tissue biomarker samples, and genetic samples will be obtained from consenting patients and stored for long-term experimental purposes.

Adverse events will be collected throughout the study (see Section 4.8). There will be an Independent Data Monitoring Committee (IDMC) responsible for the review of safety and efficacy data on an ongoing basis, as detailed in Appendix L.

A study flow chart is provided in Figure 1.

Figure 1 Study flow chart



[a] Once 690 progression events have occurred, 16 weekly assessments for progression are no longer required. Patients will be followed for progression, only as clinically indicated, and survival.

[b] Patients continuing on study drug after final analysis (590 deaths) have occurred will be followed for SAE data only.

[c] Patients who are withdrawn from the study for safety and tolerability reasons.

[redacted]

[redacted]

Table 1 D4320C00015 study plan

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7, 8 etc**	**101, 102 etc**	**200**	**201**	**301, 302 etc**	**400, 401 etc**
	Visit	**Screen**	**Baseline/ Random-isation [a]**						**On treatment follow-up post progression**	**Discontin-uation of study drug**	**28-day safety follow-up**	**Off treatment follow-up to progression**	**Off treatment follow-up for Survival post progression**
Event or Assessment	**Week [b]**		**0**	**4**	**8**	**12**	**16**	**32, 48 etc**	**6 monthly**			**Every 16 weeks**	**6 monthly**
Informed consent [c]		X											
Inclusion/ exclusion criteria		X	X										
Medical/ Surgical history		X											
Physical examination / weight		X	X	X	X	X	X	X	X	X	X		
Vital signs		X	X	X	X	X	X	X	X	X	X		
ECG [d]		X		X						X			
Adverse events [j]			X	X	X	X	X	X	X	X	X		
Clinical chemistry/ haematology [e]		X		X	X	X	X	X	X	X	X		
BNP [e]			X	X	X	X	X	X	X	X	X		
Urinalysis		X		X	X	X	X	X	X	X	X		
Prostate-specific antigen (PSA)[f]			X				X	X	X	X			
Concomitant medication		X	X	X	X	X	X	X	X	X	X		
Chemotherapy/opioid medication			X	X	X	X	X	X	X	X	X	X	X
Bone scintigraphy [g]		X					X	X				X	
Tumour Assessment (by CT/MRI) [h]		X					X	X				X	
Study medication dispensing / return			X	X	X	X	X	X	X	X			
EQ-5D (Health Status)		X	X				X	X		X			

[redacted]

[redacted]

Table 1 D4320C00015 study plan

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7, 8 etc**	**101, 102 etc**	**200**	**201**	**301, 302 etc**	**400, 401 etc**
	Visit	**Screen**	**Baseline/ Random-isation [a]**						**On treatment follow-up post progression**	**Discontin-uation of study drug**	**28-day safety follow-up**	**Off treatment follow-up to progression**	**Off treatment follow-up for Survival post progression**
Event or Assessment	**Week [b]**		**0**	**4**	**8**	**12**	**16**	**32, 48 etc**	**6 monthly**			**Every 16 weeks**	**6 monthly**
FACT-P		X	X				X	X		X			
Exploratory biomarker serum [i] sample			X				X			X			
Genetic sampling (optional)			X										
Survival									X [m]				X [m]
Enquiry about disease symptoms post progression									X				X
Tumour tissue sample for exploratory biomarker research [k]			X [l,m]										
Exploratory cell death biomarker plasma sample [n]		X		X	X	X	X	X		X			

[a] Baseline assessments must be carried out before administration of first dose of study treatment, except where specifically indicated.

[b] Visits must occur within +/- 3 days of the scheduled date for the 4 weekly visits, within +/- 2 week for the 4 monthly visits and +/- 4 weeks of the scheduled date for the 6-monthly survival visits

[c] Informed consent is to be obtained within 6 weeks before randomisation

[d] 12-Lead ECGs (2 identical copies at each time point) obtained in accordance with Section 4.7.3

[e] Clinical Chemistry and haematology to establish eligibility are to be performed a maximum of 4 weeks prior to randomisation by the central laboratory. BNP to be performed at baseline and then every following visit, however the utility of BNP data will be reviewed and if it is not found to be predictive of development of cardiac failure it will cease to be performed. Residual samples may be analysed for exploratory biomarkers.

[f] The baseline PSA and all subsequent PSAs will be from the central laboratory.

[redacted]

[redacted]

[g] A bone scan to confirm eligibility is to be performed a maximum of 4 weeks prior to randomisation. If the Investigator discontinues trial therapy for clinical reasons including PSA progression, bone scans should continue to be performed every 16 weeks until progression. Whole body anteroposterior and posteroanterior bone scans should be performed.

[h] Abdominal and pelvis CT or MRI scans to be performed a maximum of 4 weeks prior to randomisation. Additional regions (eg, chest CT) should be included where clinically indicated to exclude metastatic disease at baseline. Any other sites at which new disease is suspected should also be appropriately imaged.

[i] Exploratory biomarker serum samples to be taken at discontinuation or last assessment visit if the patient is continuing study drug.

[j] After final data cut-off patients continuing on study treatment will be followed for SAEs only and survival.

[k] On study TURP or biopsy samples freshly acquired on study treatment as clinical practice permits and patients consent to exploratory research

[l] Original diagnostic block should be located and acquired at screening visit for those patients consenting to exploratory biomarker research

[m] Telephone contact permissible for these visits (there may be an additional contact for survival data close to data cut-off)

[n] Exploratory cell death biomarker sampling will be performed by sites that have the required equipment. Residual samples may be analysed for exploratory biomarkers

[redacted]

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

This Phase III study will be randomised and blinded to minimise potential bias between the 2 different treatment arms. Currently, no agent has been proven to improve overall survival or progression free survival in men with hormone-resistant non-metastatic prostate cancer, although a number of agents are used to manage any symptoms and rising PSA values. A placebo comparator is therefore appropriate though all patients will be allowed to receive certain other medications to control disease.

Doses of 10 mg and 15 mg daily were assessed in the Phase II study (D4320C00006 (4054IL/0006)), both showed a clinical benefit in terms of improved survival compared with placebo and were well tolerated. Doses below 10 mg daily appear to have less pharmacological activity and have therefore not been studied in terms of clinical endpoints. As the 10 mg doses appears equally effective to the 15 mg dose in the Phase II setting, this is the dose selected for further study.

3.2.2 Risk/benefit and ethical assessment

ZD4054 has been studied in a number of clinical studies to date with over 200 patients being exposed to drug in the Phase II setting. The most common adverse effects, principally headache, rhinitis, oedema reflect the pharmacology of the drug and are manageable and considered tolerable rather than significant safety concerns. An increased reporting of cardiac failure was seen compared with placebo in one previous study, this was also reported with another endothelin receptor antagonist, atrasentan. The reported incidence of cardiac failure as a serious adverse event is low at approximately 5%. Investigators and patients will be made aware of safety profile from previous studies and advised on management approaches for adverse effects (see Section 3.10).

The onset of metastatic prostate cancer is associated with deterioration in quality of life, development of symptoms, particularly pain and urinary problems, and life expectancy is reduced. Given the potential to delay the onset of metastatic disease and ultimately improve survival in men with hormone-resistant prostate cancer, the benefits of studying ZD4054 are considered to outweigh the risks involved. Furthermore, it is considered appropriate to study ZD4054 in comparison with placebo in large scale Phase III studies given that patients under study are not being deprived of any active proven therapy.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled eg, patient screening log. This information is necessary to establish that the patient population was selected without bias.

[redacted]

3.3.2 Inclusion criteria

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

1. Provision of informed consent

2. Male, aged 18 years or older

3. Histological or cytological confirmation of adenocarcinoma of the prostate

4. No evidence of metastatic disease, local recurrence or pelvic lymph node disease on:

   - CT scan of chest (CT chest scan only to be performed if clinically indicated i.e. if lung metastases are suspected)
   - CT scan or MRI of abdomen/pelvis
   - Bone scan

5. Biochemical progression of prostate cancer, documented while the patient is castrate. Diagnostic studies will be performed to rule out local recurrence as the cause of the rising PSA if there is suspicion of a prostatic bed/pelvic lymph node:

   - Biochemical progression is defined as at least 2 stepwise increases in PSA over a period of ≥1 month (values do not need to be consecutive but 2 values that have increased since the previous highest value are required) with at least 14 days between each measurement irrespective of assay or laboratory
   - Historical values may be used
   - The last PSA must be an increase of ≥50 % of the first PSA value used (of the 3 values selected for assessment) or an absolute increase of ≥10 ng/mL over the initial PSA
   - The final PSA value must be ≥1.2 ng/mL in patients who have had a radical prostatectomy and ≥5 ng/mL in all other patients

6. Surgically castrated or continuously medically castrated with serum testosterone ≤2.4 nmol/L (70 ng/dL), with stable treatment for 8 weeks.

7. World Health Organisation (WHO) performance status 0 – 1

8. Life expectancy of 6 months or more.

For inclusion in the genetic research, patients must fulfil the following criterion:

1. Provision of informed consent for genetic research.

If a patient declines to participate in the genetic 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 participate.

3.3.3 Exclusion criteria

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

1. Current use (from the time that written informed consent is given) of any opiates, with the exception of opiates taken PRN for non-disease-related symptoms

2. Definitive therapy to treat the patient's primary prostate cancer (prostatectomy, radiotherapy, cryotherapy) within 3 months prior to study entry

3. Prior cytotoxic chemotherapy (such as paclitaxel, docetaxel and mitoxantrone) for the treatment of recurrent prostate cancer (prior estramustine therapy is allowed), as well as other targeted cancer therapies (such as EGF, EGFR, VEGF and VEGFR)

4. Use of intravenous bisphosphonates within 6 weeks prior to start of study treatment. Oral bisphosphonates for prevention and/or treatment of osteoporosis are permitted. Oral bisphosphonate dose must be stable for a minimum of 4 weeks prior to starting study treatment. Intravenous bisphosphonates are permitted after disease progression, however dose must be stable within trial

5. Use of potent CYP450 inducers (such as phenytoin, rifampicin, carbamazepine and phenobarbitone, St John's Wort) within 2 weeks prior to start of study treatment. Dexamethasone will be allowed if the investigator feels it is necessary but is encouraged to use a different form of steroid treatment wherever possible

6. Use of systemic retinoids within 2 weeks prior to starting study treatment

7. Have received investigational drug in another clinical study of anticancer therapy, within 4 weeks prior to starting study treatment

8. Prior therapy with endothelin receptor antagonists or family history of hypersensitivity to endothelin antagonists

9. History of past or current epilepsy, epilepsy syndrome, or other seizure disorder

10. Stage II, III or IV cardiac failure (classified according to New York Heart Association (NYHA) classification) or myocardial infarction within 6 months prior to study entry

11. QT interval corrected for heart rate (eg, by Bazett's correction) >470 msec

12. Previous history or presence of another malignancy, other than prostate cancer or treated squamous/basal cell carcinoma of the skin, within the last 5 years

[redacted]

13. In the opinion of the investigator, any evidence of severe or uncontrolled systemic disease (eg, currently unstable or uncompensated respiratory, cardiac, hepatic or renal disease) or evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the study

14. Haemoglobin (Hb) <9 g/dL. Concomitant use of erythropoietin or blood transfusions is allowed

15. Serum bilirubin greater than 1.5 times the upper limit of normal (ULN). This will not apply to patients with Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician

16. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the ULN

17. Creatinine clearance of <50 mL/minute, determined using the Cockcroft-Gault equation or by 24-hour creatinine clearance

18. Patients who discontinue after randomisation cannot be re-enrolled. Patients who fail to meet the inclusion/exclusion criteria may be reconsidered once for participation in the study. Patients who are re-enrolled must re-consent and will be assigned a new enrolment number

19. Involvement in the planning and conduct of the study ([redacted] and AstraZeneca staff or staff at the study site).

The following are regarded as exclusion criteria for genetic research:

1. The patient has undergone a previous bone marrow transplant

2. The patient has undergone a whole blood transfusion in the preceding 90 days.

3.3.4 Restrictions

1. Medically castrated patients must remain on castration therapy throughout the study, and must have been on stable treatment for a minimum of 8 weeks prior to starting study treatment. The castration therapy dose must also remain stable during the study.

2. Oral bisphosphonates must be at a dose that is stable for a minimum of 4 weeks prior to starting study treatment. The dose must also remain stable whilst on study.

3. Avoid pro-creative sex from receiving the first dose of ZD4054 until 4 months after receiving the last dose of ZD4054. All patients, if sexually active and not surgically sterile, should practice reliable methods of birth control to prevent pregnancy (eg, spermicidal foam and condoms) during the study.

3.3.5 Discontinuation of patients from treatment or assessment

Patients may be discontinued from study treatment and assessments at any time. All study assessments should be continued in patients who only discontinue from study treatment. All patients will be followed up for progression and survival, unless they withdraw consent.

3.3.5.1 Criteria for discontinuation

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

- Voluntary discontinuation by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Patient lost to follow-up.

Specific reasons which may result in discontinuing a patient from study treatment are:

- Incorrect enrolment. Patients who are found not to meet the required inclusion/exclusion criteria for the study must be discussed with the AstraZeneca study team physician. Each case will be reviewed individually and a decision made as to whether the patients must be discontinued.
- Disease progression. Investigators should consider alternative therapies in patients who progress on trial therapy; however, blinded trial therapy may be continued at investigator discretion in patients who commence alternative prostate cancer therapies as outlined in Section 3.1. The Investigator can discuss with the study team physician before making a judgement.

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s) including completion of FACT-P and EQ5D. Adverse events should be followed up and investigational products should be returned by the patient.

If study treatment is stopped during the study, the Principal Investigator/Sub-investigator should perform the best possible observation(s), test(s) and evaluation(s) as well as give

[redacted]

appropriate treatment and all possible measures for the safety of the patient. In addition, they will record on the eCRF the date of withdrawal, the reasons, and treatment at the time of withdrawal and also course, treatment and outcome after withdrawal. They will also immediately inform [redacted] of the withdrawal. Any serious adverse events should be communicated to [redacted] within the usual timelines.

All patients who have any CTC grade 3 or 4 laboratory values at the time of withdrawal should have further tests performed and the results recorded on the appropriate eCRF until the laboratory values have returned to CTC grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

At discontinuation, all on-going study-related toxicities and SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

3.3.5.3 Procedures for handling incorrect enrolled patients

Patients not meeting the inclusion/exclusion criteria for a study should not, under any circumstances, be enrolled into the study - there can be no exceptions to this rule. The inclusion and exclusion criteria must be strictly adhered to (see Sections 3.3.2 and 3.3.3). If any patient is found to have been entered into the study in violation of the selection criteria, this must be discussed with the Study Team Physician, who will make a decision regarding whether the patient should continue in this study. This must be documented in detail by the Study Team Physician, and by the investigator in the patient's medical notes.

3.3.5.4 Procedures for discontinuation from genetic aspects of the study

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

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

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

3.4 Treatments

3.4.1 Identity of investigational product and comparators

AstraZeneca will manufacture active and placebo ZD4054 beige film coated tablets for oral use. ZD4054 and placebo will be packed into white high-density polythene (HDPE) bottles with child-resistant, tamper-evident closures. Each bottle will contain 35 tablets, 4 weeks' supply plus one week clinical overage.

Table 2 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number [a]
ZD4054	10 mg beige film coated tablet	AstraZeneca	F013466	
Placebo to match ZD4054	10 mg beige film coated tablet	AstraZeneca	F013544	

[a] Batch number will be recorded in the Study Master File and identified in the Clinical Study Report

3.4.2 Doses and treatment regimens

3.4.2.1 ZD4054 or placebo regimen

Blinded doses of ZD4054 (10 mg) and matched placebo will be supplied and administered as follows:

- The doses used are as follows:
  - ZD4054 10 mg and matching placebo
  - Beige film-coated tablets for oral use
  - Once daily orally
  - To be swallowed whole with water
  - To be taken at approximately the same time each morning ±2 hours, except on study visit days when patients should not take their dose until instructed to do so by the investigator
  - Patients should not take a late dose if there are less than 12 hours before their next scheduled dose, thereby missing a dose. Missed doses will be recorded.
  - If study treatment is interrupted due to a CTCAE grade 3 or greater non-haematological adverse event or a CTCAE grade 4 haematological adverse event, there must be resolution of the event to CTCAE grade 2 or less prior to

restarting study treatment. The dose of study treatment will remain at 10 mg on restarting.

3.4.3 Labelling of ZD4054/Placebo

All investigational product supplies will be packaged, labelled and dispatched in accordance with Good Manufacturing Practice and local regulations, stating that the material is for clinical trial/Investigational use only and should be kept out of the reach of children. Bottles will be labelled with the following information:

- Name of the sponsor (AstraZeneca) and[redacted]
- Product description
- Study code
- Directions for use
- Expiry date
- Storage conditions
- Bottle number
- A space for the date of dispensing, which is to be completed at the time of dispensing.

Information from the label will be transcribed on to the eCRF at dispensing. The investigator (or their delegate) must verify the bottle number to ensure that each patient is given the correct study medication.

Investigational site dispensary staff will dispense the investigational product as prescribed by the investigator.

3.4.4 Storage

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

3.4.5 Accountability

The study treatment(s) must be used only as directed in the protocol. Records of overall dispensing and returns will be maintained by each centre. Treatment dispensed will be recorded on the eCRF.

It is the investigator's responsibility to maintain accurate records, so that at the end of the study it is possible to reconcile delivery records with records of usage and destroyed/returned

[redacted]

stock. This record keeping consists of a dispensing record including the identification of the patient to whom the study treatment was dispensed, the quantity and date of dispensing and any unused study drug returned to the investigator. This record is in addition to any drug accountability information recorded on the eCRF.

Patients must return all unused medication and empty containers to the investigator, who will retain these until they are collected by [redacted] authorised personnel, together with any study treatment not dispensed. In the case that any study drug is damaged please contact [redacted] authorised personnel for reconciliation and replacement.

At the termination of the study or at the request of the sponsor, unused drug should be destroyed locally at the study sites where the capability exists. If this is not possible the drug should be returned to the local distribution centre after the [redacted] monitor has performed drug reconciliation.

3.5 Interactive Voice Response System (IVRS)

An interactive voice response system (IVRS) (ICOPhone) will be used for site activation, patient registration, study medication assignment, verification of dispensed study drug, allocation of patient numbers as patients are randomised, treatment replacement, confirmation of study drug shipments to both sites and depots and emergency code breaks. The system is accessible by telephone 24 hours per day, 7 days per week via a toll free number. Each site will be provided with an IVRS manual containing full instructions on its use.

3.6 Method of assigning patients to treatment groups

As patients are screened for the study, they must be allocated an E-code. This number is the patient's unique identifier and is used to identify the patient on the eCRF. For this study IVRS (ICOPhone) will be used to enrol patients. When a patient is entered into screening the Investigator should contact the Centralised Registration/Randomisation Centre by telephone to register the patient. Patients will be randomised in a 1:1 ratio to ZD4054 or matched placebo stratified by centre. All screened patients are assigned an E-code irrespective of whether or not they are subsequently randomised to receive study treatment.

If a patient discontinues from the study after randomisation, the patient E-code number will not be re-used, and the patient will not be allowed to re-enter the study. If a patient fails screening, the E-code will not be re-used. If the patient is re-screened, a new E-code will be assigned.

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as patients are eligible for randomisation. Once the eligibility of a patient has been confirmed, the Investigator should contact the Centralised Registration/Randomisation Centre by telephone for the issue of a patient randomisation code and allocation of randomised therapy. Patients will be identified to the Centralised Registration/Randomisation Centre using patient initials, E-code and date of birth. The Centralised Registration/Randomisation Centre will inform the Investigator of the patient randomisation number, following which treatment will be allocated to the patient.

At each dispensing visit the medication identification number must be checked to ensure that it matches the number allocated by IVRS, prior to treatment dispensation. If a treatment is incorrectly dispensed (eg, medication identification number does not match the number allocated by IVRS), the error should be rectified and [redacted] should be notified as soon as the error is discovered.

The inclusion and exclusion criteria must be strictly adhered to (see Sections 3.3.2 and 3.3.3). If any patient is found to have been entered into the study in violation of the selection criteria, this must be discussed with the Study Team Physician, who will make a decision regarding whether the patient should continue in this study. This must be documented in detail by the Study Team Physician, and by the investigator in the patient's medical notes.

The actual treatment given to individual patients will be determined by a randomisation scheme. The Biostatistics group at AstraZeneca will generate the randomisation schedule, which will be stratified by centre. The randomisation scheme and associated codebreaks, giving details of individual patient treatment, will be produced by computer software that incorporates a standard procedure for generating random numbers. The patients will be allocated to treatment in balanced blocks.

3.7 Blinding and procedures for unblinding the study

3.7.1 Methods for ensuring blinding

The study medication (ZD4054 and placebo) will be supplied as beige film-coated tablets. ZD4054 with matching placebo will be identical and presented in the same packaging to ensure blinding of the medication. Labels will be blinded to treatment assignment. Medication will be labelled using a unique material pack code which is linked to the randomisation scheme. The Centralised Registration/Randomisation Centre will assign the bottle of study material to be dispensed to each patient at each visit.

All study personnel (except the Independent Data Monitoring Committee) will be unaware of the randomised treatment until all decisions on the evaluability of the data from all patients have been made and documented.

3.7.2 Methods for unblinding the study

The ZD4054 and placebo tablets will be identical and presented in the same packaging to ensure blinding of the medication. The patient's randomisation code break will be available through the Centralised Registration/Randomisation Centre. The procedure for this will be described in the IVRS manual that will be provided to each investigational centre.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation. Where appropriate, the investigator will consult with the study team physician to ascertain whether the situation warrants breaking the code (See Section 9.2). The investigator(s) must document and report to [redacted] any breaking of the treatment code. The investigator may break the code only after a decision has been made to withdraw the patient from the study and if the

[redacted]

investigator requires immediate knowledge of the study medication to optimise the clinical management of the patient. AstraZeneca Drug Safety retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluablility of the data from each individual patient have been made and documented. The Independent Data Monitoring Committee (IDMC) will be provided with the random scheme prior to first patient randomised; they will review grouped but blinded data initially but are free to request breaking of the blind whenever deemed necessary.

The randomisation schedule will be made available on a confidential basis to the personnel in Global Drug Metabolism and Pharmacokinetics and Bioanalysis department responsible for the analysis of any pharmacokinetic samples. This is to avoid unnecessary work in the analysis of subjects randomised to placebo.

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

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

Use of the following drugs and treatments is not allowed prior to randomisation to the study (see Section 3.3.3):

- Any opiates taken for pain related directly to prostate cancer, from the time that written informed consent is given. Opiates taken PRN for pain not directly related to prostate cancer will be allowed.
- Prostatectomy, radiotherapy or cryotherapy within 3 months prior to starting study treatment.
- Cytotoxic chemotherapy for the treatment of their prostate cancer (eg paclitaxel, docetaxel).
- Systemic retinoids within 2 weeks of starting study treatment.
- Endothelin receptor antagonists.

Patients who progress on trial therapy may commence alternative prostate cancer therapies (eg, bisphosphonates) as clinically indicated, even if, at the investigators discretion, the patient continues on blinded trial therapy.

Use of the following drugs and treatments is restricted during the study, including after disease progression while the patient is treated with ZD4054 (see Section 3.3.4):

- Patients taking oral bisphosphonates must be on a stabilised dose for a minimum of 4 weeks prior to starting study treatment, and must remain on the same dose whilst

taking part in the study. In patients where oral bisphosphonates are to be stopped prior to entry into the study, there should be a washout of 4 weeks prior to randomisation to the study.

- Medically castrated patients must remain on castration therapy throughout the study, and must have been on stable treatment for a minimum of 8 weeks prior to starting study treatment. The castration therapy dose must also remain stable during the study.

- Potent CYP450 inducers (such as phenytoin, rifampicin, carbamazepine and phenobarbitone, St John's Wort) should be avoided while on study treatment. Dexamethasone will be allowed if the investigator feels it is necessary, but is encouraged to use a different form of steroid treatment wherever possible.

Patients taking drugs with a narrow therapeutic index should be monitored closely.

Although there is currently no evidence that ZD4054 affects warfarin pharmacokinetics or pharmacodynamics, it is recommended that patients taking warfarin or a coumarin preparation should be monitored regularly for changes in prothrombin time and international normalised ratio (at least once a week during the first month and then according to findings) and adjustments made to their anticoagulant therapy accordingly.

Although there is currently no evidence that ZD4054 affects the pharmacokinetics or pharmacodynamics of digoxin, it is recommended that patients taking digoxin are monitored regularly with trough digoxin level measurements every 1 to 2 weeks in the first month and then every 1 to 3 months thereafter.

Patients are allowed to receive other cardioactive drugs, but should be monitored more closely in the first 2 months of the study.

After completion of the study patients should be treated according to local medical practice.

3.9 Treatment compliance

It is the investigator's responsibility to ensure compliance of all treatments. Patients must be instructed to bring their ZD4054 or placebo (in the original containers) with them for all clinic visits. The investigator, and/or designee, will count each patient's ZD4054 or placebo at each study visit that the patient is required to return their study drug.

If a patient loses their study medication, the patient will be dispensed a new bottle of study medication. The patient should bring both the old and new bottles to the clinic at the next visit, if found.

3.10 Management of toxicity

Dose interruptions may be used to manage any ZD4054/placebo-related toxicity, dose reductions are not possible.

[redacted]

To protect patient safety, if the patient has a CTCAE grade 3 or 4 non-haematological or CTCAE grade 4 haematological toxicity attributable to ZD4054/placebo, consideration must be given to withdrawal of ZD4054/placebo. Patients must have recovered to CTCAE grade 2 or below before ZD4054/placebo is next administered.

Dose interruptions

ZD4054 may be stopped for up to 2 weeks without consultation with the Study Team Physician. If a dose delay is greater than 2 weeks, or if there have been more than 2 dose delays, approval from the Study Team Physician must be obtained prior to restarting ZD4054/placebo. In the case of CTCAE Grade 3 or 4 cardiac failure, study treatment must not be restarted unless the case has been discussed with the Study Team Physician, and agreement made for the study medication to restart.

Interruptions in dosing will be recorded on the eCRF.

3.10.1 Treatment for headache

Any patient experiencing headache should be strongly encouraged to take appropriate analgesia eg, paracetamol/acetaminophen 1 g (unless otherwise contraindicated), as soon as the headache is experienced. If the headache continues to worsen despite the administration of full dose simple analgesia such as paracetamol/acetaminophen, then the choice of further treatment for the headaches is at the discretion of the investigator using an approved treatment within the recommendations for use as described by the product label. Patients with ongoing headaches should be advised to take appropriate analgesics. Concomitant medication and adverse event information must be reported on the appropriate eCRF.

3.10.2 Treatment for rhinitis/nasal congestion

Any patient experiencing rhinitis/nasal congestion may be treated with over-the-counter decongestants or antihistamines. Concomitant medication and adverse event information must be reported on the appropriate eCRF.

3.10.3 Treatment for peripheral oedema/heart failure

Any patient experiencing peripheral oedema or heart failure may be treated with a diuretic such as frusemide and/or other appropriate medication. If cardiac failure develops or there is suspicion of cardiac failure then cardiovascular assessment should be performed. In the event of CTC grade 3 or higher cardiac failure occurring, consideration should be given to withdrawal of trial therapy, particularly if the cause of the cardiac failure is unknown. Concomitant medication and adverse event information must be reported on the appropriate eCRF. An additional eCRF page is provided to capture additional information relating to cardiac failure or symptoms suggesting cardiac failure.

3.10.4 Other treatment

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the eCRF.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

Before administration of the Investigational Product, patients will be assessed to ensure that eligibility criteria are met. Any patient not meeting the criteria must not be entered into the study and must be documented as a screen failure. The Investigator must confirm that all entry criteria are met before the patient commences treatment.

4.1 Primary variables

The primary outcome variables in this study are the effect of ZD4054 on overall survival and time to progression compared with placebo.

Overall survival is defined as time to death from any cause.

Progression is defined as:

- One or more new bone lesions on bone scan (confirmed, if ≤3 lesions, by CT, MRI or x-ray)
- Development of malignant visceral disease on CT/MRI
- Death in absence of progression.

N.B. Local recurrence of disease resulting in urinary obstruction is not classified as progression.

4.2 Screening and demographic measurements

The data listed below will be collected onto the Web Based Data Capture (WBDC) system after patient signs informed consent:

- Inclusion/exclusion criteria
- Patient demography – date of birth, sex, race, ethnic group
- Significant medical and surgical history
- Details of previous cancer treatment
- Full physical examination
- Vital signs – HR, BP, weight, height
- WHO performance status
- Clinical chemistry, haematology and urinalysis

- Bone scan
- CT/MRI
- 12-Lead ECG
- Concurrent illnesses and therapies at time of entry to the study
- FACT-P
- EQ-5D.

4.3 Patient-Reported Outcomes (PROs)

Table 3 shows how patient reported outcomes objectives relate to patient-reported outcomes variables.

Table 3 Patient-reported outcomes objectives and variables

Objective	Variable(s)
To assess the effects of ZD4054 on Health-related Quality of Life (HRQOL) compared to placebo	Functional well being (FWB) as recorded by the FWB domain of the FACT-P and the total FACT-P score
To assess the effects of ZD4054 on health status compared to placebo	EQ-5D (EuroQol-5 Dimensions) item scores

4.3.1 FACT-P

4.3.1.1 Method of assessment

FACT-P has been developed to measure HRQOL in men with prostate cancer (Cella et al 1993, Esper et al 1997). It consists of 4 subscales (physical, emotional, functional and social/family well-being) plus a 12 item prostate-specific module, using the Prostate Cancer Symptom (PCS) subscale, that highlights concerns specific to patients with prostate cancer (Appendix I). The FACT-P questionnaire will only be administered in countries for which a validated translation is available. Refer to the study plan (Table 1) for times of assessment.

4.3.1.2 Derivation or calculation of outcome variable

For the functional well being (FWB) domain and the FACT-P Total score, changes from baseline for each time point will be calculated for each treatment group.

If less than 50% of the subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If 50% or more of the items are missing, that subscale will be treated as missing.

Responses will be assigned for each patient as the best response of "Improved", "No Change" and "Worsened". The relationship between FWB responses and clinical responses will also be explored.

The following table defines visit responses for FWB and FACT-P. This response should be maintained for 2 consecutive visits

Table 4 Definition of visit response for FWB and FACT-P

	Change from baseline	Visit response
FACT-P	≥ +6	Improved
	≤ -6	Worsened
	Otherwise	No change
FWB	≥ +2	Improved
	≤ -2	Worsened
	Otherwise	No change

Overall improvement for FWB /FACT-P is defined as a change from baseline in the FWB/FACT-P of 2 or 6 points or more sustained for 2 consecutive visits.

Therefore, at the conclusion of the study, the following criteria, as listed in Table 5 will be used to assign a best overall score response based on the individual visit responses.

Table 5 Overall score response for FWB and FACT-P

Overall score response	Criteria
Improved	Two consecutive visit responses of "improved"
No Change	Does not qualify for overall score response of "improved". Two consecutive visit responses of either "no change", or "improved" and "no change"
Worsened	Does not qualify for overall score response of "improved" or "no change". A visit response of "worsened"
Other	Does not qualify for one of the above

[redacted]

4.3.2 EQ-5D

4.3.2.1 Methods of assessment

Patient Health Status will be assessed by the EQ-5D (EuroQol-5 Dimension), a validated and well known utility measure (See Appendix H) which consists of 5 questions. This has been translated into multiple languages. The EQ-5D questionnaire will only be administered in those countries where there is a validated translation available. Refer to the study plan (Table 1) for times of assessment.

4.3.2.2 Derivation or calculation of outcome variable

The proportion of patients with each score for each item will be summarised for each time-point and by treatment allocation.

4.3.3 Completion of PRO questionnaires

Each centre must allocate responsibility for monitoring compliance with completion of the above PRO questionnaires to a specific individual (eg, a Research Nurse). The [redacted] Clinical Team will arrange for relevant training in administration of the questionnaires. The PRO questionnaires should be administered and completed at the clinic per the Study Plan, Table 1. Patients must complete the FACT-P questionnaire before completing the EQ-5D questionnaire.

It is also important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection (Fallowfield et al 1987).

The date of completion of each PRO questionnaire should be recorded.

The instructions for completion of the PRO are as follows:

1. It must be completed in private by the patient in their own time

2. It must be completed by the patient before any investigations or discussions about their disease with the clinic staff

3. On completion of the questionnaire it should be handed back to the PRO designated person who should check for completeness

4. Only 1 answer should be recorded for each question

5. The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaire (eg, is blind or illiterate) the questionnaire may be read out and responses recorded.

4.4 Health Economics measurements and variables (Not applicable)

4.5 Pharmacokinetic measurements and variables

Not applicable for this study except in countries where local protocol amendments are in place.

4.6 Efficacy and pharmacodynamic measurement and variables

Table 6 shows how efficacy variables relate to efficacy objectives.

Table 6 Efficacy and pharmacodynamic objectives and variables

Objective	Variable(s)
Primary	
To determine the effect of ZD4054 on overall survival compared to placebo	Overall survival, defined as time to death (from randomisation) from any cause
To assess the effect of ZD4054 on progression free survival compared to placebo	Progression free survival defined as the time from randomisation until documentation of progressive metastatic disease Progression defined as any of: One or more new bone lesions on bone scan (confirmed, if ≤3 lesions, by CT, MRI or x-ray) Development of malignant visceral disease on CT/MRI Death in absence of progression N.B. Local recurrence of disease resulting in urinary retention is not classified as progression
Secondary	
To investigate the effect of ZD4054 on time to prostate-specific antigen (PSA) progression compared to placebo	Time to PSA progression, defined as the time to the first PSA value ≥50% from baseline, seen in at least two consecutive PSA values
To investigate the effect of ZD4054 on time to appearance of symptomatic progression compared to placebo	Time to symptomatic progression, defined as time to pain requiring opiate analgesia due to metastatic disease (where presence of metastases was previously confirmed by bone scan or CT/MRI)

4.6.1 Overall survival

4.6.1.1 Methods of assessment

Time to death from any cause. Cause and date of death will be recorded.

[redacted]

4.6.1.2 Derivation or calculation of outcome variable

Time to death will be calculated from the date of randomisation. Patients who have not died or have been lost to follow-up at the time of statistical analysis will be censored at the time they were last known to be alive.

4.6.2 Progression-free survival

4.6.2.1 Methods of assessment

Disease progression will be defined by any 1 of the following:

- One or more new bone lesions on bone scan (confirmed, if ≤3 lesions, by CT, MRI or x-ray).
- Development of malignant visceral disease on CT/MRI.
- Death in absence of progression.

N.B. Local recurrence of disease resulting in urinary retention is not classified as progression.

4.6.2.2 Derivation or calculation of outcome variable

Progression free survival is defined as the time from randomisation until documentation of progressive disease. Death is regarded as a progression event in all patients who die in the absence of disease progression. Patients who have not progressed at the time of analysis will be censored using the last assessment date.

At the time of imaging the investigator will determine whether the patient has progressed. The Investigational site assessment will be used for the primary analysis for this study (see Section 6.4.2.2).

4.6.3 Time to PSA progression

4.6.3.1 Methods of assessment

Blood samples for PSA analysis will be collected using serum separation gel tubes. Assessments should be performed at a certified central laboratory at the time points specified in the Study Plan, Table 1. PSA progression is defined as the time to the first PSA value ≥50% from baseline, seen in at least 2 consecutive PSA values.

4.6.3.2 Derivation or calculation of outcome variable

Time to PSA progression will be calculated from date of randomisation to date of first sample which shows rise in PSA of at least 50% from baseline. Patients who have not had an event at the point of analysis will be censored at the time they were last known to have been assessed.

4.6.4 Time to symptomatic progression

4.6.4.1 Methods of assessment

Patients who have developed metastatic progression will be asked at subsequent visits about the presence of any pain. If investigators in their clinical judgement consider that any pain is due to metastatic disease and is severe enough to warrant opiate analgesia, the date of onset and site of any pain will be recorded.

4.6.4.2 Derivation or calculation of outcome variable

Time to symptomatic progression is defined as the time from randomisation to the first time pain due to metastatic disease requiring opiate analgesia is recorded. Patients who have not developed metastases or pain from any metastases at the time of the analysis will be censored using the last available assessment date.

4.6.5 Pharmacogenetics

4.6.5.1 Methods of assessment

Blood samples for this optional assessment will be collected using polypropylene tubes containing ethylenediamine tetra-acetic acid (EDTA), and processed as directed in the Laboratory Handbook for Investigators. Samples will be sent to a central laboratory for processing and storage. All blood and DNA samples will be destroyed 15 years after the main study is completed.

4.6.5.2 Derivation or calculation of outcome variable

The number of patients who will agree to participate in the genetic component of this study is unknown. It is, therefore, not possible to establish whether sufficient data will 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.

4.6.6 Tumour assessments

4.6.6.1 Methods of assessment

CT or MRI of the pelvis and abdomen is to be performed at baseline and subsequent follow-up visits at the time points specified in the Study Plan, Table 1, with additional CT or MRI performed as clinically indicated (eg, Chest CT for pulmonary metastases) Lesions must be assessed using the same method and technique on each occasion.

Bone scintigraphy is to be performed at the time points specified in the Study Plan, Table 1, with confirmatory CT, MRI or x-ray being performed if there is suspicion of bone metastases being present but 3 or fewer lesions are evident. Bone scintigraphy may also be performed when clinically indicated. If the Investigator discontinues trial therapy for clinical reasons including PSA progression, bone scans should continue to be performed every 16 weeks until progression. Whole body anteroposterior and posteroanterior bone scans should be performed

All medical imaging related to tumour assessments will be collected and centrally reviewed.

4.6.6.2 Independent central review of medical images

An independent review of all scans used in the tumour assessment for this study will be conducted.

All scans should be performed according to standardized guidelines provided by an AstraZeneca appointed CRO prior to the start of the study, and sent to this CRO for independent central analysis, on an ongoing basis. Results of this independent review will not routinely be communicated to investigators, and the management of patients will be based solely upon the results tumour assessment conducted by the investigator.

4.6.6.3 Derivation or calculation of outcome variable

A patient will be determined to have progressed if they develop malignant visceral or nodal disease or develop one or more new bone lesions.

At the time of imaging the investigator will determine whether the patient has progressed. The Investigational site assessment will be used for the primary analysis for this study (see Section 6.4.2.2).

4.7 Safety measurements and variables

The methods for collecting safety data are described below. Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times given in the study plan (Table 1).

4.7.1 Adverse events

4.7.1.1 Definitions

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

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

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

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

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

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

Other Significant Adverse Events (OAE)

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

4.7.1.2 Recording of adverse events

When to collect AEs

Collection of non-serious AEs and SAEs during run-in, baseline and treatment periods

Non-serious adverse events and SAEs should be collected from the time consent is given, throughout the treatment period and up to and including the follow-up period. After data cut-off when 590 death events have occurred, only SAE data will be collected from patients still continuing on study treatment.

Duration of post-treatment follow-up period

Adverse events will be collected throughout the study. Any AEs that occur from the time of informed consent, during the study and in the 28 days following the last administration of study treatment should be recorded.

After discontinuation from treatment any new AEs or SAEs occurring within 28 days after the last dose of study drug should be documented in the eCRF modules, if the event is an SAE it should be reported to [redacted] in the usual manner.

In addition, all study-related toxicities and SAEs must be followed until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

Post-study events

After study completion (ie, after any scheduled follow up period) there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients. However, if an investigator learns of any SAEs, including death, at anytime after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to the investigational product, the investigator should notify [redacted]

Following data cut-off, patients who are considered, by the investigator, to be deriving clinical benefit will be allowed to continue to receive study treatment. SAE data will be collected for all patients continuing on study treatment.

Handling of unresolved AEs and SAEs

Adverse events should be collected for up to 28 days after last dose administration.

All study-related AEs and all SAEs must be proactively followed until resolution, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up. Every effort should be made to obtain a resolution for all events, even if they continue after discontinuation/study completion.

Any SAE that is ongoing when the patient completes the study, or at patient discontinuation from the study, must be followed up to resolution, unless the SAE is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

[redacted] and AstraZeneca reserve the right to ask for further information/clarification on any adverse event that may be considered of interest.

Collection and reporting of discontinuations of treatment due to AE

Only AEs, which caused the patient to permanently stop taking study treatment should be reported on the AE eCRF module as a permanent discontinuation of study treatment. The reason given for withdrawal/ permanent discontinuation of study treatment should be given as 'adverse event.'

[redacted]

What AEs to collect

Handling of symptoms of Disease Under Study, Disease Progression and Endpoints

(a) Disease under study

Any events that are unequivocally due to disease under study (DUS) must not be reported as an AE or SAE. Signs and symptoms clearly associated with the DUS should not be reported as AEs unless they are newly emergent (ie, not previously observed in the patient), judged by the investigator to be unusually severe or accelerated, or if the investigator considers deterioration of disease-related signs and symptoms to be caused directly by the drug. If there is any uncertainty about an AE being solely due to the DUS it should be reported as an AE or SAE as appropriate

(b) Disease progression

Symptoms of disease progression will not be recorded as AEs.

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease or an increase in the symptoms of the disease. Expected progression of the DUS and/or expected progression of signs and symptoms of the DUS, unless more severe in intensity or more frequent than expected for the patient's condition, should not be reported as an AE. Events which are unequivocally due to disease progression must not be reported as an AE/SAE.

The development of new metastases to the primary cancer under study should be considered as disease progression and not an AE.

(c) Handling of lack of efficacy

Where there is deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or constitutes an AE. In such cases, unless the AstraZeneca or reporting physician considers that the study treatment contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered to be lack of efficacy and not an AE.

(d) Handling of 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 primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study.

(e) Handling of deaths

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

[redacted]

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

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

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

Laboratory tests and vital signs

The reporting of protocol mandated laboratory/vital signs abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless a criterion for a SAE is fulfilled, the laboratory vital signs abnormality causes the patient to discontinue treatment with the IP, or if the investigator feels strongly that it should be reported as an AE.

If an abnormal laboratory value/vital sign is associated with a diagnosis or clinical signs/symptoms, the diagnosis or sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information to support the diagnosis.

4.7.1.3 How to collect AEs

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

- information volunteered by the patient, the patient's parent or carer

- open-ended and non-leading verbal questioning of the patient at every visit such as the following: How are you feeling? Have you had any (other) medical problems since your last visit. Suggest using the protocol standard question – 'Have you had any health problems since the previous visit / last questioning?' – in the local or native language

- observation by the investigational team, other care providers or relatives.

Collection of Common Terminology Criteria for Adverse Event grade

Adverse events will be recorded by means of the CTCAE for adverse events (version 3) for all events with an assigned CTCAE grading. Where there are no assigned CTCAE grades, there is a recommendation in the CTCAE criteria that converts mild, moderate and severe into CTCAE grades (CTCAE 1 = mild, CTCAE 2 = moderate, CTCAE 3 = severe, CTCAE 4 = life threatening / disabling, CTCAE 5 = death).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For 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 usually be a SAE.

Collection of time of onset and resolution of AE

Onset and resolution dates for all AEs and SAEs should be collected and recorded on the eCRF. For events more than 24 hours' duration the precise time of onset/resolution is not deemed critical to the study and thus need not be collected.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Code breaks

All code breaks will be managed by the IVRS. Details of the procedure will be provided in the IVRS manual. Where appropriate, the investigator will consult with the study team physician to ascertain whether the situation warrants breaking the code.

The investigator may break the code only after a decision has been made to withdraw a patient from the study treatment and if the investigator requires immediate knowledge of the study medication to optimise the clinical management of the patient. The investigator must notify [redacted] of any code breaks and provide a written report which will be archived.

Pregnancy

Should a pregnancy occur in the patient's partner, it must be reported in accordance with the procedures described in Section 9.4, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

4.7.1.4 Reporting of serious adverse events

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

SAE information will be entered and submitted into the WBDC system on the relevant eCRF modules. An automated email alert will be sent to the designated [redacted] representative who will work with the investigator to ensure that all the necessary information is available in the system within the required time frames, but taking advantage of the time allocated in those timelines. The [redacted] representative will notify the appropriate AstraZeneca Drug Safety

[redacted]

department through the WBDC system via email that a completed electronic SAE module and relevant information from other appropriate eCRF modules is available in the WBDC system. If the system is unavailable, the investigator should fax a paper back-up SAE report to the [redacted] representative immediately, recognising that the same reporting time frames still apply. The investigator is responsible for completing the eCRF as soon as the system becomes available again.

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

If follow-up indicates a change in the SAE from serious to fatal or life-threatening, this information needs to be available in the WBDC system within 1 calendar day.

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

The [redacted] representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product, any other medication or to the study procedure(s). All SAEs will be recorded in the eCRF. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries implementing the EU Clinical Trials Directive, this will be taken care of by [redacted] (see Section 8.1).

4.7.2 Laboratory safety measurements and variables

Laboratory assessments will be performed at a certified central laboratory according to the Study Plan, Table 1. The date of sample collection will be recorded in the WBDC system.

All patients who have any CTCAE grade 3 or 4 laboratory values (see NCI CTCAE Version 3.0) at the time of withdrawal must be followed up until they have returned to CTCAE grade 1 or 2, unless they are not likely to improve because of the underlying disease. Additional samples may be taken, as clinically indicated.

4.7.2.1 Clinical chemistry, haematology and urinalysis

The following laboratory variables will be measured:

Table 7 Laboratory variables to be assessed.

Clinical chemistry	Haematology	Urinalysis[a]
Total protein	RBC	Glucose
Albumin	Haemoglobin	Protein
Bilirubin	Haematocrit	Blood
ALT	MCV	Specific gravity
AST	MCH	
ALP	WBC	
Phosphate	WBC differential count (in absolute values)	
Sodium	Platelet count	
Potassium		
Magnesium		
Urea		
Creatinine		
Creatinine clearance[b]		
LDH		
Calcium		
Serum Testosterone[c]		

[a] A microscopic urinalysis must be performed if any urinalysis results are positive
[b] At screening only
[c] Serum testosterone at screening only

PSA Assessment is discussed in Section 4.6.3.

BNP Assessment

A rise in BNP has been shown to be an indicator for the development of cardiac failure. Although causal relationship to therapy has not been established, a small number of patients receiving ZD4054 in previous studies have developed cardiac failure.

An exploratory objective in this study is therefore to explore the utility of BNP in monitoring patients with hormone-resistant prostate cancer receiving ZD4054. Comparison of the BNP levels over time and between ZD4054 and placebo arms will allow assessment of the effect of ZD4504 on BNP levels. Any correlation between change in BNP over time and cardiovascular adverse events will also be explored. In view of the exploratory nature of the BNP measurement, the results will not be routinely sent to investigators. However, any significant change in BNP levels will be highlighted to investigators together with recommendations as to further patient assessment and management.

The available data for BNP will be assessed along with other safety data at the regular assessment by the IDMC who will decide on its utility in the trial: in the event of it being of poor utility in patient monitoring, the IDMC may advise that further sample collection be stopped. In this event, no protocol amendment will be issued, investigators will be informed by letter to discontinue collection of this sample.

4.7.2.2 Methods of assessment

Clinical chemistry

Blood samples will be collected using serum separation gel tubes and processed as directed in the Laboratory Handbook for Investigators. Samples will be sent to a central laboratory for assessment. Results will be faxed back to the study centres by the central laboratory. A hard copy of these results will also be sent by mail.

BNP

Blood samples will be collected using 4 mL EDTA Vacutainer draw tubes and processed as directed in the Laboratory Handbook for Investigators. Samples will be sent to a central laboratory for assessment. Results will not be sent to study centres unless there are significant changes and the management of the patient needs to be discussed with the Study Team Physician.

Haematology

Blood samples will be collected using EDTA tubes and processed as directed in the Laboratory Handbook for Investigators. Samples will be sent to a central laboratory for assessment. Results will be faxed back to the study centres by the central laboratory. A hard copy of these results will also be sent by mail.

Urinalysis

A sample of urine will be collected and analysed locally at the investigator centre using dipstick analysis, as directed in the dipstick packaging.

Dipsticks will be provided to the centre by the central laboratory.

4.7.3 Vital signs, ECG and physical examination

4.7.3.1 Methods of assessment

Vital signs

Assessments must be performed at the time points specified in the Study Plan, Table 1.

Vital signs consist of heart rate and blood pressure.

Vital signs will be measured after the patient has been resting for at least 5 minutes. Blood pressure will be measured using a generally accepted cuff method. For each patient throughout the study, blood pressure will be measured using the same arm.

[redacted]

Resting 12-lead ECG

Twelve-lead ECGs will be performed for all patients at the time points indicated in the study plan (Table 1). ECGs (run at 25 mm/second) will be obtained whilst the patient is supine and has rested supine for 3 to 5 minutes. The ECGs for each patient should be carried out at the same time of day, where possible, and at a time that is consistent in relation to food intake.

Additional ECGs should be obtained if clinically justified.

ECGs must be of the highest quality and free of movement artefact or electrical interference. A repeat ECG is to be taken if the first recording is of suspect quality. ECG recording should be a minimum of 10 seconds (or 10 cycles) of artefact-free recording, without premature ventricular contractions (PVCs) if possible. It is recommended that the same machine is used for the same patient throughout the study.

Two identical paper copies of all ECGs (including any additional ECGs) should be obtained. One must be retained in the patient's medical records, and the other will be collected by the [redacted] monitor and returned to [redacted]

ECGs will be reviewed for safety by the investigator. Any clinically significant abnormal changes from screening should be recorded as AEs or SAEs.

Physical examination

A complete physical examination, including vital signs, height (screening only) and weight, will be performed at each visit, as specified in the Study Plan, Table 1. Any new conditions or exacerbation of existing conditions reported at subsequent visits will be reported on the adverse event form. Only those findings that are in addition to the condition being treated will be recorded as adverse events. Conditions that are unequivocally disease-related must not be recorded as adverse events unless they result in death during the study treatment period or within 28 days after the administration of the last dose of study treatment.

4.8 Volume of blood sampling and handling of biological samples

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

Table 8 Maximum volume of blood to be drawn from each patient in one year

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Exploratory serum biomarkers		5.0	3	15.0
Exploratory plasma cell death biomarkers [c]		2.0	8	16.0
BNP		4.0	8	32.0
Safety	Clinical chemistry (including PSA)	8.5	8	68.0
	Haematology	4.0	8	32.0
Genotyping [b]		9.0	1	9.0
Total				**172.0[a]**

[a] The number of samples, and therefore the total volumes have been calculated assuming that a patient completes visits 1 to 8 and a discontinuation from study treatment visit. Individual patients may follow a different course throughout the study and therefore total volume of blood drawn from each patient may vary from the total provided above

[b] Optional

[c] Exploratory cell death biomarker sampling will be performed by sites that have the required equipment

4.8.1 Analysis of biological samples

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

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

4.9 Genetic measurements and co-variables

4.9.1 Collection of samples for genetic research

Patients will provide a blood sample as per the inclusion criteria and visit schedule for this optional measurement.

A single venous blood sample (9 mL) will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix

thoroughly as directed in the Laboratory Handbook for Investigators. Tubes will be labelled with the protocol study number, centre number, enrolment code and date of sample collection. No personal identifiers (patient name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the eCRF.

Genotype is a stable parameter, therefore if for any reason the blood sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

4.9.1.1 Sample processing and shipping

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory within one month of collection and must remain frozen at all times. Refer to the Laboratory Manual.

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

4.9.1.2 Storage and coding of DNA samples

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

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will 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 working with the DNA.

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

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the [redacted] The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotyping results with clinical

[redacted]

data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

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

4.9.1.3 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Exploratory research may investigate genetic factors that could influence response to ZD4054. The results of the genetic research will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on ZD4054 to generate hypotheses to be tested in future studies.

4.10 Exploratory biomarker measurements and variables

4.10.1 Collection of plasma for cell death biomarkers

To collect plasma samples for investigation of M30 and M65 (at sites that have the required equipment). Blood samples for plasma markers M30 and M65 should be taken at the following time points (see also Table 1):

Pre-randomisation and weeks 4, 8, 12, 16 and every 16 weeks until withdrawal including one sample at the discontinuation visit.

Approximately 2.0 mL blood samples should be collected into Lavender cap K3 Vacuette tubes containing EDTA anti-coagulant. Samples should be thoroughly mixed and processed immediately to plasma by centrifugation at approximately 1000g for 10 minutes using a pre-chilled centrifuge set to 4°C. Two separate plasma aliquots (0.5 mL) for M30 and M65 analysis should be taken off by pipette and transferred to separate Nunc cryovials (3.6 mL). Samples should be frozen upright at -20°C within 30 minutes of the original blood draw.

The biomarker eCRF will capture consent given, date and time of sample acquisition and time of freezing.

4.10.2 Collection of serum samples for exploratory biomarkers

Patients will provide a 5 mL blood sample to be processed to 2.5 mL of serum at each of the visits referenced in the Study Plan (Table 1). This serum sample will be stored for potential retrospective analysis of serum biomarkers.

A single venous blood sample (5 mL) will be drawn into a serum tube and mixed by inversion 5 times, as directed in the Laboratory Manual. The sample is allowed to clot by standing at

room temperature for 3 hours, then centrifuged at 2000 g for 10 minutes at room temperature. The serum is carefully aspirated with a sterile transfer pipette into a second serum tube and centrifuged at 2000 g for 10 minutes at room temperature. The serum is finally transferred into 6 cryotubes (5 x 200 µL) with the remainder into a single aliquot and frozen immediately at -20°C. The samples will be labelled with -80°C resistant labels that contain a unique sample identifier comprising the patient enrolment code, identifiers of sample type and purpose and aliquot number.

The biomarker eCRF will capture consent given, date and time of sample acquisition and time of freezing.

Plasma remaining from the analysis of cell death biomarkers may be used for exploratory biomarker research in consenting patients.

4.10.2.1 Sample shipping

Samples must be shipped frozen (-20°C or below) and transported to the relevant storage site within 1 month of collection. Samples should be shipped in batches and coordinated with the receiving site to ensure their arrival within working hours. A requisition sheet should accompany the shipment that details the study number, centre number, enrolment code, date of sample collection and unique identifier for each of the samples in the shipment. Where samples are shipped to [redacted] monthly then storage at -20°C by the sites is acceptable. Otherwise, samples must be stored at -80°C.

When [redacted] ship samples to AstraZeneca, or any AstraZeneca-approved laboratory such as the [redacted] the appropriate person at the receiving institution should be advised of sample shipping 3 working days prior to the proposed shipping date. Samples originally shipped to AstraZeneca may be shipped to the [redacted] or another AstraZeneca-approved laboratory for further analysis as described in Section 4.10.4.

[redacted]

4.10.3 Collection of prostate cancer tissue samples for exploratory biomarkers

Patients will be asked to provide consent to permit exploratory biomarker analysis to be performed on their original diagnostic sample, taken before entry onto this study. Where consent is given samples should be located and shipped at ambient temp to the central laboratory.

[redacted]

Patients who undergo biopsies or operative procedures eg, TURP which provide prostate cancer specimens will be asked to consent for a sample of this tissue to undergo further exploratory biomarker analysis. These samples will be stored for potential retrospective analysis of biomarkers.

Detailed collection, processing and shipping instructions for both fixed and frozen samples are detailed within the laboratory manual.

The biomarker eCRF will capture consent given, date and time of sample acquisition and time of freezing if appropriate.

4.10.4 Summary of exploratory biomarker assessments and analysis

Possible future analysis is likely to be performed retrospectively and only the appropriate subset of samples taken forward to formal analysis. The selection of this subset will be wholly dependent on the outcome data of this and other ZD4054 clinical studies. Meta analysis of sample data may be performed which includes data from all ZD4054 studies. Exploratory analysis may enable the discovery of biomarkers characteristic of response to treatment versus placebo in the patient population or biomarkers that influence efficacy, safety and tolerability to study treatments and prognosis/progression of disease. Any data generated will not be reported as part of the clinical study report.

Serum samples may be assessed using the most appropriate profiling method available at the time of analysis. Typical methods may include two dimensional gel electrophoresis, mass spectrometry, RT-PCR or other profiling methods yet to be determined in this rapidly developing field. Quantitative measurements may be made to compare samples taken from individuals undergoing treatment, enabling the discovery of characteristic biomarkers of response to treatment.

It is not possible to determine a statistical analysis plan at this stage as the subset of samples chosen for formal analysis will only become apparent following study completion and will be dependent upon associated clinical outcome data and sample QC. A statistical analysis plan will be prepared where appropriate.

5. DATA MANAGEMENT

Data will be entered into the [redacted] 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 within 5 days. The eCRF Instructions will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, edited and Source Data Verification (SDV) performed the principal investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the eCRF will be archived at the study site.

[redacted]

In the case of genotyping data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database.

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

5.1 Reporting of genotyping results

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

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be finalised before unblinding of the data. Analyses will be performed using SAS and other validated software as appropriate.

Where data are missing, the impact and scale will be investigated. Where a baseline variable is missing, it may be possible to substitute the value recorded at a different pre-treatment visit. This would be considered for each variable independently and a decision on the strategy to deal with each variable being missing will be documented in the SAP prior to database lock.

Summaries of the safety and efficacy data will be produced using graphs and standard summary statistics. For continuous variables, these statistics will include (but not be limited to) the mean, standard deviation, median, minimum and maximum. For categorical data, these statistics will consist of frequencies and associated percentages. Missing safety and efficacy data will not be included in the numerator of the percentage calculation.

Measures of location (mean, median, minimum and maximum) will be reported to the same degree of precision as the raw data. Measures of spread (standard deviation, standard error) will be reported to one further degree of precision. Where confidence intervals are provided, unless otherwise stated, they will have been calculated using an assumption of normally distribution.

[redacted]

Assumptions made when analysing the efficacy data will be checked using appropriate methods. Output from such checks will not be included in the CSR.

6.2 Description of outcome variables in relation to objectives and hypotheses

6.2.1 Primary objectives

The primary objectives are to assess the effect of ZD4054 on overall survival and progression free survival compared with placebo.

Overall survival is defined as time from randomisation to death from any cause.

Progression is defined by one of the following:

- One or more new bone lesions on bone scan (confirmed, if ≤3 lesions, by CT, MRI or x-ray)
- Development of malignant visceral disease on CT/MRI
- Death in absence of progression.

N.B. Local recurrence of disease resulting in urinary retention and loco-regional node involvement is not classified as progression.

Progression free survival is time from randomisation to first documented progression event.

6.2.2 Secondary objectives – efficacy and pharmacodynamic measurement variables

The secondary objectives of the study are to assess:

- Time to PSA progression, defined as the time to the first PSA value ≥50% from baseline, seen in at least 2 consecutive PSA values.
- Health-related Quality of Life (HRQOL), will be measured using FACT-P.
- Time to symptomatic progression, defined as time to:
  - Pain requiring opiate analgesia due to metastatic disease (where metastatic disease has previously been confirmed by bone scan or CT/MRI).

6.2.3 Secondary objective - safety measurement variables

- Tolerability and safety
- Adverse events
- Laboratory data

- ECGs
- Vital signs.

6.2.4 Exploratory objectives – health status variables

The exploratory objectives of the study are:

- Measured by EQ-5D (EuroQol-5 Dimension).

6.2.5 Exploratory objectives – BNP measurements

BNP levels will be summarised by timepoint and treatment groups. The relationship between BNP and development of cardiac adverse events will be explored.

6.3 Description of analysis sets

Three patient analysis sets will be defined in this study:

Intention to Treat (ITT) set

The ITT set will be defined as all patients randomised.

The ITT set will be the primary set used for the efficacy analyses.

Patients in the ITT set will be analysed according to the treatment to which they were randomised rather than the treatment they actually received.

Safety set

The safety set will include patients who received at least 1 dose of study medication. Patients in the safety set will be analysed according to the treatment they received. This will be the primary set used for the safety analyses.

Quality of life set

The quality of life set will be defined as a subset of the ITT set but including only those patients who have valid baseline and at least one follow-up quality of life measure. This analysis set will be the primary set analysed for all quality of life endpoints.

6.4 Method of statistical analysis

6.4.1 Baseline data

Summaries of demographic and other baseline characteristics will be produced for the ITT population. Summaries will be produced for all patients in each population.

Listings of demographic and other baseline characteristics will be produced, including surgical history, medical history which will be summarised by System Organ Class and High Level term using the Medical Dictionary for Regulatory Activities (MedDRA).

6.4.2 Primary variables

6.4.2.1 Overall Survival

Overall survival will be analysed using the log-rank test. Overall survival will be measured from randomisation. Patients who have not died at the time of the analysis will be censored using the last available assessment date.

The primary analysis will include a factor for treatment. The analysis results will be presented as hazard ratios. A hazard ratio less than 1 would indicate that, on average, overall survival is longer on active treatment than on placebo. The hazard ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to death will be produced.

Additional analyses, plots and summaries by covariate may be presented if appropriate.

6.4.2.2 Progression free survival

Progression free survival will be analysed using the log-rank test. Progression is defined in Section 2.1. Patients who have not progressed at the time of the analysis will be censored using the last available assessment date.

The primary analysis will use the locally reviewed assessments of the scans. A confirmatory analysis using the central review of the scan assessments will also be performed. Both these analyses will include a factor for treatment. The analysis results will be presented as hazard ratios. A hazard ratio less than 1 would indicate that, on average, times to progression are longer on active treatment than on placebo. The hazard ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to progression will be produced. Tabular and graphical summaries will be produced to illustrate the consistency of the local and central review of the bone scan assessments. Additional analyses, plots and summaries by covariate may be presented if appropriate.

6.4.3 Secondary variables

PSA progression

Time to PSA progression will be analysed using the log-rank test. Patients who have not had a PSA progression at the time of the analysis will be censored using the last available assessment date. The primary model will include terms for treatment and the PSA measurement at the baseline visit.

The analysis will be presented as hazard ratios. A hazard ratio less than 1 would indicate that, on average, times to PSA progression are longer on active treatment than on placebo. The hazard ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to PSA progression will be presented.

The raw data for PSA concentration collected at baseline and subsequent study visits plus changes and percentage changes from baseline will be presented using standard summary statistics.

Patient reported outcomes

- EQ-5D

The items and the change from baseline in the items collected at all time points will be summarised by treatment group.

- FACT-P

For the FACT-P, raw data and change from baseline will be presented for each treatment group for the total score and each subscale.

The number of and percentage of patients who have worsened or improved at each visit as defined in Section 4.3.1 will be summarised by treatment. In addition, the overall response will be summarised by treatment.

Time to symptomatic progression

Time to symptomatic progression will be analysed using the log-rank test. Symptomatic progression is defined in Section 4.6.4.1. Patients who have not progressed symptomatically at the time of the analysis will be censored using the last available assessment date.

The analysis results will be presented as hazard ratios. A hazard ratio less than 1 would indicate that on average, times to symptomatic progression are longer on active treatment than on placebo.

The hazard ratios will be presented with confidence intervals and p-values. Kaplan-Meier plots of the times to symptomatic progression will be produced. Additional analyses, plots and summaries by covariate may be presented if appropriate.

6.4.4 Safety data

The Safety analysis set will be used as the primary analysis dataset for the reporting of safety data. All safety data will be listed.

6.4.4.1 Adverse events

The number of patients reporting at least one AE in any system organ class will be presented.

AEs will be summarised by preferred term within each system organ class. For each preferred term, the number and percentage of patients reporting at least one occurrence will be presented. Similar summaries of the number of patients reporting the most frequently reported AEs during the treatment period will be presented. Most frequent AEs will be those reported, at preferred term level, in a pre-defined minimum percentage of patients within at least one treatment group; this defined minimum will be set at Blind Review of data before analysis.

AEs will be summarised by causality and CTC grade. All AEs will be listed for all patients. Separate listings of all serious AEs (SAEs), deaths, other significant AEs (OAEs) or discontinuations due to AEs will be presented.

6.4.4.2 Laboratory variables

Scheduled laboratory results will be used for the summary tables. All recorded laboratory data will be listed.

All continuous laboratory parameters will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. Categorical laboratory parameters will be summarised by frequency counts and percentages at each visit by treatment group.

All laboratory safety data will be listed, with clinically relevant abnormalities, as defined by the AstraZeneca extended reference ranges explicitly noted on the listings.

6.4.4.3 ECG

The overall evaluation will be listed and summarised by treatment group.

6.4.4.4 Vital signs

The vital signs data will be summarised by absolute value at each visit by treatment group. The corresponding changes from baseline will also be presented.

Scheduled vital sign results will be used for the summary tables. All recorded vital sign data will be listed with clinically relevant abnormalities noted on the listings.

6.4.4.5 Physical examination

Physical examination details will be listed and summarised by treatment group using standard summary statistics.

6.5 Determination of sample size

Overall survival and progression free survival are co-primary endpoints for this study. To preserve the study significance level at 5%, the significance level is set at 4% for OS and 1% for PFS. A total of 590 deaths are required. If the true hazard ratio for ZD4054 versus placebo is 0.75 then the study will have 90% power to demonstrate a statistically significant effect in OS at the 4% significance. With a total of 1500 patients, a recruitment period of approximately 18 months (Japan and China approximately 24 months) from [redacted] and a median OS for the placebo group of approximately 47 months, it is estimated that 590 deaths will occur approximately 52 months after the first patient entered the study.

There will be 2 formal analyses for this study. OS and PFS will be analysed at the first analysis and OS will be analysed at the second analysis. To account for the 2 analyses of OS, the overall type I error rate of 0.04 will be split using the method proposed by Jennison and Turnbull (Jennison and Turnbull 2000). The significance level at first analysis will be set at

2.5%, and the significance level for the final analysis will subsequently be calculated to preserve the overall type I error rate of 0.04 based on the actual number of observed events at the first and final analyses. For instance, given that 410 events are observed at the first analysis and if 590 events are observed at the final analysis as planned, then the significance level for the final analysis will be 2.62%.

The first analysis will be carried when 410 deaths have occurred and it is estimated that this will be around 37 months after first patient entered the study. At this point it is estimated that 690 progression events will have occurred. If the true hazard ratio for ZD4054 versus placebo is 0.75 then the study will have greater than 85% power to demonstrate a statistically significant difference in PFS at the 1% significance level. The median PFS is assumed to be around 24 months for the placebo group, based on results from a similar study with atrasentan (presented at ASCO 2007 Multidisciplinary Prostate Cancer Symposium).

The second analysis will be carried out when 590 deaths have occurred and it is estimated that this will be around 52 months after the first patients entered the study (Jennison and Turnbull 2000, Nelson et al 2007).

6.6 Interim analyses (Not applicable)

6.7 Independent Data Monitoring Board

An Independent Data Monitoring Committee (IDMC) will be responsible for safeguarding the interests of study participants, via review of accumulating safety and efficacy data for this study and the other Phase III ZD4054 studies. The IDMC will be composed of therapeutic area experts and statisticians who do not have significant conflicts of interests and therefore, will be neither ZD4054 study investigators nor individuals employed by AstraZeneca. The IDMC will review safety data at least every 6-monthly for the first year and thereafter will recommend the intervals for subsequent reviews.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient into the study, a representative o[redacted]will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of[redacted] or its representatives. This will be documented in a Clinical Study Agreement between[redacted]and the investigator
- Discuss the specific requirements of the genetic research with the investigator(s) (and other personnel involved with the study).

[redacted]

During the study, a monitor from [redacted] 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 recorded in the eCRF, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRF with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (eg, clinic charts)
- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research.

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

7.2 Audits and inspections

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

7.3 Training of staff

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

Before the first patient is entered into the study, the investigational staff will be trained to use the WBDC system by [redacted] personnel or delegates.

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples,

[redacted]

extraction of DNA and genetic research with [redacted] personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

7.4 Changes to the protocol

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

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

If an administrative change is required, such a change must be must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then [redacted] and the centre's Ethics Committee must be notified. Approval of the revised Informed Consent Form by [redacted] and by the Ethics Committee is required before the revised form is used.

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

7.5 Study agreements

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

7.6 Study timetable and end of study

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

- Signed Clinical Study Protocol and other agreements between [redacted] and the Principal Investigator/Study Site.
- Approval of the study by the Ethics Committee.
- Approval of the study, if applicable, by the regulatory authority.

The end of study is defined as the date of the last visit of the last patient after the data cut-off has occurred when at least 590 deaths have taken place.

[redacted]

The study may be terminated at individual centres in the event of the study procedures not being performed to GCP or if recruitment is slow. Astrazeneca may also terminate the study prematurely if any concerns for patient safety arise. [redacted] reserves the right to discontinue this study for medical and/or administrative reason at any time.

8. ETHICS

8.1 Ethics review

[redacted] will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

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

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

The Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. [redacted] will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

Where there is an optional genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

8.2 Ethical conduct of the study

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

For studies including genetic analysis special precautions are taken as described in Section 4.9.

8.3 Informed consent

The principal investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of

the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

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

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

The genetic research is optional and the patient may participate in the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the genetic aspect of the study at any time.

If modifications are made according to local requirements, the new version has to be approved by[redacted]

8.4 Patient data protection

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

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by[redacted]AstraZeneca will be identified by subject number (randomisation code) / study code / initials.

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

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

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

[redacted]

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

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Study Team Physician or Study Leader at the site shown below.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
See also Supplement A "Study Team Contacts in the Event of Emergency Situations, Overdose or Pregnancy"		

9.2 Procedures in case of medical emergency

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

The treatment code may not be broken unless in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the investigator will, if time and circumstances permit, consult with [redacted]on one of the telephone numbers listed in Section 9.1 prior to breaking the treatment code. If the code is broken, the date, time and reason should be recorded and the investigator should sign the record..

9.3 Procedures in case of overdose

There is currently no known antidote to ZD4054. In the event of an overdose of study medication (more than 2 doses within a 24 hour period), appropriate symptomatic and supportive care should be given, and all details should be recorded. Any untoward effects of an overdose should be reported as an AE or SAE, as appropriate, according to the reporting requirements detailed in Section 4.7.1.

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the eCRF as an AE of 'Overdose' unless there are associated symptoms or signs.
- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRF.
- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRF. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

[redacted]

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

9.4 Procedures in case of pregnancy

9.4.1 Paternal exposure

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

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to [redacted] on the pregnancy outcomes report form. These forms should be completed as soon as possible after it has been identified that the investigational product was received during pregnancy (via paternal exposure) and sent to the appropriate Drug Safety unit within 45 days.

10. REFERENCES

American Cancer Society
Available from URL: http://www.cancer.org/docroot/home/index.asp

Cancer Research UK
Available from URL: http://www.cancerresearchuk.org

Cella et al 1993
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