AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Olaparib (AZD2281, KU-0059436)
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A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	15 August 2014		
2	13 October 2015		
Administrative change No.	**Date of Administrative Change**	**Local Administrative change No.**	**Date of local Administrative Change**
1	21 October 2013		
2	15 November 2013		

AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

International Co-ordinating Investigator

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Study centre(s) and number of patients planned

For Part A of the study, 15 to 18 evaluable patients (Cohorts 1 and 2) are planned to be enrolled from approximately 4 sites in 1 or 2 countries; a further 12 patients may be recruited into a 3rd cohort if necessary.

For Part B of the study, approximately 140 patients will be randomised from approximately 40 sites in North America and Europe.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2013	II
Estimated date of last patient enrolled	Q2 2015	
Estimated date of data cut-off for primary analysis of progression-free survival	Q2 2016	
Estimated date of last patient last visit (data cut-off for survival analysis)	Q1 2018	

Objectives

Primary

Part A, Safety run-in

To assess the safety and tolerability of olaparib when given in addition to abiraterone and to recommend, by assessment of dose-limiting toxicities and other safety and tolerability data, a dose of olaparib for further study when given in addition to abiraterone.

Part B

To compare the efficacy of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone, by assessment of radiologic progression-free survival (rPFS) using Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) and Prostate Cancer Working Group 2 (PCWG-2) criteria.

Secondary

Part A, Safety run-in

To evaluate the presence of any drug interaction between olaparib and abiraterone by determination of steady state exposure to olaparib in the presence and absence of abiraterone, and determination of steady state exposure to abiraterone in the presence and absence of olaparib.

Part B:

To compare the safety and tolerability of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone.

To assess the anti-tumour activity of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by measurement of changes in circulating prostate specific antigen (PSA) and circulating tumour cells (CTCs), calculation of overall radiological objective response rate (ORR) (by RECIST 1.1 and PCWG-2 bone scan criteria) and malignant soft tissue ORR (by RECIST 1.1), time to first subsequent therapy (TFST) for prostate cancer, and time to second subsequent therapy (TSST) for prostate cancer.

To assess the efficacy of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by assessment of overall survival (OS).

To assess the efficacy of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by assessment of time from randomisation to second progression (PFS2).

To investigate BRCA and ATM mutations as candidate predictors of response to olaparib. Note: This objective is dependent upon the number of evaluable samples obtained from the study.

Exploratory

Exploratory objectives include, in brief: to explore of the effects of olaparib compared to placebo, when given in addition to abiraterone, on pain and pain interference with daily life, bone pain, prostate cancer related symptoms, Health-Related Quality of Life (HRQL), and health utilities and resource use; to investigate the impact of treatment and disease progression on metastatic castrate-resistant prostate cancer (CRPC) management resource use; possible future exploratory research into factors that may influence development of cancer and/or

response to treatment, using tumour, CTC, blood and urine samples; to explore whether resistance mechanisms to olaparib can be identified through analysis of tumour, CTC, blood and urine samples; to collect and store optional DNA samples for future exploratory research into genes/genetic variation that may influence response to study treatments and/or susceptibility to disease.

Study design

This is a 2-part study in patients with metastatic CRPC. Part A is an open-label safety run-in study to assess the safety, tolerability and pharmacokinetics (PK) of olaparib when given in addition to abiraterone 1000 mg once daily. Part B is a randomised, double-blind, placebo-controlled comparison of the efficacy, safety and tolerability of the dose of olaparib selected from Part A when given in addition to abiraterone, versus placebo given in addition to abiraterone.

Abiraterone is indicated in combination with prednisone or prednisolone for the treatment of patients with metastatic CRPC. Prednisone or prednisolone 5 mg twice daily (bid) will be administered with the abiraterone in this study, but throughout this protocol the treatment will be referred to simply as abiraterone.

All patients will attend a screening visit within 28 days before starting study treatment.

Part A: Safety run-in/dose escalation

Patients will attend the clinic on the first day of study treatment, at 1 and 2 weeks, then every 4 weeks up to Week 52, and every 12 weeks thereafter.

Cohort 1 (up to 6 patients)

At least 3 and up to 6 evaluable patients will be enrolled in Cohort 1. Patients will receive olaparib 200 mg bid and abiraterone 1000 mg once daily. Dose-limiting toxicities (DLTs) will be assessed by a Safety Review Committee (SRC) after a minimum of 14 days' treatment.

Cohort 2 (12 patients)

If the combination of olaparib 200 mg bid and abiraterone 1000 mg once daily is tolerated, a cohort of 12 patients (split into 2 groups of 6 patients) will be treated with olaparib 300 mg bid given in addition to abiraterone 1000 mg once daily.

Dose-limiting toxicities will be assessed by the SRC after a minimum of 14 days' treatment with both olaparib and abiraterone.

Group 1:

Patients will receive olaparib alone (300 mg bid) for between 3 and 7 days. Blood samples will then be collected to determine the steady state PK profile for olaparib. Patients will then receive abiraterone (1000 mg once daily) starting from the day after the olaparib PK profile

has been collected. Olaparib and abiraterone will continue to be dosed in combination for at least 5 days, then blood samples will be collected again to determine both olaparib and abiraterone PK profiles.

Group 2:

Patients will receive abiraterone alone (1000 mg once daily) for between 5 and 7 days. Blood samples will then be collected to determine the steady state PK profile for abiraterone. Patients will receive olaparib (300 mg bid) starting immediately after the 24-hour abiraterone PK sample has been collected. Olaparib and abiraterone will continue to be dosed in combination for at least 3 days, then blood samples will be collected again to determine both olaparib and abiraterone PK profiles.

Cohort 3 (12 patients)

If 4 or more DLTs occur in Cohort 2, a further 12-patient cohort may be recruited and treated with olaparib 200 mg bid given in addition to abiraterone 1000 mg once daily and evaluated for safety, tolerability and PK as above. If ≥4 DLTs occur in this cohort, the study will be stopped.

Part B: Randomised part

Patients who have been dosed in Part A of the study may not participate in Part B.

Patients will receive olaparib or placebo (randomisation ratio 1:1), at the dose determined by Part A of the study, and abiraterone 1000 mg once daily. They will attend the clinic on the first day of study treatment, then every 4 weeks up to Week 52, and every 12 weeks thereafter.

Tumour evaluation using RECIST 1.1 and PCWG-2 criteria will be conducted at screening and then every 12 weeks from the date of randomisation until objective disease progression (every 24 weeks after Week 72). Patients will be evaluated until disease progression regardless of whether study treatment is discontinued, and will then be followed for PFS2 and survival.

An archival tumour sample will be collected, where available, to measure BRCA and ATM mutation status; other biomarkers such as ERG expression/fusion status, homologous recombination related gene mutations, androgen receptor (AR) and phosphatase and tensin homolog (PTEN) may also be measured.

Blood samples will be collected for measurement of the following:

- PSA
- Biomarkers: where assays are available for measuring markers as a surrogate for tumour tissue (urine also may be tested)

- CTCs: enumeration and characterisation where assays are available for measuring markers as a surrogate for tumour tissue.

Patient reported outcomes (PROs) will be measured using the Brief Pain Inventory – Short Form (BPI-SF), an individual item on bone pain and the FACT-P (Functional Assessment of Cancer Therapy – Prostate Cancer) questionnaires.

Both Parts A and B

Optional blood samples for pharmacogenetic research will be obtained from consenting patients and stored for long-term exploratory purposes.

A follow-up visit will be conducted 30 days (±7 days) after the last dose of study treatment (olaparib/placebo or abiraterone).

Target patient population

Patients must have a histologically or cytologically proven diagnosis of prostate cancer, and be a candidate for abiraterone therapy with documented evidence of metastatic CRPC (metastatic status is defined as at least one documented metastatic lesion on either bone scan or CT/MRI scan; CRPC is defined as rising PSA or other signs of disease progression despite treatment with androgen deprivation therapy and the presence of a castrate level of testosterone [≤50 ng/dL]). Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 with no deterioration during the previous 2 weeks. For the randomised phase, patients must have received chemotherapy in the form of docetaxel treatment for metastatic CRPC.

Investigational product and additional study drugs, dosage and mode of administration

The investigational product (olaparib) and additional study drugs (abiraterone and prednisone/prednisolone) should be taken orally with water. Patients should aim to take their doses at similar times each day, with the twice daily doses approximately 12 hours apart. Patients must fast (except water) from at least 2 hours before until 1 hour after each dose (morning and evening).

Part A, Cohort 1:
200 mg olaparib (2 x 100 mg tablets) bid.
1000 mg abiraterone (4 x 250 mg tablets) once daily in the morning and prednisone or prednisolone 5 mg (1 x 5 mg tablet) bid.

Part A, Cohort 2, Group 1:
300 mg olaparib (2 x 150 mg tablets) bid, starting on Day 1.
1000 mg abiraterone (4 x 250 mg tablets) once daily, in the morning, and prednisone or prednisolone 5 mg bid, starting the day after completion of the olaparib PK profiling.

Part A, Cohort 2, Group 2:
1000 mg abiraterone (4 x 250 mg tablets) once daily, in the morning, and prednisone or

prednisolone 5 mg bid, starting on Day 1.
300 mg olaparib (2 x 150 mg tablets) bid, starting after completion of the abiraterone PK profiling (after the 24-hour sample).

Part A, Cohort 3, Groups 1 and 2 (if required):
200 mg olaparib (2 x 100 mg tablets) bid, as described for Cohort 2, Groups 1 and 2.
1000 mg abiraterone (4 x 250 mg tablets) once daily, in the morning, and prednisone or prednisolone 5 mg bid, as described for Cohort 2, Groups 1 and 2.

Part B:
300 mg olaparib or placebo (2 x 150 mg tablets) bid (or 200 mg olaparib/placebo bid, if 3 cohorts are dosed in Part A).
1000 mg abiraterone (4 x 250 mg tablets) once daily, in the morning, and prednisone or prednisolone 5 mg (1 x 5 mg tablet) bid.

Duration of treatment

Patients will continue to receive study treatment until disease progression, or until a time when the Investigator considers that they are no longer deriving clinical benefit, or they stop taking treatment for any other reason including having met any of the criteria for treatment discontinuation.

Outcome variable(s):

Primary outcome variables – Part A:

- **Safety and tolerability**
  - Assessment of adverse events (AEs) graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.0, vital signs (including blood pressure, pulse), and evaluation of laboratory parameters (clinical chemistry and haematology).
  - Incidence of dose-limiting toxicities (DLTs)

Primary outcome variables – Part B:

- **Efficacy**
  - rPFS, defined as the time from randomisation to disease progression according to RECIST 1.1 (for soft tissue disease) and/or PCWG-2 criteria (for bone disease), or death.

Secondary outcome variables – Part A:

- **Pharmacokinetics**
  - Olaparib and abiraterone PK parameters (where the data allow): maximum plasma concentration at steady state ($C_{max\ ss}$), time to reach maximum plasma concentration at steady state ($t_{max\ ss}$), area under the plasma concentration-time curve at steady state (AUC_{ss}), minimum plasma concentration at steady state ($C_{min\ ss}$)

Secondary outcome variables – Part B:

- **Efficacy**
  - Overall survival (OS)
  - Time to second progression (PFS2)
  - Tumour response in terms of ORR (malignant soft tissue response and overall radiological response [malignant soft tissue response by RECIST 1.1 and overall radiological response by RECIST 1.1 and PCWG-2])
  - TFST for prostate cancer and TSST for prostate cancer
- **Safety and tolerability**
  - Assessment of AEs graded by CTCAE v4.0, vital signs (including blood pressure, pulse), and evaluation of laboratory parameters (clinical chemistry and haematology).
- **Biomarkers**
  - Percentage change from baseline in PSA levels and PSA response
  - Change in CTC numbers
  - BRCA and ATM mutation status; if the number of events in these groups is sufficient then the primary analysis of rPFS will be repeated in all BRCA and ATM mutation positive patients.

Exploratory outcome variables:

Exploratory outcome variables (Part B) will include, in brief: PROs including BPI-SF pain scores, worst bone pain item and FACT-P scores; pharmacogenetic correlates for the response to olaparib; changes in health utilities (as measured by EuroQuol-5 Dimensions, five level [EQ-5D-5L]); health economics outcomes; PTEN and AR status, and their correlation with response to olaparib.

Statistical methods

There is no formal sample size calculation for Part A of the study; an empirically based approach, customary to Phase I studies, was used. The primary endpoint of Part A is to assess the safety profile of olaparib, including DLTs, and to identify the recommended dose for Part B.

The primary endpoint of Part B is rPFS. The sample size of 140 patients will have 80% power to detect a significant difference at the 1-sided 10% level after 100 events have occurred in the full analysis set, if the assumed true treatment effect was hazard ratio (HR) 0.65. This translates to a 3.75 month benefit in median rPFS on olaparib given with abiraterone compared to placebo given with abiraterone. A log-rank test and Kaplan-Meier summaries will be undertaken for the primary and sensitivity analyses of rPFS, and all other secondary and exploratory time-to endpoints.

The secondary endpoint in Part A is the estimation of PK parameters to evaluate the presence of any drug-drug interaction (DDI) between olaparib and abiraterone. For inclusion in the evaluation of a DDI, patients must have provided steady state PK profiles both for olaparib/abiraterone alone and in combination, and had no protocol violations affecting the PK endpoint.

In Part B, OS will be analysed after approximately 60% deaths have occurred in the full analysis set.

Other secondary endpoints are safety (AEs, laboratory safety assessments, vital signs; these will be summarised using the safety analysis set), tumour response (PSA, CTC; descriptive statistics will be presented using the full analysis set), and efficacy endpoints (PFS2, ORR, TFST, TSST; these will use the full analysis set for time-to analyses and logistic regression of ORR).

In Part B only, if sufficient evaluable samples are obtained, analyses of rPFS will be undertaken for patients with positive ERG expression/fusion status and BRCA mutations. Other markers including PTEN, AR, disease related biomarkers, demographic and disease characteristics may be looked at in exploratory analyses. Other exploratory endpoints include PRO endpoints, which will be summarised using the full analysis set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Androgen receptor
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated gene
AUC	Area under plasma concentration-time curve from zero to infinity
AUC_{ss}	Area under the plasma concentration-time curve at steady state
bid	Twice daily (Latin: *bis die*)
BP	Blood pressure
BPI-SF	Brief Pain Inventory – Short Form
BRCA	Breast cancer gene, ie, BRCA1 and BRCA2
BRCP	Breast cancer resistance protein
CI	Confidence interval
C_{max}	Maximum plasma concentration
$C_{max\ ss}$	Maximum plasma concentration at steady state
$C_{min\ ss}$	Minimum plasma concentration at steady state
CR	Complete response
CRF	Case Report Form
CRPC	Castrate-resistant prostate cancer
CSA	Clinical Study Agreement
CSF	Colony-stimulating factor
CSR	Clinical Study Report
CT	Computed tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Event
%CV	Coefficient of variation

Abbreviation or special term	Explanation
CYP	Cytochrome P450
DAE	Discontinuation of Investigational Product due to Adverse Event
DCO	Data cut-off
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSBs	Double strand breaks
E-code	Enrolment code
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQuol-5 Dimensions, five level
ERG	Erythroblast transformation-specific (ETS) related gene
ETS	Erythroblast transformation-specific
EU	European Union
EWB	Emotional well-being
FACT-P	Functional Assessment of Cancer Therapy – Prostate Cancer
FAPSI-8	Functional Assessment of Prostate Cancer Symptoms Index 8
FISH	Fluorescence in situ hybridisation
FPI	First patient in
FWB	Functional well-being
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
%GCV	Geometric %CV
GMP	Good Manufacturing Practice
Hb	Haemoglobin
Hct	Haematocrit
HR	Hazard ratio
HRQL	Health-Related Quality of Life

Abbreviation or special term	Explanation
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICU	Intensive care unit
INR	International normalised ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LHRH	Luteinising hormone releasing hormone
LOQ	Limit of quantification
LVEF	Left ventricular ejection fraction
MATE	Multidrug and toxin extrusion protein
mCRPC	Metastatic Castration Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MDR1	Multidrug resistance protein 1
MRI	Magnetic resonance imaging
MUGA	Multi gated acquisition scan
NC	Not calculable
NCI	National Cancer Institute
NE	Non evaluable
NED	No evidence of disease
NL	New lesion
NQ	Non-quantifiable
NRS	Numerical rating scale
NTL	Non-target lesion
OAE	Other Significant Adverse Event (see definition in Section 11.2.2)
OAT	Organic anion transporter
OATP1B1	Organic anion transporter protein B1

Abbreviation or special term	Explanation
OCT1	Organic cation transporter 1
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'-diphosphoribose polymerase
PCS	Prostate cancer symptoms
PCWG-2	Prostate Cancer Working Group 2
PD	Progression of disease
PFS	Progression-free survival
PFS2	Second progression
Pgp	P-glycoprotein
PGx	Pharmacogenetic research / pharmacogenetics
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial response
PRO	Patient Reported Outcome
PSA	Prostate specific antigen
PTEN	Phosphatase and tensin homolog
PWB	Physical well-being
QTc	Corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
rPFS	Radiologic progression-free survival
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical analysis plan
SD	Stable disease
SD	Standard deviation
SRC	Safety Review Committee
SSBs	Single strand breaks
SUSARs	Suspected Unexpected Serious Adverse Reactions
SWB	Social well-being
TFST	Time to first subsequent therapy
TL	Target lesion
$t_{max\ ss}$	Time to reach maximum plasma concentration at steady state

Abbreviation or special term	Explanation
TMPRSS2	Transmembrane protease serine 2
TMPRSS2-ERG	TMPRSS2 erythroblast transformation-specific (ETS) related gene
TOI	Trial outcome index
TSST	Time to second subsequent therapy
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
WBC	White blood cells
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Investigators should be familiar with the current olaparib Investigator Brochure (IB).

1.1.1 Prostate cancer

Prostate cancer is the most prevalent form of cancer in men in the Western world. One in 6 men will be diagnosed with cancer of the prostate during their lifetime and it is the second most common cause of male cancer death. The National Cancer Institute (NCI) have estimated that 238,590 men will be diagnosed and 29,720 men will die of cancer of the prostate in the United States in 2013. According to Cancer Research UK, 40,975 men were diagnosed with prostate cancer in the UK in 2010, with 10,721 deaths from the disease.

Castrate-resistant prostate cancer (CRPC) is associated with a broad array of symptoms but is predominately characterised by bone pain, fatigue and urinary dysfunction (including incontinence, dysuria and increased urinary frequency/urgency) (Gater et al 2011, Lindqvist et al 2008). These symptoms can have a profound impact on men's daily lives and contribute to diminished levels of health-related quality of life (HRQL) observed in this population (Eton and Lepore 2002).

1.1.2 Olaparib and PARP inhibition

Olaparib (AZD2281, KU-0059436) is a potent polyadenosine 5'diphosphoribose [poly ADP ribose] polymerase (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours with deficiencies in deoxyribonucleic acid (DNA) repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more significant DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair.

1.1.3 Rationale for olaparib in prostate cancer

Prostate cancer is a heterogeneous disease and androgen deprivation therapy with luteinising hormone releasing hormone (LHRH) analogs or orchidectomy is usually initially effective at controlling metastatic disease, but patients inevitably progress from an androgen-sensitive to a castration-resistant phenotype. Until recently, effective treatment at this stage has been largely limited to docetaxel chemotherapy after studies showed it could improve overall survival in this population. Cabazitaxel, enzalutamide, abiraterone acetate (hereafter referred to as abiraterone) and radium-223 (Parker et al 2013) have now been shown to give further improvements in time to progression and overall survival when used after docetaxel therapy. The optimum strategy for managing patients after docetaxel has not been established, but in many countries all 4 of these agents are licensed for use in the post-docetaxel phase of

metastatic CRPC, with enzalutamide and abiraterone, which both target the androgen receptor (AR) pathway, being preferred because of their good tolerability profiles and absence of chemotherapy-associated side effects. In Part A of this study, metastatic CRPC patients will be recruited irrespective of whether they have already had chemotherapy in order to facilitate recruitment to this part of the study.

Recent pre-clinical data demonstrate a role for PARP-1, distinct from its role in DNA repair, in AR-dependent transcriptional signalling. Specifically relevant to this study is the observation that PARP-1 inhibition co-operates with androgen depletion to suppress cell proliferation (Schiewer et al 2012). Furthermore, chromosomal rearrangements placing coding region on erythroblast transformation-specific (ETS) genes (eg, ETS-related gene [ERG]) occur with high frequency in prostate cancer and result in AR-dependent expression of pro-tumourigenic ETS genes. ERG has been shown to physically interact with PARP-1, and PARP-1 inhibition preferentially sensitises ETS over-expressing xenografts to PARP inhibition (Brenner et al 2011). In addition, over-expression of ERG leads to accelerated carcinogenesis in mouse prostates with phosphatase and tensin homolog (PTEN) deletion, and PTEN loss itself has been suggested to sensitise cells to PARP inhibitors (Mendes-Pereira 2009). Hence, there is a rationale for combination of olaparib with abiraterone in prostate cancer and a possibility that this combination may be preferentially active based on measures of ETS fusions (eg, ERG expression), AR status and PTEN. There may also be a small number of patients who may benefit due to the presence of a BRCA mutation in their tumour. Although only a small number of patients have germline mutations (Castro et al 2013), the number with somatic mutations may be significantly higher (Beltran et al 2013). Recent clinical data suggest that PTEN and TMPRSS2-ERG are not key determinants of PARP inhibitor sensitivity in mCRPC but do strongly suggest that mutations in DNA repair genes, in particular BRCA2 and ATM, are associated with response to, and duration of therapy on, olaparib (Mateo et al 2015).

This study will evaluate the investigational drug olaparib when given on a background of the approved drug abiraterone in patients with metastatic CRPC. Part A of this study will provide an initial assessment of safety/tolerability and potential for pharmacokinetic (PK) interaction between the drugs. For the randomised phase of this study, only post-chemotherapy CRPC patients will be studied. This therefore facilitates a robust assessment of the primary endpoint of radiologic progression-free survival (radiologic PFS, rPFS) within a reasonable timeframe for a Phase II study.

1.1.4 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib IB.

1.1.5 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies, eg, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic, or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of olaparib. Ex vivo studies have confirmed that olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test in vitro. When dosed orally, olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

Further information can be found in the current version of the olaparib IB.

1.1.6 Clinical experience

The clinical experience with olaparib is fully described in the current version of the olaparib IB.

1.1.6.1 Patient experience

As of 20 May 2013, an estimated 2034 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumours are estimated to have received treatment with either olaparib tablets or capsules across the dose range 10 mg once daily to 600 mg twice daily (bid). Olaparib has been given as either monotherapy or combination therapy.

1.1.6.2 Clinical pharmacokinetics

Following administration of single oral doses of the tablet formulation at doses of 25, 50 and 250 mg (n=6 per cohort), absorption was rapid and slightly more rapid than seen following the capsule dose. The maximum plasma concentration (C_{max}) was typically achieved between 0.5 hours and 2 hours after dosing. Following the peak, plasma concentrations declined biphasically with a terminal half-life ($t_{½}$) across all 3 dose levels, of between 5 and 9 hours (average = 6.97 hours ±1.03 standard deviation [SD]). Both geometric mean C_{max} and area under the plasma concentration-time curve from zero to infinity (AUC) increased approximately proportionally with dose (8- and 12-fold, respectively, for a 10-fold increase in dose). The mean volume of distribution (V_z/F) of olaparib was 54.9 L ±30.2 SD and the mean apparent plasma clearance following oral administration (CL/F) was 5.42 L/h ±2.62 SD.

Further information on the PK and metabolism of olaparib is provided in the current version of the IB.

1.2 Research hypothesis

Administration of olaparib when given in addition to abiraterone will result in greater efficacy, as determined by rPFS, in patients with metastatic CRPC than treatment with abiraterone alone.

1.3 Rationale for conducting this study

The primary objective for Part A of this study is to perform an initial evaluation of the safety and tolerability of olaparib when given in addition to abiraterone and to establish a recommended Phase II combination dose of olaparib with abiraterone. Secondary objectives for Part A include establishing whether there is a drug interaction between olaparib and abiraterone.

Pre-clinical data provide evidence for the role of PARP-1 in mediating AR-dependent gene expression. AstraZeneca therefore believe that olaparib may be used to enhance prostate cancer sensitivity to AR-directed therapeutics such as abiraterone, with the potential for olaparib therapy on a background of abiraterone being more effective than abiraterone alone. The primary objective of the randomised part of this study, Part B, is therefore to assess the efficacy of olaparib when given in addition to abiraterone compared with abiraterone alone, as measured by rPFS.

Supportive secondary objectives for the study include the additional assessment of efficacy as defined by overall survival (OS) and objective response rate (ORR), the assessment of efficacy as defined by time from randomisation to second progression (PFS2), times to first and second subsequent therapies for prostate cancer, and the determination of safety and tolerability.

It is important to assess how a patient functions and feels due to their disease and its treatment. This study will also explore patients' experience of treatment with olaparib when given in addition to abiraterone, compared to placebo with abiraterone, by assessment of patient-reported symptoms and HRQL using patient reported outcome instruments.

As part of the clinical drug development program for olaparib, AstraZeneca plans to include investigations into variations in pharmacodynamic and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, ribonucleic acids (RNA), proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders, or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future meta-analysis of data derived from a number of studies with olaparib.

AstraZeneca intends to perform pharmacogenetic research in the olaparib clinical development programme to explore how genetic variations may affect the clinical parameters associated with olaparib. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guided treatment strategies.

1.4 Benefit/risk and ethical assessment

Once patients with prostate cancer have progressed from an androgen-sensitive to a castration-resistant phenotype, docetaxel is an accepted first-line treatment, with cabazitaxel, enzalutamide and abiraterone indicated in the post-docetaxel phase. There is a clear clinical need to enhance the care of patients who have suffered disease progression during or following docetaxel therapy. Because of abiraterone's effectiveness in this setting and the promise of PARP inhibition enhancing its effects, a randomised trial comparing olaparib plus abiraterone to placebo plus abiraterone is appropriate.

In view of the potential for olaparib, given in addition to abiraterone, to have anti-tumour activity in metastatic CRPC population, the current study is designed to allow for patients to continue on olaparib/abiraterone therapy until progression of disease. However, patients may stop treatment at any time if they choose to do so or if the Investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing or stopping olaparib are provided. The assessment of HRQL will provide information on patients' experience of the treatment and will be part of the benefit-risk assessment.

The molecular targeting of olaparib to specific subsets of tumours may provide an opportunity for more effective and potentially less toxic cancer treatments in the advanced disease setting compared with currently available regimens. Based on the available data on efficacy and safety (see the olaparib IB), AstraZeneca believes that olaparib continues to demonstrate an overall positive benefit-risk balance to support its further clinical development. The benefit-risk assessment, therefore, strongly favours the current and proposed olaparib study in patients with advanced prostate cancer.

Full details of the benefits and risks of olaparib are provided in the current olaparib IB. The Investigator should refer to the abiraterone prescribing information for details on the risks of abiraterone.

2. STUDY OBJECTIVES

2.1 Primary objectives

Table 1 Primary objectives

Primary objective	Primary outcome variable
Part A, Safety run-in:	
To assess the safety and tolerability of olaparib when given in addition to abiraterone and to recommend, by assessment of dose-limiting toxicities and other safety and tolerability data, a dose of olaparib for further study when given in addition to abiraterone.	Assessment of AEs graded by CTCAE v4.0, vital signs (including BP, pulse), and evaluation of laboratory parameters (clinical chemistry and haematology. Incidence of dose-limiting toxicities during the initial evaluation period.

Table 1 Primary objectives

Primary objective	Primary outcome variable
Part B:	
To compare the efficacy of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone, by assessment of rPFS using RECIST 1.1 and PCWG-2 criteria.	rPFS, defined as the time from randomisation to disease progression according to RECIST 1.1 (for soft tissue disease) and/or PCWG-2 criteria (for bone disease), or death.

AE adverse event; BP blood pressure; CTCAE Common Terminology Criteria for Adverse Event;
PCWG-2 Prostate Cancer Working Group 2;
RECIST 1.1 Response Evaluation Criteria in Solid Tumours version 1.1;
rPFS Radiologic progression-free survival.

2.2 Secondary objectives

Table 2 Secondary objectives

Secondary objective	Secondary outcome variables
Part A, Safety run-in:	
To evaluate the presence of any drug interaction between olaparib and abiraterone by determination of steady state exposure to olaparib in the presence and absence of abiraterone, and determination of steady state exposure to abiraterone in the presence and absence of olaparib.	Olaparib and abiraterone PK parameters (where the data allow): $C_{max\ ss}$, $t_{max\ ss}$, $C_{min\ ss}$, AUC_{ss}.
Part B:	
To compare the safety and tolerability of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone.	Assessment of AEs graded by CTCAE v4.0, vital signs (including BP, pulse), and evaluation of laboratory parameters (clinical chemistry and haematology).

Table 2 Secondary objectives

Secondary objective	Secondary outcome variables
To assess the anti-tumour activity of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by measurement of changes in circulating prostate specific antigen (PSA) and circulating tumour cells (CTCs), calculation of overall radiological objective response rate (ORR) (by RECIST 1.1 and PCWG-2 bone scan criteria) and malignant soft tissue ORR (by RECIST 1.1), time to first subsequent therapy (TFST) for prostate cancer, and time to second subsequent therapy (TSST) for prostate cancer.	Percentage change from baseline in PSA levels and PSA response. Change in CTC numbers. Tumour response in terms of ORR (malignant soft tissue response and overall radiological response [malignant soft tissue response by RECIST 1.1 and overall radiological response by RECIST 1.1 and PCWG-2]). TFST and TSST.
To assess the efficacy of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by assessment of OS.	OS, defined as time from randomisation to the date of death from any cause.
To assess the efficacy of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by assessment of time from randomisation to PFS2.	PFS2. Progression defined by local standard clinical practice. May involve any of: objective radiological progression, symptomatic progression, rises in PSA or death.
To investigate BRCA and ATM mutations as candidate predictors of response to olaparib. Note: This objective is dependent upon the number of evaluable samples obtained from the study.	BRCA and ATM mutation status; if the number of events in these groups is sufficient then the primary analysis of rPFS will be repeated in all patients with BRCA and ATM mutations.

AE adverse event; AUC_{ss} area under the plasma concentration-time curve at steady state; BP blood pressure
BRCA Breast cancer gene; $C_{max\ ss}$ maximum plasma concentration at steady state;
$C_{min\ ss}$ minimum plasma concentration at steady state; CTCs circulating tumour cells;
DoR duration of response; ERG Erythroblast transformation-specific related gene;
ORR objective response rate; OS overall survival; PFS2 second progression; PSA prostate specific antigen;
$t_{max\ ss}$ time to reach maximum plasma concentration at steady state;
TFST time to first subsequent therapy; TSST time to second subsequent therapy

2.3 Exploratory objectives

Table 3 Exploratory objectives

Exploratory objectives	Exploratory outcome variables
To explore the effects of olaparib on pain and other prostate cancer-related symptoms compared to placebo.	Change from baseline in worst pain, general pain and pain interference in daily activities scales of the BPI-SF and the worst bone pain item. Change from baseline in the FAPSI-8, as derived from 8 items within the FACT-P, and the PCS, as derived from the 12 items in the prostate-specific module of the FACT-P.
To explore the effects of olaparib on HRQL compared to placebo.	Change from baseline, as measured by the FACT-P scales: FWB, PWB, EWB, SWB, the Total FACT-P score, and the TOI score (the sum of the PWB, FWB and PCS scores).
To assess the time to deterioration in pain.	Time to deterioration in the BPI-SF worst pain item and time to deterioration in the worst bone pain item.
To assess time to deterioration in HRQL.	Time to deterioration in HRQL, as measured by FACT-P TOI score.
To explore the impact of treatment and disease state on health state utility.	EQ-5D-5L health state utility index.
To investigate the impact of treatment and disease progression on metastatic CRPC management resource use.	Resource use will be captured, focussing on in-patient and ICU admissions, length of stay, palliative interventions and reason for admission into hospital and interventions.
Future exploratory research into factors that may influence development of cancer (including PTEN, AR status) and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (where available), blood samples (mandatory), urine samples (mandatory), and CTC samples (mandatory).	PTEN and AR status in archival tumour tissue (where available), CTCs, blood and urine samples – the primary analysis of rPFS may be repeated by patient PTEN and AR status.

Table 3 Exploratory objectives

Exploratory objectives	Exploratory outcome variables
To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour sample (where available), blood sample at baseline and on disease recurrence (mandatory), urine samples at baseline and disease recurrence (mandatory), and CTC samples (mandatory).	Analysis and outcome variables yet to be defined.
CCI	CCI

AR Androgen receptor; BPI-SF Brief Pain Inventory – Short Form;
EQ-5D-5L EuroQuol-5 Dimensions, five-level; EWB Emotional well-being;
ERG Erythroblast transformation-specific related gene
FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer;
FAPSI-8 Functional Assessment of Prostate Cancer Symptoms Index 8; ICU intensive care unit
FWB Functional well-being; HRQL health-related quality of life; PCS Prostate cancer symptoms;
PTEN phosphatase and tensin homolog; PWB Physical well-being; SWB Social well-being;
TOI Trial outcome index

The exploratory analyses, including statistical methods for the exploratory endpoints, will be defined and reported separately.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a 2-part study in patients with metastatic CRPC. Part A is an open-label safety run-in study to assess the safety, tolerability and PK of olaparib when given in addition to abiraterone 1000 mg once daily. Part B is a randomised, double-blind, placebo-controlled comparison of the efficacy, safety and tolerability of the dose of olaparib selected from Part A when given in addition to abiraterone, versus placebo in addition to abiraterone.

Abiraterone is indicated in combination with prednisone or prednisolone for the treatment of patients with metastatic CRPC. Prednisone or prednisolone 5 mg bid will be administered with the abiraterone in this study, but throughout this protocol the treatment will be referred to simply as abiraterone.

For Part A of the study, 15 to 18 evaluable patients (Cohorts 1 and 2) are planned to be enrolled from approximately 4 sites in approximately 1 or 2 countries, and a further 12 patients may be recruited into a 3rd cohort if necessary.

For Part B of the study, approximately 140 patients who have received prior chemotherapy containing docetaxel will be randomised from approximately 40 sites in North America and Europe. Patients who have been dosed in Part A of the study may not participate in Part B.

A flow chart of Part A of the study and dose decisions is illustrated in Figure 1.

3.1.1 Part A: Safety run-in/dose escalation

Patients will attend the clinic for assessments on the first day of study treatment, at 1 and 2 weeks, then every 4 weeks up to Week 52, and every 12 weeks thereafter. They will also attend for study treatment supplies at 16 weeks and every 4 weeks thereafter.

3.1.1.1 Cohort 1 (up to 6 patients)

At least 3 and up to 6 evaluable patients with metastatic CRPC will be enrolled in Cohort 1 using a rolling 6 design (Skolnik et al 2008). Patients will receive olaparib 200 mg bid and abiraterone 1000 mg once daily. Patients will attend the clinic for safety assessments as shown in the flow chart (Figure 2) and study plan (Table 4).

Dose-limiting toxicities (DLTs) from all patients will be assessed by a Safety Review Committee (SRC; see Section 3.1.6) after a minimum of 3 patients have received a minimum of 14 days' treatment. Dose escalation will follow the scheme below, according to the following logic:

- Dose increases will be permitted after review of data from a minimum of 3 evaluable patients has been performed. Evaluable patients will be those that have completed at least 14 days of dosing with olaparib and abiraterone. If no DLT is observed (for definition see Section 3.1.1.4) in the initial cohort of 3 to 6 evaluable patients, then dose escalation may occur.

- If 1 patient experiences a DLT in the initial cohort of 3 or more evaluable patients then the cohort will be expanded to include a total of 6 evaluable patients. If only 1 DLT is observed in the complete cohort of 6 evaluable patients then dose escalation may occur.

- If 2 or more patients experience a DLT in Cohort 1, irrespective of the number of patients enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. The study may be terminated at this stage or

amended to allow doses below 200 mg bid of olaparib to be studied following review of safety data.

3.1.1.2 Cohort 2 (12 patients)

If the combination of olaparib 200 mg bid and abiraterone 1000 mg once daily is tolerated, a cohort of 12 patients (split into 2 groups of 6 patients) will be treated with olaparib 300 mg bid given in addition to abiraterone 1000 mg once daily, and will be evaluated for safety, tolerability and PK.

Group 1:

Patients will receive olaparib alone (300 mg bid) for between 3 and 7 days. Blood samples will be collected to determine the steady state PK profile for olaparib; this may be done on any day between Days 3 and 7, starting after the morning dose.

Patients will then receive abiraterone (1000 mg once daily) starting from the day after the olaparib PK profile has been collected. Olaparib and abiraterone will continue to be dosed in combination for at least 5 days, then blood samples will be collected again to determine both olaparib and abiraterone PK profiles.

A flow chart of the study visits is shown in Figure 3. Visits and assessments will be conducted as shown in Table 5. The timings for starting the olaparib and abiraterone doses, and the corresponding options for PK sampling days, are provided in Table 6.

Group 2:

Patients will receive abiraterone alone (1000 mg once daily) for between 5 and 7 days. Blood samples will be collected to determine the steady state PK profile for abiraterone (any day between Days 5 and 7).

Patients will receive olaparib (300 mg bid) starting immediately after the 24-hour abiraterone PK sample has been collected. Olaparib and abiraterone will continue to be dosed in combination for at least 3 days, then blood samples will be collected again to determine both olaparib and abiraterone PK profiles.

A flow chart of the study visits is shown in Figure 4. Visits and assessments will be conducted as shown in Table 5. The timings for starting the olaparib and abiraterone doses, and the corresponding options for PK sampling days, are provided in Table 7.

Dose-limiting toxicities will be assessed by the SRC after a minimum of 14 days' treatment with both olaparib and abiraterone. If <2 DLTs occur in the first 9 patients that have completed at least 14 days' dosing with both olaparib and abiraterone, then the randomised part of the study, Part B, may commence with this dose combination and the remaining 3 patients to be dosed in Part A may be recruited in parallel with Part B. If 2 or more DLTs occur then all 12 patients must be dosed before a decision is made to progress to Part B. If <4 DLTs occur in this cohort of 12 patients (Groups 1 and 2), then the randomised part of the study, Part B, will commence with this dose combination.

3.1.1.3 Cohort 3 (12 patients)

If 4 or more DLTs occur in Cohort 2, a further 12-patient cohort may be recruited and treated with olaparib 200 mg bid in combination with abiraterone 1000 mg once daily and evaluated for safety, tolerability and PK as described for Cohort 2 (see Section 3.1.1.2).

If Cohort 3 is dosed and there are <4 DLTs, then Part B may proceed using a 200 mg bid dose of olaparib. If 4 or more DLTs are observed, then the study will be terminated.

3.1.1.4 Definition of dose-limiting toxicity

A DLT is defined as any toxicity which is not a recognised adverse effect of abiraterone or prednisolone, and not attributable to the disease or disease-related processes under investigation, which occurs during a minimum of 14 days' treatment and which includes:

1. Haematological toxicity ≥ CTCAE Grade 4 present for more than 4 days
   - Except anaemia
2. Non-haematological toxicity ≥ CTCAE Grade 3 including:
   - Infection including febrile neutropenia
   - Corrected QT interval (QTc) prolongation (> 500 msec)
3. Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care, results in a disruption of dosing schedule of 7 days or more, or is judged to be a DLT by the SRC

A DLT excludes:

1. Alopecia of any grade
2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

3.1.2 Part B: Randomised part

Progression to Part B will be based on a review of all available safety, tolerability and PK data from Part A of the study. This will be performed when sufficient evaluable patients in both of the patient groups in Part A Cohort 2 (or Cohort 3 if necessary) have completed a minimum of 14 days' treatment. The selection of the dose for Part B will be taken by the SRC and AstraZeneca (see Section 3.1.6). This review may be conducted on pre-database lock data that have not been formally analysed.

Patients will receive olaparib/placebo 300 mg bid (or 200 mg bid, if 200 mg bid is the maximum tolerated dose in Part A) and abiraterone 1000 mg once daily. They will attend the clinic for assessments on the first day of study treatment, then every 4 weeks up to Week 52,

and every 12 weeks thereafter. They will also attend for study treatment supplies at 16 weeks and every 4 weeks thereafter.

Tumours will be evaluated using RECIST 1.1 and PCWG-2 criteria (see Appendix F). Baseline assessments should be performed no more than 28 days before the date of randomisation and ideally should be performed as close as possible to the date of randomisation. Follow-up assessments will be performed every 12 weeks (±1 week) from the date of randomisation (every 24 weeks after Week 72). Malignant soft tissue RECIST v1.1 assessments will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) scans of chest, abdomen and pelvis. Bone lesion PCWG-2 assessments will be performed using bone scan (preferably whole body).

An archival tumour sample will be collected, where available, to measure ERG expression/fusion status and BRCA mutation; other biomarkers such as AR and PTEN may also be measured.

Blood samples will be collected for measurement of the following:

- PSA
- Biomarkers: where assays are available for measuring markers as a surrogate for tumour tissue (urine also may be tested)
- CTCs: enumeration and characterisation where assays are available for measuring markers as a surrogate for tumour tissue.

Patient reported outcomes (PROs) will be measured using the BPI-SF, an individual item on bone pain and the FACT-P questionnaires.

A flow chart of the study visits is shown in Figure 5. Visits and assessments will be conducted as shown in Table 8.

Patients will be evaluated until disease progression regardless of whether study treatment is discontinued. The collection of RECIST 1.1/PCWG-2 data will then stop and patients will be followed for PFS2 and survival.

The primary analysis will be performed once approximately 100 progression events have occurred (see Section 9.5).

3.1.3 Discontinuation

Patients will continue to receive study treatment until disease progression, or until a time when the Investigator considers that they are no longer deriving clinical benefit, or they stop taking treatment for any other reason including having met any of the criteria for treatment discontinuation.

Once patients on olaparib/placebo have been discontinued from treatment, other treatment options will be at the discretion of the Investigator. All subsequent therapies should continue to be recorded on the appropriate eCRF.

For further details on discontinuation, see Sections 5.8 and 5.9.

3.1.4 30-Day follow-up

A follow-up visit should be conducted 30 days (±7 days) after the last dose of study treatment (olaparib/placebo or abiraterone). Any serious and/or non-serious AEs ongoing at the time of the treatment discontinuation visit or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Sections 6.4.3 and 6.4.4). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the Investigator, until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the electronic Case Report Form (eCRF). The assessments to be carried out at the 30-day follow-up visit are detailed in the study plan (Table 8).

3.1.5 Survival follow-up (Part B only)

Assessments for PFS2 and survival should be made every 12 weeks following objective disease progression. Information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. If the contact is with the patient directly, the BPI-SF worst pain item and the worst bone pain item will also be administered over the telephone (see Section 6.5.3). The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected. Survival and PFS2 data will be collected up to the time of the final OS analysis.

In addition, patients should be contacted in the 2 weeks following the data cut-off (DCO) and survival status and latest date known to be alive recorded for the final survival analyses to provide complete survival data.

All patients will be followed for PFS2 and survival data until approximately 60% of patients have died at which point the final analysis will occur and the database will be closed (see Section 9.5). Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib/placebo and abiraterone.

Survival status for withdrawn consent and lost to follow up patients

At the time of OS analyses, all patients' survival status should be re-checked; this includes those patients that withdrew consent or are classified as 'lost to follow up'.

- Lost to Follow up – site personnel should check hospital records, the patients' current physician and a publicly available death registry (if available) to obtain a current survival status in the 2 weeks following DCO

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

For US-based patients, the FDA provides guidance to this point in 'Guidance for Sponsors, Clinical Investigators, and IRBs. Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials'.
http://www.fda.gov/downloads/regulatoryinforamtion/guidances/ucm126489.pdf

- Patients who have withdrawn consent – site personnel should check a publicly available death registry (if available) in the 2 weeks following DCO.

For further information on patient withdrawal, see Section 5.9.

3.1.6 Safety Review Committee (SRC)

The SRC will consist of:

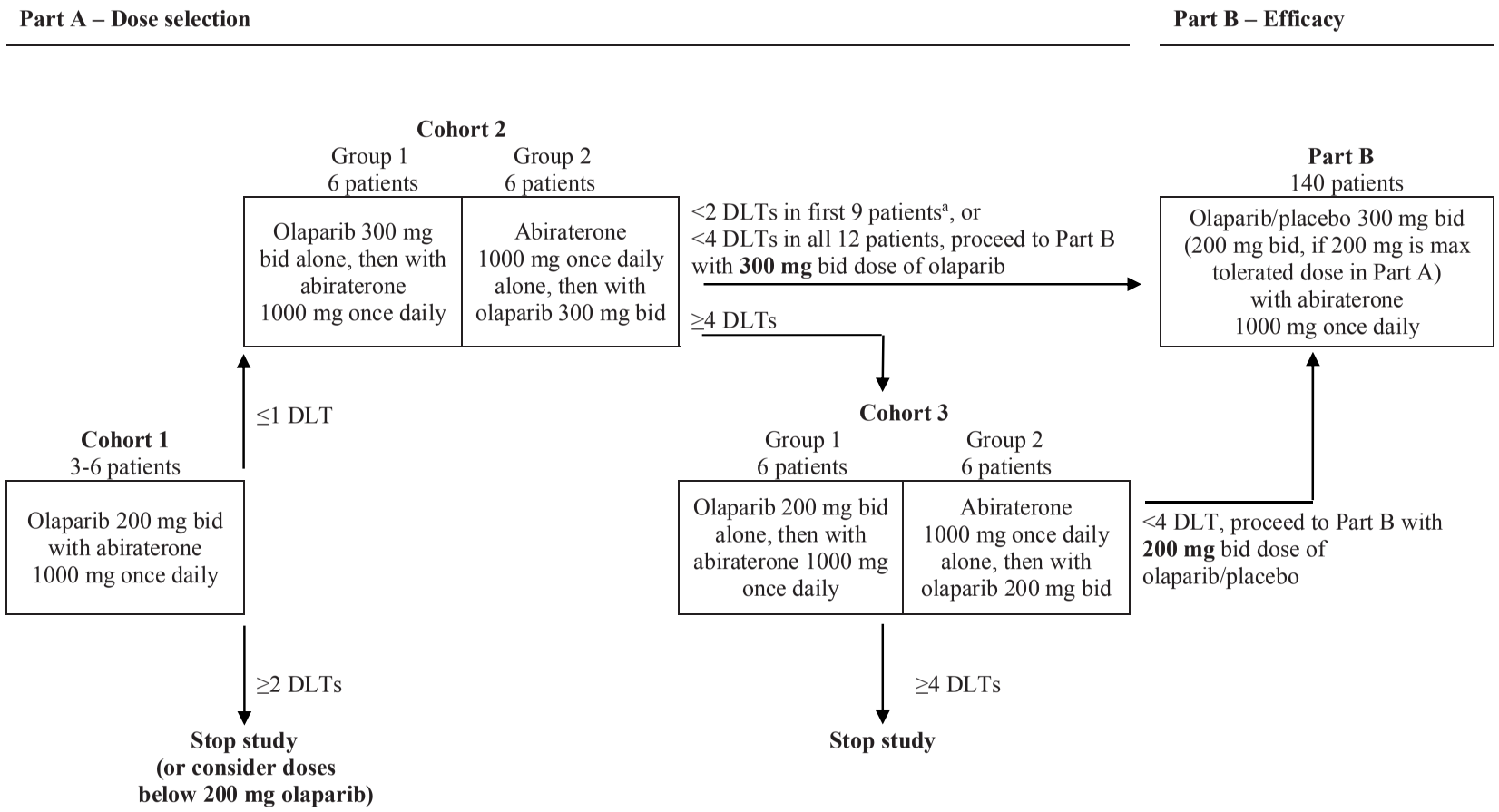
- AstraZeneca Study Physician, or delegate, who will chair the committee
- Quintiles Study Team Physician, or delegate
- Principal Investigator (PI), or delegate, from each investigational site.

Other physicians and representatives from AstraZeneca and Quintiles, such as the Global Safety Physician, will also be invited, as appropriate.

Further internal or external experts may be consulted by the SRC, as necessary. Any PI can request an ad hoc SRC meeting at any time in order to facilitate the immediate communication of any emerging safety issues during the course of the study.

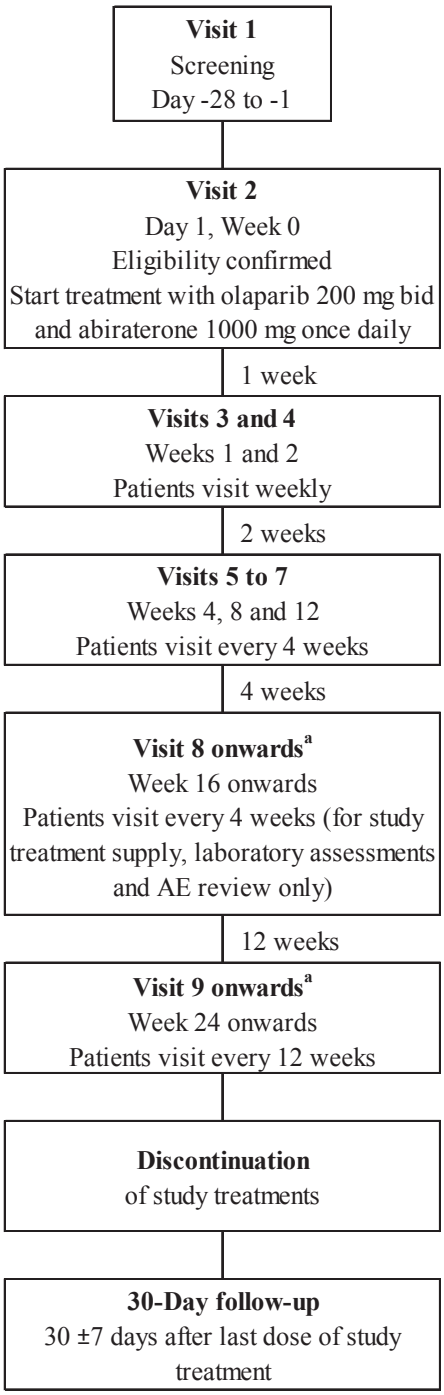
The SRC will evaluate available safety, tolerability, PK and anti-tumour data, and in agreement with AstraZeneca, will define the recommended dose for Part B.

Figure 1 Study design flow chart



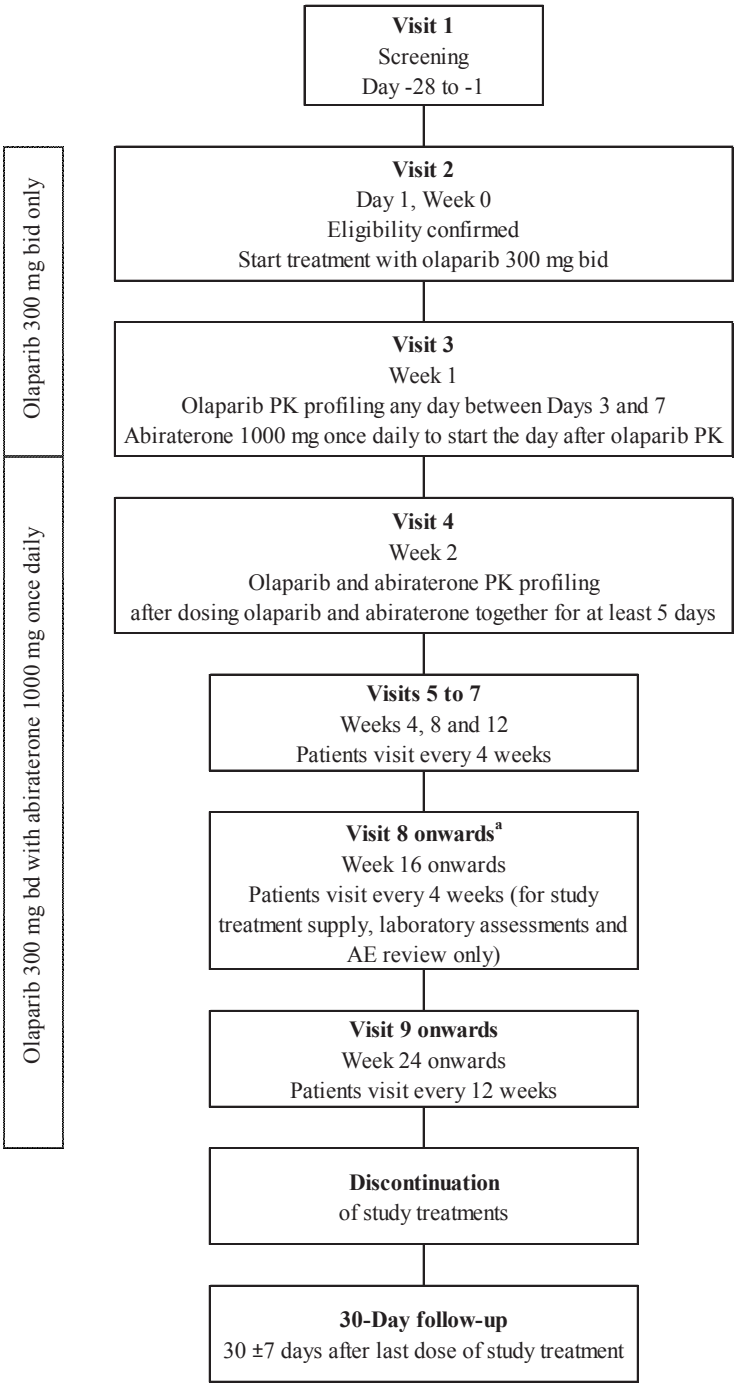
[a] <2 DLTs in the first 9 patients that have completed at least 14 days' dosing with both olaparib and abiraterone; the remaining 3 patients in the cohort may then be recruited in parallel with Part B

Figure 2 Flow chart for Part A, Cohort 1



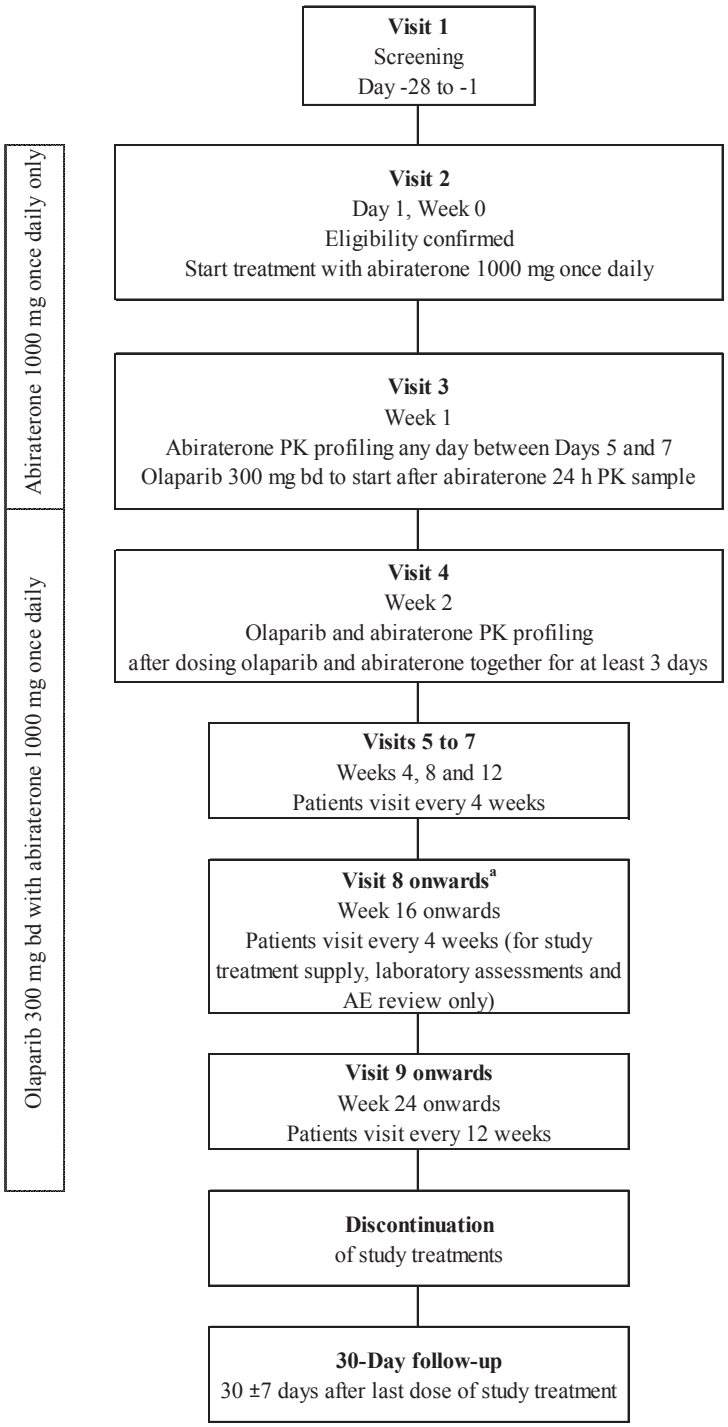
[a] Unless patients discontinue study treatment, they will remain in the study and be assessed every 12 weeks. Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.

Figure 3 Flow chart for Part A, Cohort 2, Group 1



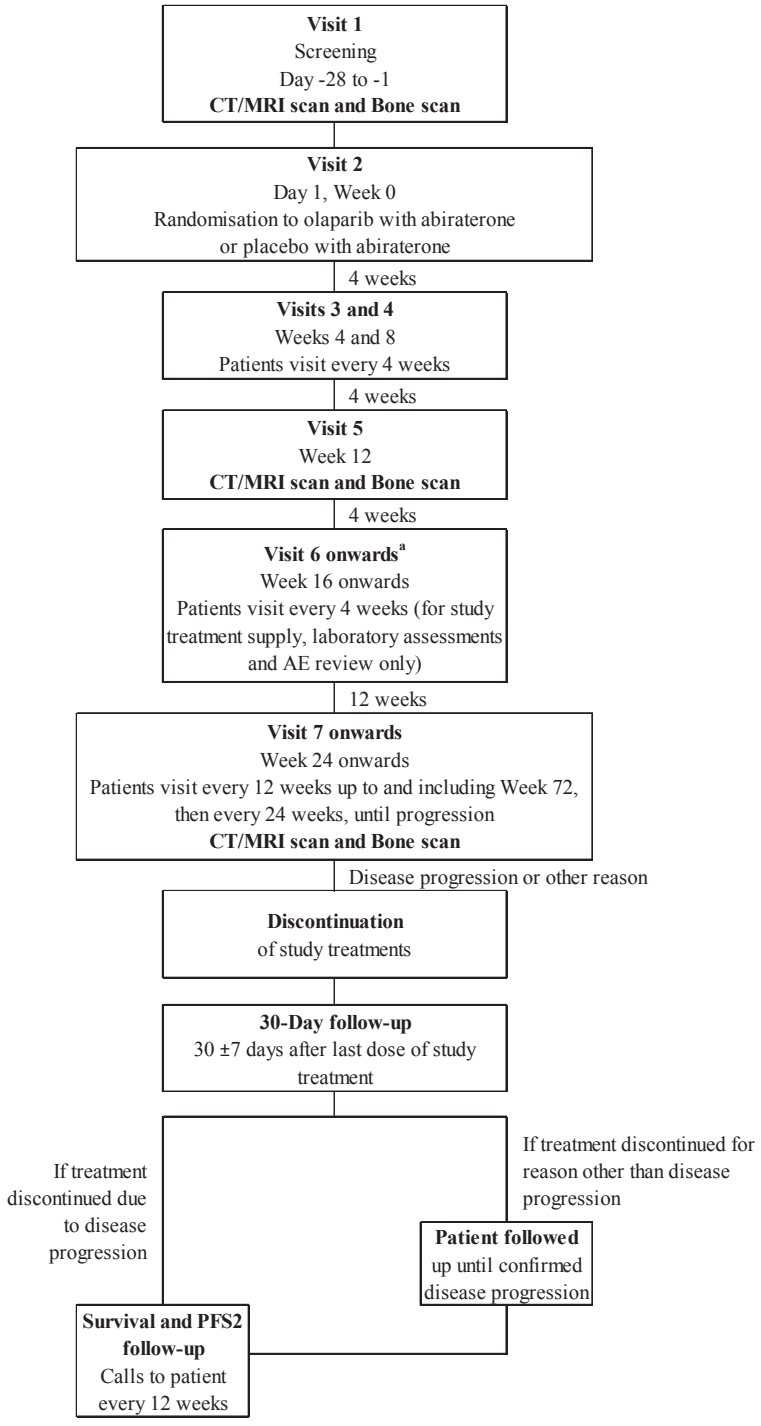
[a] Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.

Figure 4 Flow chart for Part A, Cohort 2, Group 2



[a] Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.

Figure 5 Flow chart for Part B



[a] Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.

Table 4 Study Plan – Part A, Cohort 1 (Olaparib 200 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+[j]**	**Discontin-uation of IP**	**30-day follow-up[k]**
Visit window (days)	**–28 to -1**	**±0**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	-	**1**	**8**	**15**	**29**	**57**	**85**	**113+**	**169+**	-	-
Written informed consent	X										
Demographics[a]	X										
Physical examination, height and weight[b]	X										X
Medical/surgical history	X										
ECOG Performance status	X										
Inclusion/exclusion criteria	X	X									
Collect PSA and BRCA status data (local)[c]	X										
12-lead ECG[d]	X										
Vital signs[e]	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication[f]	X	X	X	X	X	X	X		X	X	X
AE and SAE review[g]	X	X	X	X	X	X	X	X	X	X	X
Haematology, clinical chemistry (local)[h]	X	X	X	X	X	X	X	X (up to Week 52)	X (from Week 64)	X	X
PGx blood sample (optional)[i]		X									

Table 4 Study Plan – Part A, Cohort 1 (Olaparib 200 mg bid + Abiraterone)

Visit	1 Screening	2	3	4	5	6	7	8+	9+[j]	Discontin-uation of IP	30-day follow-up[k]
Visit window (days)	**–28 to -1**	**±0**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**8**	**15**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Treatment dispensed/returned		X	X	X	X	X	X	X	X	X	

AE adverse event; BRCA Breast cancer gene; ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; IP investigational product; PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race, and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[d] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[e] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[f] Concomitant medication should include all medications taken by the patient before and during the study.

[g] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[h] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). From Visit 8 (Week 16) onwards, laboratory assessments will be performed every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment. See Section 6.4.5 for a complete list of haematology and chemistry assessments.

[i] Sample will only be collected if separate PGx informed consent has been signed.

[j] Assessments apply to Visit 9 and subsequent visits occurring every 12 weeks thereafter.

[k] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

Table 5 Study Plan – Part A, Cohort 2 (Olaparib 300 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+[j]**	**Discontin-uation of IP**	**30-day follow-up[k]**
Visit window (days)	**–28 to -1**	**±0**	**±0**	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	-	**1**	**3-7**	**12-14**	**29**	**57**	**85**	**113+**	**169+**	-	-
Written informed	X										
Demographics[a]	X										
Physical examination, height and weight[b]	X										X
Medical/surgical history	X										
ECOG Performance Status	X										
Inclusion/exclusion criteria	X	X									
Collect PSA and BRCA status data (local)[c]	X										
12-lead ECG[d]	X										
Vital signs[e]	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication[f]	X	X	X	X	X	X	X		X	X	X
AE and SAE review[g]	X	X	X	X	X	X	X	X	X	X	X

Table 5 Study Plan – Part A, Cohort 2 (Olaparib 300 mg bid + Abiraterone)

Visit	1 Screening	2	3	4	5	6	7	8+	9+[j]	Discontinuation of IP	30-day follow-up[k]
Visit window (days)	**–28 to -1**	**±0**	**±0**	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	-	**1**	**3-7**	**12-14**	**29**	**57**	**85**	**113+**	**169+**	-	-
Haematology, clinical chemistry (local)[h]	X	X	X	X	X	X	X	X (up to Week 52)	X (from Week 64)	X	X
PK profile			X[l,m,n]	X[l,m,n]							
PGx blood sample (optional)[i]		X									
Olaparib/abiraterone dispensed/returned		X	X[l]	X[l]	X	X	X	X	X		
Patient complicance questionnaire[o]		X	X	X							

AE Adverse event; BRCA Breast cancer gene; ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; IP investigational product; PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race, and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[d] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[e] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[f] Concomitant medication should include all medications taken by the patient before and during the study.

[g] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[h] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). From Visit 8 (Week 16) onwards, laboratory assessments will be performed every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment. See Section 6.4.5 for a complete list of haematology and chemistry assessments.

[i] Sample will only be collected if separate PGx informed consent has been signed.

[j] Assessments apply to Visit 9 and subsequent visits occurring every 12 weeks thereafter.

[k] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

[l] **Group 1:** Olaparib (300 mg bid) dosing starts Day 1. Olaparib steady state PK profile collected any day between Days 3 and 7 after morning dose. Abiraterone (1000 mg) dosing to start the day after the olaparib PK profile has been collected.
Continue dosing both drugs together for at least 5 days then collect both olaparib and abiraterone PK profiles. See Table 6.
Group 2: Abiraterone (1000 mg) dosing starts Day 1. Abiraterone steady state PK profile collected any day between Days 5 and 7 after morning dose. Olaparib dosing (300 mg bid) to start after the abiraterone PK profile has been collected (immediately after the 24-hour sample).
Continue dosing both drugs together for at least 3 days then collect both olaparib and abiraterone PK profiles. See Table 7.

[m] Blood samples for determination of olaparib to be collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after morning dose on each sampling day.

[n] Blood samples for determination of abiraterone to be collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after morning dose on each sampling day.

[o] Patients will be asked to complete a questionnaire to assess their study treatment compliance from Day 1 until after the PK profiling has been completed.

Table 6 Dosing and PK sampling options for Cohort 2, Group 1

Day olaparib dosing starts	Day of PK sampling for olaparib	Day abiraterone dosing starts (olaparib ongoing)	Day of PK sampling for olaparib and abiraterone[a]
1	3	4	9 – 14
1	4	5	10 – 14
1	5	6	11 – 14
1	6	7	12 – 14
1	7	8	13 – 14

[a] Samples for PK profiling may be collected on any one of the listed days.

Table 7 Dosing and PK sampling options for Cohort 2, Group 2

Day abiraterone dosing starts	Day of PK sampling for abiraterone	Day olaparib dosing starts (abiraterone ongoing)	Day of PK sampling for olaparib and abiraterone[a]
1	5	6	9 – 14
1	6	7	10 – 14
1	7	8	11 – 14

[a] Samples for PK profiling may be collected on any one of the listed days.

Table 8 Study Plan – Part B, Randomised Part

Visit	1 Screening	2	3	4	5	6+	7+[o]	Discontin-uation of IP	30-day follow-up[p]
Visit window	-28 to -1	±0	±3	±3	±3	±7	±7		
Week		0	4	8	12	16+ (every 4 weeks)	24+ (every 12 weeks[o])		
Day	-	1	29	57	85	113+	169+	-	-
Written informed consent including consent for archival tissue sample provision	X								
Demographics[a]	X								
Physical examination, height and weight[b]	X								X
Medical/surgical history	X								
ECOG Performance Status	X				X		X	X	
Inclusion/exclusion criteria	X	X							
CT or MRI scan of the chest, abdomen and pelvis (RECIST 1.1)[c]	X				X		X		
Bone scan[d]	X				X		X		
Collect PSA and BRCA status data (local)[e]	X								
12-lead ECG[f]	X								

Table 8 Study Plan – Part B, Randomised Part

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6+**	**7+[o]**	**Discontin-uation of IP**	**30-day follow-up[p]**
Visit window	**-28 to -1**	**±0**	**±3**	**±3**	**±3**	**±7**	**±7**		
Week		**0**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks[o])**		
Day	-	**1**	**29**	**57**	**85**	**113+**	**169+**	-	-
Vital signs[g]	X	X	X	X	X		X	X	X
Prior and concomitant medication[h]	X	X	X	X	X		X	X	X
AE and SAE review[i]	X	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (local)[j]	X	X	X	X	X	X (up to Week 52)	X (from Week 60)	X	X
CTC blood sample (Veridex assay, central)[k]	X	X	X		X			X	
CTC blood sample (EPIC assay, central)[k]		X			X				
PSA blood sample (local)		X	X	X	X		X		
PGx blood sample (optional)[l]		X							
Blood biomarker sample (mandatory)		X						X	
Urine biomarker sample (mandatory)		X						X	

Table 8 Study Plan – Part B, Randomised Part

Visit	1 Screening	2	3	4	5	6+	7+[o]	Discontin-uation of IP	30-day follow-up[p]
Visit window	-28 to -1	±0	±3	±3	±3	±7	±7		
Week		0	4	8	12	16+ (every 4 weeks)	24+ (every 12 weeks[o])		
Day	-	1	29	57	85	113+	169+	-	-
Archival tumour sample (where available)		X							
BPI-SF instrument and individual bone pain item[m]		X	X	X	X		X	X	X
FACT-P[m,n]		X	X	X	X		X	X	X
EQ-5D-5L questionnaire[n]		X	X	X	X		X	X	X
Oncology resource use[n]		X	X	X	X		X	X	X
Randomisation to study treatment		X							
Treatment dispensed/returned		X	X	X	X	X	X	X	

AE Adverse event; BPI-SF Brief Pain Inventory – Short Form; BRCA Breast cancer gene; CT Computed tomography;
ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; EQ-5D-5L EuroQuol-5 Dimensions, five-level;
FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer; IP investigational product; MRI magnetic resonance imaging;
PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Baseline assessments should be performed no more than 28 days before the date of randomisation, and ideally should be performed as close to the date of randomisation as possible.

Follow up assessments will be performed every 12 weeks (±1 week) relative to the date of randomisation up to and including Week 72. Thereafter, assessments will be conducted every 24 weeks until objective progression.

Bone lesion PCWG-2 assessments will be performed using bone scan (preferably whole body).

Malignant soft tissue RECIST v1.1 assessments will be performed using CT or MRI scans of chest, abdomen, pelvis.

[d] Bone scan required to confirm progression due to new bone lesions, preferably at the next scheduled visit for a bone scan and at least 6 weeks later.

[e] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[f] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[g] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[h] Concomitant medication should include all medications taken by the patient before and during the study.

[i] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[j] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). From Visit 6 (Week 16) onwards, laboratory assessments will be performed every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment. See Section 6.4.5 for a complete list of haematology, chemistry assessments.

[k] Visit 2 (Day 1) sample to be collected pre-dose.

[l] Sample will only be collected if separate PGx informed consent has been signed.

[m] The patient should complete the PRO questionnaires in a quiet place before any investigations have been carried out. Site personnel should not influence the patient's answers to the questions. Please refer to Section 6.5.

[n] If the patient discontinues study treatment for reasons other than RECIST or PCWG-2 progression, the 'Oncology Hospital Admission' form, FACT-P and EQ-5D-5L should continue to be administered until progression has been confirmed. After progression, see Table 9.

[o] With the exception of laboratory assessments (see Footnote j for details), assessments apply to Visit 7 and subsequent visits occurring every 12 weeks up to and including Week 72, and every 24 weeks thereafter.

[p] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

Table 9 Study plan – Randomised part (follow-up post discontinuation of study treatment)

Visit	**Off treatment follow-up for:** Patients who have discontinued study treatment due to reasons other than disease progression **Visits every 12 weeks** **Follow up for 1st progression**	**Time to second progression (PFS2) and survival for:** Patients who have discontinued study treatment due to disease progression Patients who have progressed off treatment **Patients followed up by telephone every 12 weeks post discontinuation of study treatment**
Visit window	±7 days	±7 days
ECOG Performance Status	X	X
CT or MRI scan of the chest, abdomen and pelvis (RECIST 1.1)[a]	X	
Bone scan (PCWG-2)[a]	X	
BPI-SF and bone pain item	X	
BPI-SF worst pain item and worst bone pain item[b]		X
PSA blood sample (local)[c]	X	
Subsequent cancer therapy following discontinuation of study treatment[d]	X	X
EQ-5D-5L questionnaire	X	
FACT-P	X	
Oncology resource use[e]	X	X[b]
Time to second progression		X
Survival[f,g]	X	X

BPI-SF Brief Pain Inventory – Short Form; CT CT Computed tomography; MRI magnetic resonance imaging;
PCWG-2 Prostate Cancer Working Group 2; PFS2 second progression; PSA prostate specific antigen

[a] Patients will continue to be assessed by objective tumour assessments every 12 weeks (±1 week) relative to date of randomisation up to and including Week 72, then every 24 weeks until progression, via RECIST 1.1 and PCWG-2.

[b] Administered by the Investigator over the telephone.

[c] Scheduled PSA samples will not be collected during the PFS2 and OS follow-up, but a standard of care local PSA value should be collected at the time of PFS2 and included on the database.

[d] All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

[e] The full 'Oncology Hospital Admission' form will be completed until rPFS; thereafter, an abridged version will be completed.

[f] The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 3.1.5).

[g] In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis.

3.2 Rationale for study design, doses and control groups

3.2.1 Patient population

In Part A, metastatic CRPC patients may be recruited regardless of whether they have already had chemotherapy or not to facilitate recruitment of suitable patients. For the randomised phase of this study, only post-chemotherapy CRPC patients will be studied, as this is a patient population for whom abiraterone is an approved therapy with proven benefit but there is still a relatively short time to disease progression and patients could benefit from additional agents.

3.2.2 Dose

Part A of the study, the safety run-in, will use an initial dose of 200 mg bid olaparib, to minimise the risk of unexpected AEs when olaparib is given for the first time on a background of abiraterone. If there is ≤1 DLT, then 300 mg bid olaparib will be administered with abiraterone to the next cohort of patients. If this is well tolerated (<4 DLTs in 12 patients), then the 300 mg bid dose will be used in Part B of the study. The 300 mg bid dose of olaparib will deliver exposure that has been previously demonstrated to be tolerated in cancer patients (see olaparib IB), and is the dose to be used in the monotherapy maintenance setting in the ovarian cancer Phase III programme.

3.2.3 Part A

The design of the Part A safety run-in allows an escalation of dose with intensive safety monitoring to ensure the safety of the patients.

The cohort size of at least 3 and up to 6 patients ('rolling six design') has been employed to improve the rate of accrual of patients to cohorts nearer the presumed therapeutic dose by reducing the need for late replacement of patients who become non-evaluable during the minimum 14-day treatment period, whilst not compromising collection of safety data (Skolnik et al 2008).

To date, no in vivo drug-drug interaction (DDI) studies have been performed for olaparib. In in vitro experiments, olaparib produced little or no competitive inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 but produced modest inhibition of CYP3A4 at the highest concentration tested (100 μM). Olaparib was not a time-dependent inhibitor or an inducer of CYPs. The compound is itself a substrate for CYP3A4 and is cleared predominantly via metabolic clearance. It has also been shown to be a substrate for multidrug resistance protein 1 (MDR1) and an inhibitor of organic anion transporter protein B1 (OATP1B1) and organic cation transporter 1 (OCT1). Thus there is the potential for it to be a victim of DDIs through CYP3A or MDR1 inhibition/induction and for it to be a perpetrator of DDIs with substrates of OATP1B1 and OCT1.

Abiraterone is reported, in vitro, to be an inhibitor of CYPs 1A2, 2C8, 2C9, 2C19 and 3A4/5. In vivo it has been shown to be an inhibitor of CYP2D6. It has also been shown, in vitro, to be an inhibitor but not a substrate of MDR1; no studies have been conducted with other transporter proteins. Its 2 main circulating metabolites are produced via CYP3A4 and SULT2A1. Thus there is the potential for it to be a victim of DDIs through CYP3A

inhibition/induction and for it to be a perpetrator of DDIs with substrates of CYP2D6 and MDR1.

Based on this information, the potential for a DDI between olaparib and abiraterone does exist but the likelihood is considered to be low. However, it was considered prudent to take the opportunity to conduct PK sampling to evaluate the presence of any DDI within Part A of the study as this is examining the safety and tolerability of olaparib in combination with abiraterone in a small number of patients prior to the larger randomised part.

3.2.4 Part B

3.2.4.1 Randomisation and blinding

The study design is randomised and double-blinded in order to minimise bias when assessing whether olaparib given with abiraterone shows better efficacy than placebo given with abiraterone.

3.2.4.2 Choice of endpoints

Radiological progression-free survival is considered to be the most appropriate primary endpoint for this Phase II study because it is a widely used and accepted measure that can be measured robustly. The primary assessment of rPFS will be based on objective radiological findings as per the RECIST 1.1 guidelines (for malignant soft tissue disease) and/or PCWG-2 recommendations (for bone lesions) to determine progression, or death. It is believed that the use of a rPFS primary endpoint in this study will provide a good predictor for survival results in a future Phase III trial. Progression-free survival can be assessed in less time than OS to allow a quicker decision to progress to Phase III. Although a formal link between a PFS outcome in clinical trials and OS outcomes has not been established, a positive correlation between PFS and OS outcomes has been reported in a CRPC population (Ryan et al 2013).

The secondary endpoints of the study include other measures of clinical benefit including OS, ORR, PSA and CTC measurements, PFS2, TFST, TSST and the exploratory PRO endpoints of symptoms and HRQL, to provide supportive data on the benefit of olaparib.

Safety and tolerability are also secondary endpoints of the study. These data will add to the safety database for patients with advanced solid malignancies treated with oral olaparib.

3.2.4.3 Use of placebo and abiraterone

The use of a placebo control in Part B of this study provides for a robust assessment of the benefit of olaparib when given in addition to abiraterone, and is considered appropriate in this patient population because abiraterone is approved for use as a 2nd line treatment of patients with prostate cancer. Abiraterone, in combination with prednisone/prednisolone, is one of the most commonly prescribed drugs for treatment of metastatic CRPC in the post-docetaxel phase, at a dose of 1000 mg once daily, and remains a recognised standard of care in this setting. As such, all patients, including those randomised to the placebo/olaparib arm, will be receiving an approved post-docetaxel therapy for metastatic CRPC.

3.2.4.4 Rationale for patient reported outcomes (PROs)

In addition to assessing survival in oncology clinical trials it is important to understand how patients feel and function. This will be addressed by symptom assessment as well as HRQL assessment throughout the study. As many patients will be asymptomatic or mildly symptomatic as they enter the study, assessment of their cancer symptoms in future studies will support the efficacy evaluation. The results from this study will guide selection of future PRO instruments and endpoints.

The main purpose of the HRQL assessment is to show the overall influence of the benefits and toxicity of the treatment from a patient perspective, and to aid understanding of the risk-benefit evaluation. The PRO instruments were selected because they include the most relevant symptoms and domains of prostate cancer impact. Both the BPI-SF and FACT-P are well-established instruments that have been previously included in prostate cancer clinical trials, including abiraterone. The instruments were developed specifically for use in cancer and prostate cancer studies and both the BPI-SF (Gater et al 2011, Cleeland 2008, Cleeland et al 2005, Di Lorenzo et al 2007a, Di Lorenzo et al 2007b, Hong et al 2007) and the FACT-P (LoRusso et al 2003, Tester et al 2006, Esper et al 1997, Rosenfeld et al 2004, Yount et al 2003, Cella et al 2009) have been shown to be valid, reliable and responsive to changes in underlying prostate cancer. The FACT-P includes scales assessing domains of HRQL, and also supports the calculation of a symptom score, the FAPSI-8, which is calculated from 8 symptom items within the FACT-P. Thus the FACT-P supports the assessment of both symptoms and relevant domains of HRQL.

Bone pain is of primary interest in advanced prostate cancer and has emerged in literature review and patient interviews as being important to patients. As bone pain is not included in either of the 2 selected instruments, a ‘worst bone pain’ item similar to the ‘worst pain item’ in the BPI-SF was developed for this study. The item differs from the wording of the BPI-SF pain item only by the addition of ‘bone’ in front of ‘pain’ in the item. Based upon patient interviews, Gater et al 2011 reported that patients can distinguish between bone pain and other types of pain, based not only on the pain’s location, but also on its intensity and temporal features, including onset, frequency and duration. Patients will rate their bone pain severity at its worst on a 0 to 10 point numeric rating scale (NRS). This bone pain item will appear after the BPI SF paper-based instrument and will be administered at the same time as the BPI SF, at the clinic visits.

3.2.4.5 Rationale for health economics: utilities and resource use

The EuroQuol-5 Dimensions five-level (EQ-5D-5L) questionnaire will be used to explore the impact of treatment and disease state on health state utility. This exploratory analysis will be primarily used to support future economic evaluations of olaparib.

The assessment of interventions (resource use) will increase the understanding of the relationship between treatment impact on tumour and related cancer symptoms and resource use, such as the need for palliative procedures, including transurethral resection of the prostate (TURP), colostomy or nephrostomy.

3.2.4.6 Rationale for biomarkers

The objective of the tumour, blood and urine biomarker research is to collect and store samples for future exploratory research to identify possible resistance mechanisms to olaparib, and to identify biomarkers that may allow selection of sub-populations that can benefit from olaparib treatment.

Molecular profiling of late stage prostate cancers has defined a number of key genes that may identify sub-groups of patients with different risk factors. Androgen receptor amplification and splice variants, PTEN loss, and transmembrane protease serine 2-ERG (TMPRSS2-ERG) fusion, have been implicated in regulating disease progression. The presence of BRCA mutations may predict for worse prostate cancer prognosis (Castro et al 2013).

Phosphatase and tensin homolog (PTEN) loss, occurring in approximately 70% of late stage prostate cancers, has been suggested to sensitise cells to PARP inhibitors. Fusion of TMPRSS2 and ERG, found in approximately 50% of late stage prostate cancers, leads to the aberrant expression of ERG (an ETS family transcription factor), in response to androgen activation of the TMPRSS2 promoter, and consequent activation of genes implicated in tumour progression. Furthermore, ERG has been shown to physically interact with PARP-1, and PARP-1 inhibition has been shown to preferentially sensitise ERG over-expressing xenograft tumours to PARP inhibition. Finally, AR splice variants have been associated with continued AR signalling and resistance to AR-directed treatments such as abiraterone, and as a consequence activation of AR-regulated gene expression such as TMPRSS2-ERG. Hence, there is a rationale for combination of olaparib with abiraterone in prostate cancer, and a possibility that this combination may be preferentially active based on measures of TMPRSS2-ERG fusion/ERG expression, BRCA mutation, AR and PTEN.

3.2.4.7 Rationale for pharmacogenetic samples

Please refer to Appendix D.

4. PATIENT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

2. Male aged 18 years and older.

3. Histologically or cytologically proven diagnosis of prostate cancer.

4. Candidate for abiraterone therapy with documented evidence of metastatic castration-resistant prostate cancer. Metastatic status is defined as at least one documented metastatic lesion on either bone scan or CT/MRI scan. Castration-resistant prostate cancer is defined as rising PSA or other signs of disease progression despite treatment with androgen deprivation therapy and the presence of a castrate level of testosterone (≤50 ng/dL).

5. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 with no deterioration over the previous 2 weeks.

6. Patients must have a life expectancy ≥12 weeks.

7. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations, and completing PRO instruments.

8. Patients must be on a stable concomitant medication regimen, defined as no changes in medication or in dose within 2 weeks prior to start of olaparib dosing, except for bisphosphonates, denosumab and corticosteroids, which should be stable for at least 4 weeks prior to start of olaparib dosing.

9. **For the randomised phase only**, patients must have received chemotherapy in the form of docetaxel treatment for metastatic castration-resistant prostate cancer. Note: patients who discontinued docetaxel for toxicity reasons and without completing the full course will still be eligible to enter this study provided they received at least 2 cycles of chemotherapy.

Please refer to Section 3.1 of Appendix D ('Pharmacogenetics Research') for inclusion criteria for the optional pharmacogenetics research.

4.2 Exclusion criteria

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

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

2. Previous treatment in the present study.

3. Treatment with any of the following:

   – Previous exposure to any 2nd generation anti-hormonal including abiraterone and enzalutamide

   – More than 2 prior courses of chemotherapy for metastatic prostate cancer

- Previous use of immunotherapy or radium-223 for the treatment of metastatic prostate cancer

- Any investigational agents or study drugs from a previous clinical study within 30 days of the first dose of study treatment

- Any previous exposure to a CYP17 (17α-hydroxylase/C17,20-lyase) inhibitor

- Substrates of CYP2D6 with a narrow therapeutic index (eg, thioridazine)

- Potent inhibitors or inducers of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort)

- Any previous treatment with a PARP inhibitor, including olaparib.

4. With the exception of alopecia or toxicities related to the use of gonadotropin-releasing hormone agonists, any unresolved toxicities from prior therapy greater than CTCAE Grade 2 at the time of starting study treatment.

5. Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids for at least 4 weeks prior to start of study treatment.

6. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

7. Any of the following cardiac criteria:

   - Mean resting QTc >470 msec obtained from 3 ECGs

   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block

   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.

8. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years.

9. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

- Absolute neutrophil count (ANC) <1.5 x 10^9/L
- Platelet count <100 x 10^9/L
- Haemoglobin (Hb) <100 g/L
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 x upper limit of normal (ULN) if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases
- Total bilirubin >1.5 x ULN if no liver metastases or >3 x ULN in the presence of liver metastases (except in the case of Gilbert's disease)
- Creatinine >1.5 x ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 x ULN
- If bone metastases are present and liver function is otherwise considered adequate by the Investigator then elevated alkaline phosphatase (ALP) will not exclude the patient.

10. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of olaparib or abiraterone.

11. History of hypersensitivity to active or inactive excipients of olaparib or abiraterone or drugs with a similar chemical structure or class to olaparib or abiraterone.

12. Patients with myelodysplastic syndrome/acute myeloid leukaemia.

13. Current disease or condition known to interfere with absorption, distribution, metabolism, or excretion of drugs, at the Investigator's discretion.

14. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

15. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

Please refer to Section 3.1 of Appendix D ('Pharmacogenetics Research') for exclusion criteria for the optional pharmacogenetics research.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Contraception

Patients and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination, throughout the period of taking study treatment and for 3 months after last dose of study drugs due to the unknown effects of the study drugs on the sperm, or they must totally/truly abstain from any form of sexual intercourse when this is in line with their preferred and usual lifestyle. Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drugs.

If patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

See Appendix L for details of acceptable birth control methods to be used within the study.

Concomitant medications

For restrictions regarding concomitant medications, please see Section 5.6.

Other restrictions

Patients will be required to fast from at least 2 hours before until 1 hour after each dose of olaparib or abiraterone, due to a potential effect of food on absorption. Water can be allowed as desired.

5.2 Patient enrolment and randomisation and initiation of investigational product

5.2.1 Procedures for enrolment

5.2.1.1 Part A

The PI will:

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

2. Obtain signed informed consent from the potential patient before any study-specific procedures are performed.

3. Assign each potential patient a unique enrolment code (E-code) beginning with 'E#' after written informed consent has been obtained, using the centralised Interactive

Voice/Web Response System (IVRS/IWRS). The E-code (EXXXXYYY) will consist of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY) issued in order of informed consent taken.

Patient codes will be assigned strictly sequentially as patients are eligible for dosing.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. If patients discontinue their participation in the study, then they cannot re-enter the study.

5.2.1.2 Part B

Informed consent and enrolment using the centralised IVRS/IWRS must occur no more than 28 days before randomisation (ie, Day -28).

The PI or delegate will contact the IVRS/IWRS, by telephone or using the web, to register the patient when they are entered into the study, and will record a unique E-code assigned to the patient by IVRS/IWRS in the patient medical records. The E-code (EXXXXYYY) will consist of a 4-digit centre number (XXXX) and a 3-digit serial number (YYY). This number is the patient's unique identifier and is used to identify the patient on the eCRF. The E code numbers used in Part A will not be used in Part B.

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

If a patient discontinues their participation in the study, they cannot re-enter the study.

5.2.2 Procedures for randomisation (Part B only)

At Visit 2, eligible patients will be randomised centrally using IVRS/IWRS, according to the randomisation scheme generated by the Biostatistics Group, AstraZeneca or delegate. The randomisation scheme will be produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers. Patients will be randomised in a 1:1 ratio to either olaparib in combination with abiraterone or matching placebo in combination with abiraterone. The randomisation scheme will not be stratified for any factors and will not be stratified by centre or country.

Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the centralised IVRS/IWRS, by telephone or using the web, for allocation of randomised therapy. Patients will be identified to the centralised IVRS/IWRS using patient E-code and date of birth (where local regulations allow collection of full date of birth). The IVRS/IWRS will inform the Investigator of the Kit ID number to be allocated to the patient at the randomisation visit.

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

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

Where patients that do not meet the inclusion and/or exclusion criteria, are enrolled in error, or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Physician or his/her representative and the Investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

The AstraZeneca Physician or his/her representative is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached in terms of how best to manage the patient going forward, the patient should have their study therapy stopped and a discontinuation visit should be arranged.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Part A of the study, the safety run-in, is open-label.

In Part B of the study, olaparib and placebo-matched olaparib treatment will be blinded.

For Part B of the study, the study medication will be labelled using a unique Kit ID number, which is linked to the randomisation scheme. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the study medication.

5.4.2 Methods for unblinding the study

Part A of the study, the safety run-in, is open-label.

For Part B of the study, individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

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

AstraZeneca or its representative retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the

planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The study will be centrally unblinded at the time of the primary analysis, but patients and Investigators will remain blinded until after the database is verified and closed, and 60% of patients have died (the trigger for the OS analysis).

5.5 Treatments

5.5.1 Identity of investigational product(s)

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply the olaparib and matching placebo to the Investigator as green film-coated tablets. Details of the IPs are shown in Table 10.

Table 10 Identity of investigational product (Olaparib)

Investigational product	Dosage form and strength
Olaparib	100 mg tablet
Olaparib	150 mg tablet
Placebo to olaparib 100 mg	Placebo to match olaparib 100 mg tablet
Placebo to olaparib 150 mg	Placebo to match olaparib 150 mg tablet

Full descriptive information for olaparib can be found in the IB.

For all centres, olaparib and matching placebo will be packed in high density polyethylene (HDPE) bottles with child resistant closures. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

5.5.2 Doses and treatment regimens – overview

In Part A, all patients will take olaparib. In Part B, patients will be randomised to receive either olaparib or placebo. The olaparib/placebo will be taken bid, in the morning and evening. The doses administered are described in Section 5.5.3.

All patients will take abiraterone, 1000 mg once daily, at the same time as the olaparib/placebo morning dose. They will also take prednisone or prednisolone 5 mg bid (at the same times as the olaparib doses); this medication is indicated in combination with abiraterone for the treatment of patients with metastatic CRPC.

Patients will be required to fast (except water) from at least 2 hours before until 1 hour after each dose. The fasting is a requirement for abiraterone dosing, but will be applied to all study treatment doses, for simplicity.

Patients in Part A, Cohort 2 (and Cohort 3, if required), will receive olaparib alone (Group 1) or abiraterone alone (Group 2) for a few days before starting the other treatment in

combination, so that steady state olaparib/abiraterone PK can be determined in the absence of the other treatment. The schedules are described in Section 5.5.3, and in Table 6 and Table 7.

Patients will continue to receive study treatment (ie, olaparib/placebo given in addition to abiraterone and prednisone/prednisolone) until disease progression, or until a time when the Investigator considers that they are no longer deriving clinical benefit, or they stop taking treatment for any other reason including having met any of the criteria for treatment discontinuation.

5.5.3 Doses and treatment regimens – olaparib/placebo

5.5.3.1 Part A

The olaparib tablets will be administered orally with approximately 240 mL water. The patient will administer their study medication themselves on Day 1, under the supervision of the Investigator or his/her delegate, after the required assessments have been completed. Thereafter, patients should aim to take their doses at similar times each day, approximately 12 hours apart. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

Cohort 1

Each patient will receive 200 mg olaparib (administered as 2 x 100 mg tablets), bid.

Cohort 2, Group 1

Each patient will receive 300 mg olaparib (administered as 2 x 150 mg tablets) bid, as described for Cohort 1, starting on Day 1.

Cohort 2, Group 2

Each patient will receive 300 mg olaparib (administered as 2 x 150 mg tablets) bid, as described for Cohort 1, starting after completion of the abiraterone PK profiling (after the 24-hour sample; see Table 7).

Cohort 3

If a 3rd cohort is required, patients will receive 200 mg olaparib (administered as 2 x 100 mg tablets) bid, as described for Cohort 2.

All cohorts

On clinic days on which PK samples are scheduled to be taken, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken and any other pre-dose assessments have been performed. Patients should not take their dose until instructed to do so by the Investigator/Study Nurse. If a patient takes their dose study medication before arrival at the clinic, he or she should return to the clinic the next day (or another suitable day) to have the dose and PK samples taken as instructed.

Wherever possible, doses should not be missed. If a patient misses taking a scheduled dose, window ±2 hours, they should take the next dose at the next scheduled time and the missed dose will not be made up.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Any deviations from dosing schedule, dose interruptions, dose reductions and dose adjustments should be recorded in the eCRF. This includes details of vomiting after taking study medication (only required for Cohorts 2 and 3), eg, date and time of vomiting in relation to dosing.

5.5.3.2 Part B

For Part B of the study, each patient will receive 300 mg olaparib/placebo (administered as 2 x 150 mg tablets) bid (or 200 mg bid, if 200 mg bid is the maximum tolerated dose in Part A) or placebo. The olaparib/placebo will be administered orally with approximately 240 mL water. The patient will administer their study medication themselves on Day 1, under the supervision of the Investigator or his/her delegate, after the required assessments have been completed. Thereafter, patients should aim to take their doses at similar times each day, approximately 12 hours apart. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. In the event of vomiting, the procedures should be followed as described in Section 5.5.3.

The initial dose of olaparib/placebo can be reduced/adjusted under circumstances described in Section 5.10.

5.5.4 Additional study drug – abiraterone and prednisone/prednisolone

Details of the additional study drugs are shown in Table 11. Abiraterone and prednisolone or prednisolone will be sourced locally as commercially available materials.

Table 11 Identity of additional study drugs

Additional study drugs	Dosage form and strength
Abiraterone acetate	250 mg tablet
Prednisone	5 mg tablet
Prednisolone	5 mg tablet

Dose interruptions and reductions will not be permitted for abiraterone, prednisone or prednisolone only during part A. Dose modifications strategies of abiraterone and prednisone or prednisolone during part B are detailed in Section 5.10.1.9.

5.5.4.1 Part A

Cohort 1

Patients will receive 1000 mg abiraterone once daily in the morning and prednisone or prednisolone 5 mg bid. The tablets should be swallowed whole with water and not crushed or chewed. The patient will administer their study medication themselves on Day 1, under the supervision of the Investigator or his/her delegate, after the required assessments have been completed. Patients should aim to take their doses at similar times each day, with the prednisone/prednisolone doses approximately 12 hours apart.

Cohort 2, Group 1

Patients will receive 1000 mg abiraterone once daily in the morning and prednisone or prednisolone 5 mg bid, as described for Cohort 1, starting the day after completion of the olaparib PK profiling (any day of Day 4, 5, 6 or 7).

Cohort 2, Group 2

Patients will receive 1000 mg abiraterone once daily in the morning and prednisone or prednisolone 5 mg bid, as described for Cohort 1, starting on Day 1.

Cohort 3

If a 3rd cohort is required, patients will receive abiraterone and prednisone/prednisolone as described for Cohort 2, Groups 1 and 2.

5.5.4.2 Part B

Patients will receive 1000 mg abiraterone once daily in the morning and prednisone or prednisolone 5 mg bid. The patient will administer their study medication themselves on Day 1, under the supervision of the Investigator or his/her delegate, after the required assessments have been completed. The abiraterone tablets should be swallowed whole with water and not crushed or chewed. Patients should aim to take their doses at similar times each day, with the prednisone/prednisolone doses approximately 12 hours apart.

5.5.5 Labelling

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

Specific dosing instructions will not be included on the label; the site must complete the 'Patient Dispensing Card' with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.

Abiraterone, prednisone and prednisolone will be supplied and labelled locally in accordance with local procedures if applicable.

5.5.6 Storage

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

5.6 Concomitant and post-study treatment(s)

5.6.1 Olaparib and drug-drug interactions

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

Effect of Other Drugs on Olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Clinical studies to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a potent CYP3A inhibitor increased olaparib Cmax 1.42-fold (90% CI: 1.33-1.52) and increased mean AUC 2.70-fold (90% CI: 2.44-2.97) and that co-administration of a potent CYP inducer decreased Cmax by 71% (Treatment ratio: 0.29; 90% CI: 0.24-0.33) and mean AUC by 87% (Treatment ratio: 0.13; 90% CI: 0.11-0.16). It is therefore recommended that known strong inhibitors or inducers of these isozymes should be avoided with olaparib.

While this is not an exhaustive list, it covers the known potent CYP3A4/5 inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, boosted protease inhibitors (ritonavir, indinavir, saquinavir, telithromycin, nelfinavir, boceprevir, telaprevir) and clarithromycin

For patients taking any of the above, the required washout period prior to starting olaparib is 1 week.

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4/5 inducers should be avoided:

- phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbital, nevirapine, modafinil, and St. John's Wort

For patients taking any of the above CYP3A4/5 inducers, the required washout periods prior to starting olaparib in Part A are:

- phenobarbital, 5 weeks
- for any of the others, 3 weeks.

If the use of any potent inducers or inhibitors of CYP3A4/5are considered necessary for the patient's safety and welfare during Part B, the Investigator must contact the AstraZeneca Physician or their designated Medical Monitor. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Long term use of potent inducers and inhibitors of CYP3A4/5should be avoided. If a decision is made to allow patients to use a potent inducer or inhibitor then they must be monitored carefully for any change in efficacy or safety of olaparib.

In vitro olaparib is a substrate for the efflux transporter Pgp. Clinical studies to evaluate the impact of known Pgp inhibitors and inducers have not been conducted.

Effect of Olaparib on Other Drugs

Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP3A4 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and Pgp is unknown. It cannot be excluded that olaparib upon co administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

In vitro olaparib has been shown to be an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. It cannot be excluded that olaparib may increase the exposure to substrates of Pgp (eg. statins, digoxin, dabigatran, colchicine), OATP1B1 (eg, bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (eg, metformin), OCT2 (eg, serum creatinine), OAT3, MATE1 and MATE2K. In particular, caution should be exercised if olaparib is administered in combination with any statin.

5.6.2 Other concomitant medications

Any medications, with the exceptions noted in Section 5.6.4 below, which are considered necessary for the patient's welfare, and which are believed will not interfere with the IP, may

be given at the discretion of the Investigator, providing the medications, the doses, dates, and reasons for administration are recorded in the eCRF.

In addition, any unplanned diagnostic, therapeutic, or surgical procedure performed during the study period must be recorded in the comments section of the corresponding AE report.

Anticoagulant therapy: Patients who are taking warfarin may participate in this study; however, it is recommended that prothrombin time (international normalised ratio [INR] and activated partial thromboplastin time [aPTT]) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Anti-emetics/anti-diarrhoeals: Prophylactic anti-emetics and/or anti-diarrhoeals will not be routinely given. Should a patient develop nausea, vomiting, and/or diarrhoea, which, in the Investigator's opinion, is considered related to the IP, then appropriate treatment may be given.

Leukopenia and/or anaemia treatment: The use of colony-stimulating factors (CSFs) (eg, granulocyte-CSF [G-CSF], or granulocyte-macrophage CSF [GM-CSF]) should be managed as deemed appropriate by the Investigator for the treatment of haematological AEs during Part B of the study (see Section 5.10).

The reason(s) for use, doses, and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF.

All medications (prescriptions or over-the-counter medications) present at the start of the study or started during the study or until 30 days from the end of the last protocol treatment and different from the IP must be documented in the eCRF.

5.6.3 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided they cannot be managed with local or systemic analgesics and that the Investigator does not feel that these are indicative of clinical disease progression during the study.

5.6.4 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy (chemotherapy, immunotherapy, biological therapy or other novel agent), including investigational agents, while on IP. Patients may continue the use of bisphosphonates or denosumab for bone disease, and corticosteroids, provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning IP (see Section 4.1 and Section 4.2). The use of LHRH-analogues is permitted.

5.6.5 Live virus and bacterial vaccines

Live virus and bacterial vaccines should not be administered whilst the patient is receiving IP and during the 30-day follow-up period. An increased risk of infection by the administration

of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

5.6.6 Abiraterone, prednisone and prednisolone interactions

The Investigator should refer to the respective prescribing information for restrictions and cautions required when administering concomitant medications with abiraterone, prednisone or prednisolone.

5.7 Treatment compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the eCRF.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib or matching placebo, abiraterone and prednisone/prednisolone. Compliance of the first dose and any doses taken on the day of any study visit (except for study treatment supply visits) will be assured by supervised administration by the Investigator or delegate. Study site pharmacy staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the Investigative site until reconciliation is completed by the study monitor. All patients must return their bottles of study medication at the appropriate scheduled visit, when new bottles will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF.

Patients in Cohort 2 (and Cohort 3, if conducted), ie, the PK part of the study, will be asked to complete a questionnaire to assess their study treatment compliance.

5.7.1 Accountability

The study medications provided for this study are for use only as directed in the study protocol. It is the Investigator/institution's responsibility to establish a system for handling study treatments, including IPs, so as to ensure that:

- Deliveries of such products from AstraZeneca or its representative are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study patients in accordance with the protocol.

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

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

Study site personnel will account for additional study drugs (ie, abiraterone and prednisolone/ prednisone) locally procured at the site, and for appropriate destruction.

Dispensing and accountability records will continue to be collected for as long as patients continue to receive study treatment, although they will not be entered on the database after the database has closed.

5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is free to discontinue treatment at any time, without prejudice to further treatment
- Adverse event
- Severe non-compliance to study protocol
- Objective progression according to RECIST 1.1/PCWG-2 criteria
- The Investigator believes they are no longer deriving clinical benefit.

In Part B of the study, if patients are discontinued from randomised study treatment for reasons other than objective disease progression, they should continue to be followed for confirmed progressive disease (RECIST1.1/PCWG-2). All patients should be followed for PFS2 and survival according to the study schedule, unless consent is withdrawn.

Withdrawal of consent for pharmacogenetic and biological sampling is included in Section 7.5.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s) who will perform the best possible observation(s), test(s), and evaluation(s), as well as give appropriate medication and all possible measures for the safety of the patient (see Table 4, Table 5 and Table 8 for assessments conducted upon discontinuation). In addition, the Investigator will record on the eCRF the date of discontinuation, the reasons, manifestation, and treatment at the time of discontinuation. The patient should return all IP.

Any patient discontinuing IP should also be seen at 30 days (±7 days) after their last dose for the evaluations outlined in the study schedule. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

After discontinuation of the IP at any point in the study, all ongoing AEs or SAEs must be followed until resolution or stabilisation, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up (see Sections 6.4.3 and 6.4.4). All new AEs and SAEs occurring during the 30 calendar days after the last dose of IP must be reported (if SAEs, they must be reported to AstraZeneca or its representative within 24 hours as described in Section 6.4.4) and followed to resolution as above.

Patients in Part B should continue to be followed for disease progression (radiologic and PFS2) unless they withdraw consent from these assessments and/or the study (see Section 5.9).

If patients discontinue IP, the AstraZeneca monitor or its representative must be informed immediately.

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

5.8.1.1 Discontinuation of olaparib/placebo only

If a patient discontinues olaparib/placebo but remains on abiraterone, procedures should be followed for the discontinuation and follow-up visits. For randomised part B see Table 9.

5.8.1.2 Discontinuation of abiraterone only

Patients who discontinue abiraterone and remain on olaparib/placebo should continue to be seen and have assessments performed as outlined in the study plans (see Table 4, Table 5 and Table 8). Once olaparib/placebo treatment is permanently discontinued, procedures should be followed for the discontinuation and follow-up visits. For randomised part B see Table 9.

The date and reasons for discontinuation of abiraterone should be captured in the eCRF.

5.9 Withdrawal from study

Patients are free to withdraw from the study (IP and assessments) at any time, without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator (see Table 4, Table 5 and Table 8 for assessments conducted upon discontinuation). Adverse events will be followed up (see Sections 6.4.3 and 6.4.4). All study drugs should be returned by the patient.

In Part A of the study, the safety run-in, non-evaluable patients can be replaced to ensure a minimum of 3 evaluable patients.

Withdrawn patients will not be replaced in Part B of the study.

Reasons for withdrawal from the study may include:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca or its representative
- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up (defined by the inability to reach the patient after 3 documented phone calls, faxes or emails, and lack of response by the patient to one letter by registered/certified mail; all attempts at contact should be documented in the patient's medical records).

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- further participation in the study including any further follow up (eg, survival calls)
- the use of any samples (see Section 7.5).

If a patient wishes to withdraw their consent to further participation in the study, including survival follow-up, this should be clearly documented in the patient notes and in the clinical study database.

The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

After withdrawal from the study, patients will continue to receive standard treatment according to their own doctor's discretion.

See Appendix D for details of withdrawal from optional pharmacogenetic research.

5.10 Guidance for Investigators

5.10.1 Dose reduction and toxicity management strategy

Dose interruptions are not permitted in Part A of the study until after all PK assessments are complete.

If a patient's dose is reduced or interrupted at the time of a scheduled study visit, they should still attend the clinic for the scheduled assessments.

For olaparib/placebo, once dose is reduced escalation is not permitted.

5.10.1.1 Management of toxicity of study treatment

Any toxicity observed during the course of the study may be managed by interruption of the dose of study treatment if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. Study treatment must be interrupted until the patient recovers completely or the toxicity reverts to CTCAE Grade 1 or less.

Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment. Treatment must be interrupted if any CTCAE Grade 3 or 4 AE occurs which the Investigator considers to be related to administration of study treatment.

5.10.1.2 Management of anaemia

Adverse events of anaemia CTCAE Grade 1 or 2 (Hb ≥8 g/dL) should be investigated and managed as deemed appropriate by the Investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. For reference see Table 12.

Table 12 Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb**< 10 *but* ≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dl	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases,

management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE Grade 3 [Hb <8 g/dL] or worse anaemia and/or development of blood transfusion dependence), refer to Section 5.10.1.5 for the management of this.

5.10.1.3 Management of neutropenia and leukopenia

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow-up and interruption of study drug if CTCAE Grade 3 or worse neutropenia occurs. Primary prophylaxis with G-CSF is not recommended; however, if the patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of study treatment.

Study treatment can be restarted at the same dose if an AE of neutropenia or leucopenia have been recovered up to CTCAE Grade >1 (ANC >1.5 x 10^9/L). Growth factor support should be stopped at least 24 hours before restarting study drug (7 days for pegylated G-CSF). Any subsequent interruptions will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

5.10.1.4 Management of thrombocytopenia

An AE of thrombocytopenia should be managed as deemed appropriate by the Investigator. If a patient develops thrombocytopenia CTCAE Grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. In some cases, management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

5.10.1.5 Management of prolonged haematological toxicities while on study treatment

If the patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (ANC <1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse thrombocytopenia (platelets <50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index, RI[1]) and peripheral blood smear should be performed. If blood parameters remain clinically abnormal after 4 weeks of dose interruption or if more than one blood cell line is affected, the

[1] RI = reticulocyte count x haematocrit (Hct)/normal Hct. A value of 45 is usually used for normal Hct.

patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage; see Section 6.4.5.3.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as a SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

5.10.1.6 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician or representative.

5.10.1.7 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019, nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients, and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE Grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter in accordance with local treatment practice guidelines.

5.10.1.8 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the AstraZeneca Study Physician or representative.

If a patient discontinues treatment for intercurrent condition and progresses while off treatment, they can restart study treatment if the Investigator feels the patient is receiving clinical benefit. Please note that evidence of objective radiological disease progression is required.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

If a patient discontinues study treatment whilst having a dose interruption, the discontinuation should be recorded using the date at which the decision to discontinue was made and not the last dose of study treatment.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

The dose reduction schedule is shown in Table 13.

Table 13 Dose reductions for olaparib

Reduction	Dose level (tablets)
Initial dose level	300 mg bid (2 x 150 mg tablets)
1st dose reduction due to CTCAE Grade 3 or 4 treatment-related SAE/AEs	250 mg bid (1 x 150 mg tablet and 1 x 100 mg tablet)
2nd dose reduction due to CTCAE Grade 3 or 4 treatment related SAE/AEs	200 mg bid (2 x 100 mg tablets)

5.10.1.9 Dose management of abiraterone and prednisone/prednisolone

Please refer to the respective, locally applicable prescribing information for further details and for any additional restrictions or cautions required due to the administration of abiraterone or prednisone/prednisolone.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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

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

6.2 Data collection at enrolment and follow-up

See Table 4, Table 5 and Table 8 and refer to Section 3.1 for details on procedures/ assessments required at all time points throughout the study.

It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence to be followed at a particular post-dose time point is:

1. Vital signs
2. PK blood sample (at scheduled time)
3. Any other assessments.

6.2.1 Post-treatment

For patients who discontinue study treatment in Part A, there will be no further follow-up or data collection after their 30-day follow-up visit.

Patients who discontinue study treatment in Part B will be followed up until disease progression. Thereafter, they will be followed up for PFS2 and survival in accordance with the study plan (see Table 8).

Dispensing and accountability records will continue to be collected after follow-up for as long as patients continue to receive IP.

6.3 Efficacy

The primary and all secondary endpoints will be analysed using the full analysis set unless otherwise stated.

6.3.1 Measures of tumour progression and response

Disease progression will be deemed to have occurred if one or more of the following criteria is met:

- Soft tissue disease progression as defined by RECIST 1.1
- Bone lesion progression as defined by PCWG-2 bone scan
- Death.

6.3.1.1 RECIST 1.1 assessment of soft tissue malignant disease

RECIST v1.1 guidelines for the assessment of target lesions (TLs), non-target lesions (NTLs), new lesions (NLs), and malignant soft tissue tumour response are presented in Appendix F.

In this study, bone lesions will not be included in the RECIST assessment as NTLs. For bone lesion assessments, see Section 6.3.1.2.

Baseline tumour assessments (CT/MRI scans of the chest, abdomen and pelvis) may include additional areas that may be involved, based on signs and symptoms of individual patients.

Baseline assessments should be performed no more than 4 weeks (28 days) before randomisation and should be performed as close as possible to the start of study treatment.

The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Assessments should be repeated every 12 weeks (±1 week) from start of olaparib treatment until disease progression, death, or withdrawal of consent (every 24 weeks after Week 72). Any other sites at which new disease is suspected should be managed appropriately. If an unscheduled assessment is performed and there is no evidence of disease progression, every attempt should be made to perform subsequent assessments at the scheduled visits.

Categorisation of objective tumour response assessment of soft tissue lesions will be based on the RECIST v1.1 guidelines for response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), no evidence of disease (NED) and not evaluable (NE). Target lesion progression will be calculated by comparing the tumour burden at progression with the smallest burden (ie, the smallest sum of diameters) observed at any prior assessment during the study. In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

Patients with no disease at baseline will be assessed according to RECIST 1.1 criteria for new lesions, with responses of NED or progression of disease.

For patients who only have non-measurable disease at baseline, categorisation of objective tumour response assessment will be based on the modified RECIST v1.1 guidelines for response for NTLs: CR, PD and Non CR/Non PD.

If the Investigator is in doubt as to whether progression has occurred, particularly with regard to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the tumour burden at the next scheduled assessment or sooner if clinically indicated.

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

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Table 8, and to Appendix F.

6.3.1.2 PCWG-2 bone scan

Bone lesions will be assessed by bone scintigraphy (bone scans). Guidelines for the assessment of bone lesions are presented in Appendix F. A baseline bone scan should be performed no more than 28 days before randomisation, and ideally should be performed as close as possible to the start of study treatment. Subsequent assessments will be performed every 12 weeks (±1 week) from the start of treatment until disease progression, death, or withdrawal of consent (every 24 weeks after Week 72).

Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment. Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions.

If an unscheduled assessment, eg, confirmation of progression scan, is performed and there is no evidence of disease progression, every attempt should be made to perform the subsequent assessments at their scheduled visits while the patient remains on study treatment.

Progression on a bone scan is assessed as:

- **At the 12 week scan:**

  If 2 or more new metastatic bone lesions are observed on the first 12-week scan, the confirmatory scan performed, preferably at the next scheduled visit for a bone scan (ie, Week 24) and at least 6 weeks later, must show 2 or more additional new metastatic bone lesions (for a total of 4 or more new metastatic bone lesions since the baseline assessment) for progression to be documented.

- **After the 12 week scan:**

  If 2 or more new metastatic bone lesions are observed on scans obtained after the first 12-week assessment, confirmatory scan performed preferably at the next scheduled visit for a bone scan (eg, Week 36) and at least 6 weeks later needs to show the persistence of or an increase in the number of metastatic bone lesions compared to the prior scan.

The date of progression is the date of the first scan that shows the change.

If the Investigator is in doubt as to whether progression has occurred, it is advisable to continue study treatment and reassess the bone lesion status at the next scheduled assessment, or sooner if clinically indicated.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Table 8, and to Appendix F.

Table 14 provides the definitions of the criteria to determine tumour visit response for bone lesions.

Table 14 Overall PCWG-2 response for bone lesions

Non–progressive disease (non-PD)	Persistence of one or more bone lesions or disappearance of all bone lesions
Progressive disease (PD)	Bone lesions fulfilling the requirements for new lesions and confirmation of progression
Non evaluable (NE)	Only relevant if a bone scan is not performed at that visit

For full details of the bone lesions assessments, please see Appendix F.

6.3.1.3 Second progression

Following the progression event used for the primary variable rPFS (the first progression), patients will be assessed every 12 weeks for PFS2 (using the patient's status at first progression as the reference for assessment of PFS2). A patient's PFS2 status is defined according to local standard clinical practice and may involve any of: objective radiological progression, symptomatic progression, PSA or death (see Section 11.1.3.1). RECIST 1.1 and PCWG-2 assessments will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

Standard of care local PSA values should be collected at the time of PFS2 and included on the database.

6.3.2 Overall survival (OS)

Assessments for survival will be conducted every 12 weeks following objective disease progression or treatment discontinuation. Survival information may be obtained via telephone contact with the patient, patient's family, by contact with the patient's current physician, or local death registries as described in Section 3.1.5. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

6.3.3 Time to subsequent therapies for prostate cancer

Following the discontinuation of olaparib, the time from randomisation to first and second subsequent therapies for prostate cancer (TFST and TSST) will be measured.

6.3.4 Patient management post-primary analysis

The data cut-off date for the statistical analysis for the primary objective of the study will be established when ~100 confirmed progression events are expected to have occurred.

The study will be centrally unblinded at this time, but patients and Investigators will remain blinded. After the primary rPFS analysis, patients will continue to be assessed by RECIST 1.1/PCWG-2 until disease progression; assessments will be conducted every 12 weeks up to and including Week 72, and every 24 weeks thereafter. Patients on study treatment at the time

of the data cut-off will continue to receive study treatment until they meet any discontinuation criteria as described in Section 5.8.

6.3.5 Patient management post-final analysis

The data cut off date for the final statistical analysis of the study will be established when ~60% deaths have occurred.

At this time point, the clinical study database will close to new data and all patients will be unblinded. Patients who are still receiving olaparib can either choose to discontinue from the study or, where the Investigator believes patients are gaining clinical benefit, patients may continue to receive olaparib. All patients will receive follow-up care in accordance with standard local clinical practice. Patients that are on placebo will not be offered olaparib as a study treatment.

Serious adverse events will continue to be reported to AstraZeneca Patient Safety Department, for any patients who continue on olaparib until 30 days after study treatment is discontinued, in accordance with Section 6.4.4. Additionally, as stated, any SAE or non-serious AE that is ongoing at the end of the study must be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow-up. If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the Investigator should notify AstraZeneca, Patient Safety.

Drug accountability should continue to be performed until the patient stops study treatment completely.

6.4 Safety

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

6.4.1 Definition of adverse events

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

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

6.4.2 Definitions of serious adverse event

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

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

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from the time of signature of informed consent, throughout the treatment periods, and up to and including the 30-day (±7 days) follow-up visit after discontinuation of study treatment, until the time of the final analysis (rPFS).

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study (ie, 30-day follow-up visit) are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post follow-up adverse events

After study treatment completion (ie, after any scheduled post-treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. However, if an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to olaparib, the Investigator should notify AstraZeneca, Patient Safety department or its representative.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade attained
- Whether the AE is serious or not
- Investigator causality rating against olaparib/placebo (yes or no)
- Action taken with regard to olaparib/placebo
- Causality assessment in relation to abiraterone, prednisone or prednisolone
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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

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

Severity of AE

The grading scales found in the revised National Cancer Institute CTCAE (NCI-CTCAE) version 4.0 will be utilised for all events with an assigned CTCAE grading

(CTCAE v4.03 2010). For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute website (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) .

For each episode, the highest severity grade attained should be reported.

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

Causality collection

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

Causal relationship will also be assessed for additional study drug (AEs and SAEs) and study procedures (SAEs only). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

Adverse events based on signs and symptoms

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

Adverse events based on examinations and tests

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

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

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

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

NB. Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST **or** ALT ≥3xULN **together with** total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law' for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law.

Disease progression

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 under study and/or increases in the symptoms of the disease. Expected progression of the patient's cancer and/or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition, should be considered as disease progression and not as an AE. Any events that are unequivocally due to disease progression should not be reported as an AE during the study.

New cancers

The development of a new primary cancer (including skin cancers) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.4.2). New primary cancers are those that are not the primary reason for the administration of the IP and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

Lack of efficacy

When there is deterioration in the condition for which the IP(s) is being used (prostate cancer), there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the IP contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of IP, must be reported as follows:

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

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.4.2 for further details). 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. This information can be captured in the 'death CRF'.

- 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 or its representative within the usual timeframes.

6.4.4 Reporting of serious adverse events

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

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

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

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

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

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

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

The reference document for definition of expectedness/listedness is the IB for olaparib and the European Union (EU) Summary of Product Characteristics (SPC) for the abiraterone, prednisone and prednisolone.

6.4.5 Laboratory safety assessment

Blood samples for determination of clinical chemistry and haematology will be taken at the times indicated in the Study Plans (see Table 4, Table 5 and Table 8).

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated. Routine urinalysis should be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

For blood volume see Section 7.1.

The following laboratory variables will be measured:

6.4.5.1 Full haematology assessments for safety

- Haemoglobin
- Red blood cells [RBC]
- Platelets
- Mean cell volume [MCV]
- Mean cell haemoglobin concentration [MCHC]
- Mean cell haemoglobin [MCH]
- White blood cells [WBC]
- Absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count (ANC) or segmented neutrophil count and band forms should be performed at each visit and when clinically indicated; if absolute differentials not available please provide % differentials
- Activated partial thromboblastin time (APTT) and international normalised ratio (INR) will be performed if clinically indicated. For patients taking warfarin, INR

and APTT should be measured at baseline, and periodic monitoring during the study is recommended as described in Section 5.6.2.

6.4.5.2 Clinical chemistry assessments for safety

- Sodium
- Potassium
- Calcium
- Creatinine
- Total bilirubin
- ALP
- AST
- ALT
- Urea or blood urea nitrogen [BUN]
- Total protein
- Albumin
- Lactic dehydrogenase [LDH].

NB. In case a patient shows an AST **or** ALT ≥3xULN **together with** total bilirubin ≥2xULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

If a patient has an AST or ALT ≥5xULN or total bilirubin ≥3xULN, then abiraterone treatment should be interrupted and liver function tests closely monitored.

6.4.5.3 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 5.10.1.5.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database.

6.4.6 Physical examination

For timing of individual measurements, please refer to the study plans (see Table 4, Table 5 and Table 8).

Full physical examinations will be performed, including height and weight (screening only), BP, pulse and temperature.

Performance status will be assessed using the ECOG scale (see Appendix G) at baseline and as outlined in the study schedule.

6.4.7 Resting 12-lead ECG

Twelve-lead ECGs will be conducted at screening and when clinically indicated.

The ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. All 12-lead ECGs should be recorded while the patient is in the supine position. The Investigator or designated physician will review the paper copies of each 12-lead ECG.

All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal or not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. A copy of the ECG indicating the study number, without patient identifiers, will be included in the patient's study file for monitoring by the study monitor.

6.4.8 Vital signs

Vital signs (including body temperature, where indicated) will be measured at the times specified in the study plans (see Table 4, Table 5 and Table 8). However, the Investigator reserves the right to add extra assessments if there are any abnormal findings or for any other reason the Investigator feels meets this requirement.

6.4.8.1 Pulse and blood pressure

Supine BP and pulse will be measured using a semi-automatic BP recording device with an appropriate cuff size after the patient has been resting in bed for 10 minutes.

Deterioration as compared with baseline in protocol-mandated vital signs should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP, or the Investigator insists the abnormality should be reported as an AE.

6.4.8.2 Body temperature

Body temperature will be measured in degrees Celsius.

6.4.9 Safety guidance for the use of abiraterone

The prescribing information for abiraterone suggests the following assessments. These additional data do not need to be recorded on the study database.

- Serum transaminases should be measured every 2 weeks for the first 3 months of treatment and monthly thereafter

- Blood pressure, serum potassium and fluid retention should be monitored monthly

- To mitigate the risk of hypokalaemia and also QTc prolongation, the patient's potassium level should be maintained at ≥4.0 mM at inclusion and during the study.

6.5 Patient reported outcomes (PRO)

Each centre must allocate responsibility for monitoring compliance with completion of the PRO questionnaires described in this section to a specific individual (eg, a Research Nurse). The Clinical Team will arrange for relevant training in administration of the questionnaires. The PRO questionnaires should be administered and completed at the clinic in accordance with the study plans (see Table 8 and Table 9). Patients must complete the BPI-SF, the worst bone pain item, then the FACT-P questionnaire. These instruments should be completed prior to the EQ-5D-5L.

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.

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

The instructions for completion of each 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; this should be documented, along with the reason why, on the cover page.

Once a patient has left the clinic, they cannot be queried (for example, if they missed an item). The clinical nurse should quickly make sure that no items have been skipped as soon as the patient turns in the form. If he/she notices an item is missing, the patient can be asked if they would mind completing the one item. If the patient replies that they do not wish to complete the item, then it should be left blank and it should be noted by the clinical nurse that this was checked.

Health-related quality of life data should be monitored on a site by site basis. If it is noted that a site has a lot of missing HRQL forms or a lot of missing data within forms, the clinical trials monitor should contact the site and assess what is causing the difficulty and take measures to improve the situation. AstraZeneca may be involved in this.

6.5.1 Brief Pain Inventory – Short Form (BPI-SF)

Worst pain, general pain and pain's interference with daily life will be assessed during Part B of the study using the BPI-SF (see Appendix H) at the times outlined in the study plan (Table 8). The BPI-SF comprises a total of 15 items measuring 2 domains: pain severity and pain interference. Items measuring pain severity (including 'worst pain') are rated on an 11-point NRS ranging from 0=No pain to 10=Pain as bad as you can imagine. All BPI-SF items are measured using a 24-hour recall period.

6.5.2 Bone pain item

Patients will also be asked to rate their worst bone pain severity on a 0 to 10 point NRS at the same times as the BPI-SF, as outlined in the study plan (Table 8). The worst bone pain item will be developed specifically for this study, following the same format as the BPI-SF worst pain item, again with a 24-hour recall period (see Appendix I).

6.5.3 Investigator administration of BPI-SF and bone pain item over the telephone

The BPI-SF 'worst pain' item and the newly developed 'worst bone pain' item will be administered over the telephone to patients being followed up for PFS2 and survival (see Table 9). The instructions, questions and response options for these items will all be read out to the patient, and the patients will provide responses to each question over the telephone. The individual responsible for administering the questions must accurately record the patient's responses onto the paper questionnaire. Following completion of the questionnaire items with the patient over the telephone, the site staff can either enter the information into the electronic database system or arrange to have the paper questionnaire items sent to the Data Management centre for database entry.

Each centre must allocate the responsibility for the administration of the questionnaire items to a specific individual (eg, a research nurse, study co-ordinator) and if possible assign a back-up person to cover if that individual is absent. The AstraZeneca Study Team (or delegate) will provide relevant training in administration of the questionnaires. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection. Additionally, as the questionnaire items are to be administered over the telephone, individuals administering the questionnaires to patients must adhere to all instruction for completion, which are as follows:

- The items must be completed prior to any discussion of disease progress to avoid biasing the patient's responses to the questions.
- All instructions, questions and available response options for each item should be read aloud by the administrator word for word, with absolutely no paraphrasing.

- All instructions, questions and response options should be read slowly to the patient.
  - If a patient misheard any aspect of the instructions, items or response options, all information should be **repeated** to the patient, slowly.
- The patient should be given sufficient time to provide a response to each question at their own pace.
- The patient should not receive help from relatives, friends or clinic staff to answer the questions. If a patient asks for help, s/he should be instructed to answer on their own.
- One answer should be recorded for each question.
  - If a patient has difficulty choosing between 2 response options, s/he should be instructed to choose the worse or more severe option.
  - If a patient wishes to change a response, the individual administering the questionnaire items should put a line through the incorrect response, circle the correct response, and initial the change.
- Repeat each selected response back to the patient to confirm it is has been accurately recorded.
- Upon completion of the questionnaire items, the individual administrating them should check for completeness. If any questions are missing it should be pointed out to the patient and s/he should be encouraged to answer.
  - If the patient is unable to provide responses to the item, the reason for this should be recorded by the individual responsible for administering the items.
- It is highly important that missing PRO data is minimised; if there are high levels of missing data, PRO results become meaningless.

6.5.4 FACT-P

The FACT-P was developed to measure HRQL in men with prostate cancer (Esper et al 1997, Cella et al 1993). It consists of 4 subscales (physical, emotional, functional and social/family well-being) plus a 12-item prostate-specific module, the Prostate Cancer Symptoms (PCS) subscale, which highlights concerns specific to patients with prostate cancer (see Appendix J). In addition, the FACT-P also supports the calculation of a TOI score (the sum of the PWB, FWB and PCS scores), and the FAPSI-8, a symptom score made up of 8 items from within the FACT-P (pain [n=3], fatigue [n=1], weight loss [n=1], urinary conditions [n=2], and concerns about the condition getting worse [n=1]). Changes in all of these scores are included as

exploratory endpoints, in addition to time to deterioration in the TOI score. The FACT-P will be measured at the times outlined in the study plans (Table 8 and Table 9).

6.6 Pharmacokinetics

6.6.1 Collection of samples

Part A

Blood samples for determination of olaparib (2 mL) and abiraterone (2 mL) in plasma will be taken at the times presented in the Cohort 2 study plan (see Table 5) and in Table 6 and Table 7.

On PK sampling days, the morning dose of study medications should not occur until the pre-dose PK samples have been taken. The second dose of olaparib should be taken after the last PK samples have been taken on that day and approximately 12 hours after the first dose.

Although every attempt should be made to collect all samples as per protocol, it is accepted that this will not always be possible and therefore it is essential that the actual time and date of collection of each blood sample (whether collected as per protocol or not) is recorded in the eCRF.

For blood volume see Section 7.1.

Samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual.

6.6.2 Determination of drug concentration

Samples for determination of olaparib and abiraterone concentrations in plasma will be analysed by Covance on behalf of the Clinical Bioanalysis Alliance, AstraZeneca R&D, using appropriate bioanalytical methods. Full details of the bioanalytical methods used will be described in a separate bioanalytical report.

Results will only be reported for plasma samples shipped within a timeframe for which the stability of olaparib and abiraterone in the samples has been validated and shown to be acceptable.

Additional analyses may be conducted on the olaparib PK plasma samples to further investigate the presence and/or identity of drug metabolites and/or to investigate reproducibility of incurred samples. Any results from these exploratory analyses will not be reported in the CSR but will be reported separately in a metabolism or a bioanalytical report.

6.7 Biomarkers

6.7.1 Collection of biomarker samples

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volumes see Section 7.1.

6.7.1.1 Prostate specific antigen (PSA)

Blood samples (approximately 5 mL, depending on local laboratory requirements) will be taken for PSA assessment at the times indicated in the study plans (Table 4, Table 5 and Table 8). PSA will continue to be collected after discontinuation of study treatment and after primary disease progression until PFS2. The samples will be analysed at the local laboratory.

6.7.1.2 Circulating tumour cells

In Part B of the study, CTC analysis will support secondary (CTC enumeration) and exploratory (biomarker) research objectives.

Whole blood samples (10 mL) will be taken for analysis of CTCs using the Veridex assay (for CTC enumeration) and the EPIC assay (for CTC enumeration and biomarker measurement) at the times shown in the study plan (see Table 8).

Samples will be shipped under ambient conditions on the day of acquisition so as to be received by the AstraZeneca approved laboratory within 48 hours of blood sampling.

The biomarker samples will be assessed for the expression of ERG fusion and ERG protein, and possibly for other exploratory biomarkers, eg, PTEN and AR status.

6.7.1.3 Archival tumour samples for biomarker analysis

An archival tumour sample will be collected from all patients, where available.

The tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the primary tumour or a metastatic site). If this is not possible, 10 to 20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided. If an archival sample is not available, a fresh biopsy (formalin fixed and paraffin embedded) may be taken if the investigator deems this to be appropriate.

Tumour samples (where available) will be assessed for BRCA and ATM mutations, and possibly other exploratory biomarkers such as AR and PTEN. Where validated assays are available, other study samples may be used as surrogates of tumour to increase the numbers of patients within molecularly defined subgroups.

6.7.1.4 Blood samples for biomarker analysis

The following blood samples will be taken at Visit 2 and discontinuation of study treatment:

- 1 x 2.5 mL whole blood
- 1 x 8.5 mL whole blood to provide plasma

Samples may be analysed for ERG expression/fusion status, and possibly other oncology biomarkers such as AR and PTEN, which may correlate to drug response.

6.7.1.5 Urine samples for biomarker analysis

Patients in Part B will be required to provide a urine sample (40 to 50 mL) at Visit 2 and discontinuation of study treatment. These samples may be analysed for ERG expression/fusion status and possibly other oncology biomarkers, such as PTEN and AR, which may correlate with drug response.

6.8 Pharmacogenetics (optional)

6.8.1 Collection of pharmacogenetic samples

See Appendix D ('Pharmacogenetics Research') for details.

For blood volume see Section 7.1.

6.9 Health economics

6.9.1 Utilities: EQ-5D-5L

Patient reported health state utility will be assessed at the times outlined in the study plans (Table 8 and Table 9) by the EQ-5D-5L, a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care (see Appendix K). The instrument asks patients to respond to 5 different dimensions covering mobility, self-care, usual activities, pain/discomfort, anxiety/depression, as well as rate how they feel on the day of assessment via a visual analogue scale. The instrument has been reported to be sensitive to the bowel discomfort associated with prostate cancer.

6.9.2 Resource use

The 'Oncology Hospital Admission' form will be completed by the Investigator at the visits shown in the study plan (Table 8). Any procedures undertaken, and the reason for the procedure, should be captured on the form.

Resource use relating to analgesic use will be derived from the concomitant medications form.

If a patient discontinues study treatment for reasons other than RECIST or PCWG-2 progression, the 'Oncology Hospital Admission' form should continue to be administered at each clinic visit until progression has been confirmed. After progression, fewer details will be collected on an abridged version of the form (see Table 9).

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in each part of this study is shown in Table 15 (Part A, Cohort 1), Table 16 (Part A, Cohort 2) and Table 17 (Part B).

Table 15 Volume of blood to be drawn from each patient in Cohort 1, Part A

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	12[a]	32.4
	Haematology	2.7	12[a]	32.4
Pharmacogenetics (optional)		9	1	9
Total				**73.8**[b]

[a] 12 samples taken at: Visits 1 to 9, discontinuation and follow-up.
[b] From Visit 8 (Week 16) onwards, a further 5.4 mL blood will be collected (for safety analyses) every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.

The total volumes of blood given in Table 14 are based upon a patient remaining in the study for 24 weeks. Subsequent visits beyond Week 24 will result in additional blood sampling as indicated in the table footnote.

Table 16 Volume of blood to be drawn from each patient in Cohort 2, Part A

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	12[a]	32.4
	Haematology	2.7	12[a]	32.4
Pharmacokinetic	Olaparib (Group 1)	2.0	18	36
	Abiraterone (Group 1)	2.0	10	20
	Olaparib (Group 2)	2.0	9	18
	Abiraterone (Group 2)	2.0	20	40
Pharmacogenetics	(Optional)	9	1	9
Total	Group 1			**129.8**[b]
	Group 2			**131.8**[b]

[a] 12 samples taken at: Visits 1 to 9, discontinuation and follow-up.
[b] From Visit 8 (Week 16) onwards, a further 5.4 mL blood will be collected (for safety analyses) every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.

The total volumes of blood given in Table 15 are based upon a patient remaining in the study for 24 weeks. Subsequent visits beyond Week 24 will result in additional blood sampling as indicated in the table footnote.

Table 17 Volume of blood to be drawn from each patient in Part B

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	10[a]	27
	Haematology	2.7	10[a]	27
Biomarker	PSA	5	5[b]	25
	CTC (enumeration)	10	5	50
	CTC (biomarkers)	10	2	20
	Exploratory	11	2	22
Pharmacogenetics	(Optional)	9	1	9
Total				**180**[c]

[a] 10 samples taken at: Visits 1 to 7, discontinuation and follow-up.
[b] 5 samples taken at: Visits 1, 3, 4, 5 and 6.
[c] From Visit 6 (Week 16) onwards, a further 5.4 mL blood will be collected (for safety analyses) every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks

for as long as the patient is on treatment. In addition, from Visit 7 (Week 24) a 5 mL blood sample will be taken every 12 weeks for PSA analysis.

The total volumes of blood given in Table 16 are based upon a patient remaining in the study for 24 weeks. Subsequent visits beyond Week 24 will result in additional blood sampling as indicated in the table footnote.

Clinical chemistry and haematology samples are analysed locally, therefore volumes may vary according to local practice.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples (blood, urine and tumour samples) for future research will be retained at a secure laboratory on behalf of AstraZeneca for a maximum of 15 years following the Last Patient's Last Visit in the study. The results from future analysis will be reported separately from the CSR.

7.2.1 Pharmacokinetic samples

Pharmacokinetic samples may be disposed of or destroyed or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Pharmacokinetic samples will be disposed of after finalisation of the Bioanalytical Report or 6 months after issuing the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR, but separately in a Bioanalytical Report.

7.2.2 Pharmacogenetic samples (optional)

For details concerning the coding and storage of pharmacogenetic samples please refer to Appendix D 'Pharmacogenetics Research'.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

Circulating tumour cell samples will be stored at EPIC Sciences (LaJolla, Ca) for up to 12 months after completion of the study.

7.5 Withdrawal of informed consent for donated biological samples

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

The Principal Investigator:

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

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

Pharmacogenetic samples: Patients may withdraw from the pharmacogenetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

For details regarding pharmacogenetic research and data protection, please see Appendix D ('Pharmacogenetics Research').

8.3 Ethics and regulatory review

An Ethics Committee (EC) or Institutional Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients, eg, FACT-P questionnaire. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

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

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

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

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

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

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

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

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

AstraZeneca or its representative is responsible for informing the Regulatory Authority of SAEs/SUSARs as per the EU Clinical Trials Directive and/or local country regulations and guidelines.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

The pharmacogenetic component of the study is optional and will be detailed on a separate informed consent form.

8.5 Changes to the protocol and informed consent form

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

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

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

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

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

This study will be managed by Quintiles, on behalf of AstraZeneca, and Quintiles will act as the AstraZeneca representatives.

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures, including the WBDC system, how to best administer the PRO questionnaires and the IVRS/IWRS system utilised.

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

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

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and host pharmacogenetic research with AstraZeneca personnel or delegate. 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.

9.3 Monitoring of the study

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

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

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

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The study is expected to start in Q4 2013 for Part A, and Q2 2014 for Part B, and to be completed (LPLV) by Q1 2018 (or by Q2 2016 for the primary variable, rPFS).

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

The end of the clinical part of the study is defined as ‘the date of the last patient stopping study treatment or the data cut-off for the 60% survival analysis, whichever is the later’.

The database for Part A and Part B are one database, and therefore the data will be analysed at the same time. Part A patients continue beyond their initial 14 days treatment as specified in Section 5.5.2.

The primary analysis will be performed once approximately 100 progression events have occurred. Patients who have progressed will be followed for PFS2 and survival data until approximately 60% of patients have died at which point the final analysis will occur and the study database will be closed. Patients who have not progressed at the time of the primary analysis will continue to be followed to first disease progression.

Patients are permitted to continue to receive olaparib beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from it (see Section 5.5.2). Patients may also continue to receive abiraterone and prednisolone which are sourced locally as commercially available materials. For patients who do continue to receive treatment with olaparib beyond the time of this data cut-off, Investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after olaparib is discontinued, in accordance with Section 6.4.4. Note: SAEs are not required to be reported for patients who continue with abiraterone without olaparib; Investigators should follow local requirements for reporting any SAEs to regulatory agencies and/or manufacturers of abiraterone. Additionally,

as stated in Section 6.4.3, any SAE or non-serious AE that is ongoing at the time of this data cut-off must be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow-up.

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

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by Quintiles.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA®). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by Quintiles.

Patient reported outcomes data should be entered as the patients respond. If 2 adjacent responses are marked, then the worst response should be entered. If 2 responses are marked but they are not adjacent, then that item should be missing.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

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

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

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

For details on the management of pharmacogenetic data, please see Appendix D ('Pharmacogenetics research').

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Tumour response rate: malignant soft tissue response (RECIST v1.1)

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST v1.1 for malignant soft tissue disease (see Appendix F). Metastatic bone lesions will not be part of this assessment.

At each visit, the Investigator-assessed RECIST data for a patient will be programmatically assigned a response of CR, PR, SD, PD, NED or NE depending on the status of the disease compared with baseline and previous assessments.

Progression of TLs will be calculated in comparison with what the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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

For TL measurements, if ≤1/3 of the TL sizes are missing (either not evaluable or not read, or the scan was not done), then a scaling up rule will be applied as follows:

- If ≤1/3 of lesions recorded at baseline are missing, then the results will be scaled up (based on the baseline sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the baseline sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)

- If >1/3 of lesions recorded at baseline are missing, then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by >20% compared to the smallest sum of diameters on study and has an absolute increase ≥5 mm), PD takes precedence over NE

- A visit response of CR will not be allowed if any of the TL data are missing.

For patients who only have non-measurable disease at baseline, categorisation of objective tumour response assessment will be based on the modified RECIST 1.1 guidelines for response for NTLs: CR, PD and Non CR/Non PD or NE.

Patients with absence of target and non-target lesions at baseline, and with no progression by new lesions at follow-up, will be categorised as 'no evidence of disease' (NED). If there is progression due to new soft tissue lesions they will be categorised as PD.

11.1.2 Metastatic bone disease status

Metastatic bone disease status will be reported from the bone lesion assessment on bone scan as non-progressive disease or progressive disease, separately from RECIST 1.1 soft tissue and PSA response assessments, according to PCWG-2 criteria (see Section 6.3.1.2 for the definition of progression on bone scan).

The date of progression is the date of the first scan which is defined as showing a progression.

11.1.3 Radiologic progression-free survival (rPFS)

The primary endpoint is rPFS (defined by RECIST 1.1 and/or PCWG-2 as assessed by the Investigator).

Progression-free survival (weeks) is defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed (defined as CR, PR or SD by RECIST 1.1, or non-PD by PCWG-2 bone scan) or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 or PCWG-2 assessment. However, if the patient progresses or dies after 2 or more missed RECIST 1.1/PCWG-2 visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 or PCWG-2 assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline (in which case their date of death will be used).

The rPFS time will always be derived based on scan/assessment dates not visit dates.

When the Investigator is in doubt as to whether PD has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

RECIST 1.1/PCWG-2 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a patient for rPFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

11.1.3.1 Time to second progression (PFS2)

Time from randomisation to PFS2 is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable rPFS, or death. The date of PFS2 will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of: objective radiological progression, symptomatic progression, PSA or death (see also Section 6.3.1.3). PFS2 status will be reviewed every 12 weeks following the progression event used for the primary variable rPFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression (ie, censored at the latest of the rPFS or PFS2 assessment date if the patient has not had a second progression or death).

11.1.4 Overall survival (OS)

Overall survival (months) is defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note, survival calls will be made in the 2 weeks following the date of DCO for the analysis, and if patients are confirmed to be alive (eg, alive post DCO date or if the death date is post the DCO date) these patients will be censored in the analyses as of the date of DCO.

Patients will enter the OS phase of the study following confirmed progression by the Investigator. All patients will be followed for survival data until approximately 60% of patients have died.

11.1.5 Objective response rate and associated variables

For soft tissue disease ORR, only patients with measurable disease (target lesions) at entry will be included in the denominator. A responder will be any patient with a best overall response of PR or CR in their soft tissue disease assessed by RECIST 1.1, irrespective of the bone scan status assessed by PCWG-2.

For overall radiological ORR, again only patients with measurable disease (target lesions) at entry will be included in the denominator. A responder demonstrating overall radiological response will be any patient with a best overall response of PR or CR in soft tissue disease assessed by RECIST 1.1 and also bone scan status of non-PD or NE for their bone assessed by PCWG-2. Soft tissue response rate will thus be equal to or higher than the overall radiological ORR.

Duration of overall radiological response (RECIST 1.1 soft tissue disease response of PR or CR, with a PCWG-2 response of non-PD/NE) will be defined as the time from overall radiological response until date of documented radiological progression by RECIST 1.1 for soft tissue disease or PCWG-2 for bone lesions, or death in the absence of disease progression; the end of response should coincide with the date of progression or death from any cause used for the rPFS endpoint. The time of the initial overall radiological response

will be defined as the time from randomisation until the earliest of the dates where an overall radiological response is seen.

If a patient does not progress following an overall radiological response, then their DoR will be censored at the rPFS censoring time.

Duration of response will not be defined for those patients who do not have documented overall radiological response.

11.1.6 Time to subsequent therapies

Time to first subsequent therapy (TFST) for prostate cancer is defined as the time from randomisation to the date of the first subsequent therapy for prostate cancer following discontinuation of olaparib. Similarly, time to second subsequent therapy (TSST) for prostate cancer is defined as the time from randomisation to the date of the second subsequent therapy for prostate cancer.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Adverse events

An AE is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent. All AEs will be coded using the MedDRA® dictionary to provide the system organ class and preferred term for each AE. AEs will be grouped separately as AE onset before and after first dose of study drug.

Any AE commencing (or worsening) on the same day as the first dose of study treatment, will be assumed to occur after study treatment has been administered. A treatment emergent AE (TEAE) will therefore be defined as an AE with the start date on or after the first dose date, and up to and including the 30-day (±7 days) follow-up visit after discontinuation of study treatment, until the time of the final analysis (rPFS).

11.2.2 Other significant adverse events

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

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

11.2.3 Dose-limiting toxicities (DLT)

Dose-limiting toxicities are defined in Section 3.1.1.4.

11.2.4 Concomitant medications

Concomitant medications will be classified according to the current version of the AstraZeneca Drug Dictionary.

Concomitant medications will be classed as either:

1. Concomitant medications starting prior to first dose (pre-study)

2. Concomitant medications starting on or after first dose date (on study).

Medications that start on the same day as the first dose of study treatment will be assumed to occur after study treatment has been administered, and be classified as on-study.

11.2.5 Compliance and exposure

Study drug exposure (days) will be defined as time from first dose of olaparib to last dose. Exposure to abiraterone will be calculated in the same way.

Exposure will be defined as:

Last dose date – first dose date + 1.

If the last dose date is unknown, the soonest available date afterwards where it is confirmed that no drug is being taken will be used instead.

Percentage compliance will be defined as:

{(No. tablets dispensed in period – no. tablets returned from period)/
(no. days of study drug exposure in period * expected tablets per day)} * 100%

where expected tablets per day will take into account once daily or bid dosing.

Overall compliance may be calculated over various periods if the dose has been modified, to take into account the differing expected tablets per day or the protocol-specified dose interruptions. Missed doses will not be adjusted for; the overall compliance will be reduced.

11.3 Calculation or derivation of patient reported outcome variables

The primary outcome measure for the PRO measures will be BPI-SF.

11.3.1 Brief Pain Inventory – Short Form (BPI-SF)

Scoring of the BPI-SF will be as per the developers' instructions. Change in the BPI-SF pain and pain interference scores will be calculated as change from baseline at each clinic visit.

Time to worsening of pain is defined as the time from the date of randomisation to the date of first assessment of worsening of pain, or death from any cause (as long as the death occurs within 2 BPI-SF assessment visits of the last evaluable assessment of BPI-SF and regardless

of whether the patient withdraws from study treatment or receives another anti-cancer therapy. Worsening of pain is defined as an increase in worst pain BPI-SF score by at least 2 points on the 0 to 10 scale.

11.3.2 Worst bone pain item

The worst bone pain item will be scored as is (0-10 scale, with 10 being worst imaginable bone pain). Change in the worst bone pain item will be calculated as change from baseline at each clinic visit.

Time to worsening of bone pain is defined as the time from the date of randomisation to the date of first assessment of worsening of bone pain, or death from any cause (as long as the death occurs within 2 PRO assessment visits of the last evaluable assessment of worst bone pain and regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy. Worsening of bone pain is defined as an increase in worst bone pain score by at least 2 points.

11.3.3 FACT-P

Scoring of the FACT-P will be as recommended by the developers. Higher scores equate to better quality of life.

For the FACT-P total score, TOI, FAPSI-8, and PCS, FWB, PWB, EWB and SWB sub-scales, changes from baseline for each time point will be calculated for each treatment group.

A best response of 'Improved', 'No Change' and 'Worsened', defined according to Table 18 and Table 19, will be calculated for each patient for scales assessing prostate cancer symptoms, impact on physical/functional well-being and overall HRQL (TOI, FAPSI-8, PCS, PWB and FWB scales and FACT-P total score).

If less than 50% of the subscale items are missing from a returned questionnaire, the subscale score will be calculated by replacing the missing items with the mean of the non-missing items in the scale. If 50% or more of the items are missing, that visit will be treated as missing.

Table 18 details how responders will be defined for the FACT-P TOI, FAPSI-8, PCS and FWB scores (Cella et al 2009).

Table 18 Definition of visit response for FACT-P, FAPSI-8, TOI, PCS and FWB

FACT-P scale	Change from baseline	Visit response
FACT-P-Total	≥ +6	Improved
	≤ -6	Worsened
	Otherwise (ie, >-6 and <+6)	No change
	Missing/non-calculable score	Not evaluable
FAPSI-8	≥ +3	Improved
	≤ -3	Worsened
	Otherwise (ie, >-3 and <+3)	No change
	Missing/non-calculable score	Not evaluable
TOI	≥ +5	Improved
	≤ -5	Worsened
	Otherwise (ie, >-5 and <+5)	No change
	Missing/non-calculable score	Not evaluable
PCS	≥ +3	Improved
	≤ -3	Worsened
	Otherwise (ie, >-3 and <+3)	No change
	Missing/non-calculable score	Not evaluable
FWB	≥ +2	Improved
	≤ -2	Worsened
	Otherwise (ie, >-2 and <+2)	No change
	Missing/non-calculable score	Not evaluable

Overall improvement for the FACT-P scores is defined as a change from baseline in the required number of points or more, as stated in Table 18 for 2 consecutive visits.

At the conclusion of the study, the criteria listed in Table 19 will be used to assign a best overall response score based on the individual visit responses.

Table 19 Overall score response for FACT-P, FAPSI-8, TOI, PCS, FWB

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

11.4 Calculation or derivation of pharmacokinetic variables

The PK analysis of the plasma concentration data for olaparib and abiraterone will be performed at (or on behalf of) AstraZeneca R&D. The actual sampling times will be used in the PK calculations, except for the pre-dose sample for which the time will be set to zero. All PK computations will be performed using Phoenix™ for WinNonlin.

Patients who withdraw from the study following dosing, but prior to study completion, will be included in the PK analysis provided they have evaluable profiles over the planned collection period. Patients with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

If sufficient data are available for estimation, the following multiple-dose PK parameters will be calculated for olaparib and abiraterone in Part A:

- Maximum plasma concentration at steady state ($C_{max\ ss}$) obtained directly from the observed concentration versus time data
- Minimum plasma concentration at steady state ($C_{min\ ss}$) obtained directly from the observed concentration versus time data
- Time to reach maximum plasma concentration at steady state ($t_{max\ ss}$) obtained directly from the observed concentration versus time data
- Area under the plasma concentration-time curve at steady state (AUC_{ss}) calculated by linear up/logarithmic down trapezoidal summation of the area under the steady state plasma concentration time curve from zero to the end of the dosing interval (12 hours for olaparib; 24 hours for abiraterone).

Additional PK parameters may be determined if deemed appropriate.

Any value below the limit of quantification (LOQ) in a pre-dose sample will be set to zero; an LOQ value elsewhere in the profile will be excluded from the analysis.

11.5 Calculation or derivation of biomarker variable(s)

11.5.1 Prostate specific antigen

11.5.1.1 PSA response

- A patient will be regarded as having a single PSA visit response if their PSA level at any post-dose visit is reduced by 50% or more compared with baseline
- A patient will be regarded as having a confirmed PSA response if they have a reduction in PSA level of 50% or more compared with baseline that is confirmed at the next assessment at least 4 weeks later (ie, decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 4 weeks apart).

11.5.1.2 PSA changes on continuous scale

- PSA levels will be evaluated in terms of percentage change from baseline which will be derived for each post baseline visit where PSA data are available
- % change = [(post-dose PSA level – baseline PSA level) / baseline PSA level] *100
- Best percentage change from baseline in PSA will be derived as the biggest reduction in PSA level compared with baseline (or the smallest increase in the absence of a reduction) taking account of all PSA values collected for each patient

11.5.2 Circulating tumour cell counts

- Conversion: change of CTC from ≥5 at baseline to <5 post baseline
- Change in CTC counts as a continuous variable following treatment with olaparib/placebo and abiraterone (calculated as post-dose CTC count - baseline CTC count).
- Change in CTC count at 12 weeks.

11.5.3 ATM mutation

Samples will be assessed for ATM mutation. Full details of categorisation will be given in the statistical analysis plan (SAP).

11.5.4 BRCA mutation

Samples will be assessed for BRCA mutation. Full details of categorisation will be given in the SAP.

11.5.5 Further biomarker research analysis

Tumour (where available), blood, urine and CTC samples will be stored for future exploratory analysis of biomarkers such as PTEN and AR.

Methods of analysis for all other biomarker research may include investigation of genetic variability, gene expression profiling and/or protein expression profiling.

11.6 Calculation or derivation of pharmacogenetic variables

Please see Appendix D ('Pharmacogenetics research') for details.

11.7 Calculation or derivation of health economic variables

11.7.1 Utilities: EQ-5D-5L

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the UK valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents also assess their health today on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately. The evaluable population will comprise the full analysis set.

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

11.7.2 Resource use

Resource use will be analysed from procedures captured on the 'Oncology Hospital Admission' form and the standard concomitant medication eCRF, and, where required, supplemented with data on hospitalisation length of stay logged as part of SAE recording. Frequency of palliative interventions and the reasons for the intervention will be estimated from the 'Oncology Hospital Admission' form. The evaluable population will comprise the full analysis set. The analysis will be conducted on blinded data.

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

12.1 Description of analysis sets

The study physician, pharmacokineticist, and statistician will agree on the strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed.

12.1.1 Full analysis set

Intention to treat (ITT): The primary statistical analysis of the efficacy of olaparib when given in addition to abiraterone will include all randomised patients in Part B, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the full analysis set.

12.1.2 PK analysis set

All patients in Part A (Cohorts 2 and 3, as applicable) of the study who provide at least one post-dose analysable plasma sample for PK analysis will be included in the plasma concentration listings. On each sampling occasion, PK parameters will be derived for all patients who provide a full PK profile and these parameters will be included in the PK parameter listings and summaries. However, for inclusion in the evaluation of a DDI, patients must provide steady state PK profiles both for olaparib/abiraterone alone and in combination, and have no protocol violations affecting the PK endpoint.

The population for the DDI evaluation will be defined by the study team physician, pharmacokineticist and statistician prior to any analyses being performed.

If a patient has a major protocol deviation that affects the evaluability of the PK profile, then the patient will not form part of the DDI evaluation.

Major protocol deviations include changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK. Examples include, but may not be limited to, vomiting following oral dosing occurring within the time frame of 2 times the median $t_{max\ ss}$, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. In the case of a major protocol deviation, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Major deviations will be listed and summarised in the CSR.

12.1.3 Safety analysis sets

Part A safety analysis set: All patients in Part A of the study who receive at least 1 dose of study treatment. Treatment group comparisons will be based on the initial dose of study treatment actually received.

Part B safety analysis set: All patients randomised into Part B of the study who receive at least 1 dose of study treatment. Treatment group comparisons will be based on the initial dose of study treatment actually received.

When assessing safety and tolerability, summaries will be produced based on the safety analysis sets.

12.2 Methods of statistical analyses

The following text applies to demographic, efficacy and safety analyses only; PK is discussed separately.

Statistical analyses will be performed by Quintiles under the direction of the Biostatistics Group, AstraZeneca using SAS® version 9.1 or higher and, where appropriate, additional validated software.

A comprehensive SAP will be prepared before database lock. For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, SD, median, minimum, and maximum values. Where appropriate, assessments will be summarised by visit.

The number of patients who were screened, confirmed eligible (Part A)/randomised (Part B), received treatment and completed the study will be produced for each of the treatment groups in Part A (using the Part A safety analysis set) and Part B (using the full analysis set). A summary table of analysis sets will be produced. Demographic and baseline characteristics will be summarised using the Part A safety analysis set and the full analysis set, for Parts A and B of the study, respectively.

Treatment duration will be summarised. Treatment duration is based on the dates of first and last dose.

Study day will be calculated as follows:

Days prior to first dose: Study day = date – first dose date.

Days on or after first dose: Study day = date – first dose date + 1.

In general, missing data will not be imputed. For the date variables of historical data (ie, any data referring to the period prior to the informed consent date), if the year is missing then the value will not be imputed. If the month or day is missing, the value will be imputed: month will be imputed with June; day will be imputed as 15th.

12.2.1 Efficacy data

The following efficacy analyses will be performed using the full analysis set.

12.2.1.1 Radiological progression-free survival

The primary endpoint of Part B, rPFS (weeks), is defined in Section 11.1.3. Once approximately 100 progression events have occurred, the primary analysis will be performed. Radiological progression-free survival will be analysed using a log-rank test. The hazard ratio (HR) and 80% confidence interval (CI) will be estimated from the U and V statistics obtained directly from the LIFETEST model with inclusion of STRATA terms for the stratification variables (and using the Breslow approach for handling ties). A HR less than 1 will favour Olaparib.

The HR and its confidence interval can be estimated from the log-rank as follows (Berry et al 1999, Sellke et al 1983):

$$HR = exp(U/V)$$

$$80\%\ CI\ for\ HR = (exp\{U/V - 1.28/\sqrt{V}\}, exp\{U/V + 1.28/\sqrt{V}\})$$

Where $U = \sum_i (d_{1i} - e_{1i})$ is the log-rank test statistic(with d_{1i} and e_{1i} the observed and expected events in group 1) and $\sqrt{V}$ the standard deviation of the log-rank test statistic as produced in the LIFETEST output.

The HR (Olaparib vs. placebo) together with its corresponding 80% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour Olaparib).

Kaplan-Meier survival curves (product-limit estimates) of rPFS will be presented by treatment group, together with a summary of associated statistics (median rPFS time, and 6, 12, 18, 24 and 30 month survival rate estimates). Summaries of the number and percentage of patients experiencing a rPFS event, and the type of event (RECIST progression, PCWG-2 progression or death) will also be presented.

Listings of rPFS per patient will be produced.

The assumption of proportionality will be assessed. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time-dependent covariate would be fitted to assess the extent to which this represents random variation.

Separate log-rank tests of rPFS will be undertaken using patients who have BRCA or ATM mutations, using the same model as for the primary analysis. If the number of patients in each subgroup is small, consideration will be given to merging the subgroups prior to analysis.

As an exploratory analysis, a Cox proportional hazards model of rPFS may be undertaken including some or all of the following factors: PTEN, AR status, disease related biomarkers, demographic and disease characteristics.

If there are too few events available for a meaningful analysis (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), only descriptive statistics will be provided.

Sensitivity analyses for rPFS

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (ie, differential assessment times between treatment groups). Summary statistics for the number of weeks between rPFS time and the last evaluable assessment prior to progression will be presented for each treatment group.

(a) Evaluation-time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable assessment (RECIST or PCWG-2) will be analysed as described for the primary analysis of rPFS. This approach has been shown to be robust to even highly asymmetric schedules (Sun and Chen 2010).

(b) Attrition bias

Attrition bias will be assessed by repeating the primary rPFS analysis except that the actual rPFS event times, rather than the censored time, of patients who progressed or died in the absence of progression immediately following 2, or more, non-evaluable tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

(c) Censoring bias

A Kaplan-Meier plot of the time to censoring will be produced, where the censoring indicator of the primary rPFS analysis is reversed.

12.2.1.2 Time to second progression (PFS2)

The secondary endpoint of PFS2 (weeks), as defined in Section 11.1.3.1, will be analysed using the same time-to analysis as rPFS: log-rank test, Kaplan-Meier and summary statistics.

Listings of PFS2 time per patient will also be produced.

12.2.1.3 Overall survival (OS)

The secondary efficacy endpoint for Part B, OS (months), as defined in Section 11.1.4, will be performed when approximately 60% of patients have died; patients who have not died at that point will be censored.

The same time-to analyses will be undertaken as for rPFS: log-rank test, Kaplan-Meier and summary statistics. A listing of OS time per patient will also be produced.

In addition, to provide further information, listings of first and subsequent therapies will be produced.

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment (or other potentially active investigational agents) may be performed if a sufficient proportion of patients switch. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (Robins 1993) and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Details will be pre-specified in the SAP and Payer analysis plan.

12.2.1.4 Objective response rate

The secondary efficacy endpoint for Part B, ORR for soft tissue disease response and overall radiological response, will be performed at the time of the rPFS analysis.

Patients with at least one visit response of CR or PR (the numerator of ORR, as defined in Section 11.1.5) will be analysed using logistic regression, adjusting for the same set of covariates as for rPFS. The effect of treatment will be estimated using the adjusted odds ratio and its corresponding 80% CIs.

Objective response rate will be formally analysed for both soft tissue ORR and overall radiological ORR using logistic regression. However, the other associated endpoints (best overall soft tissue disease response, best overall radiological response, duration of response, time to response) will be summarised only.

Best objective response (soft tissue disease and overall radiological response) at each scheduled visit will be summarised.

Duration of overall radiological response (months) and time to response (months), are defined in Section 11.1.5. A listing of DoR and time to response per patient will be produced, and the data will be summarised.

12.2.1.5 Time to subsequent therapies

The TFST and TSST are defined in Section 11.1.6. A listing of TFST and TSST per patient will be produced, and the data will be summarised.

12.2.2 Biomarker data (PSA and CTCs)

Proportion of patients achieving a PSA response will be presented with 80% CIs.

Proportion of patients achieving a CTC conversion will be presented with 80% CIs.

PSA percentage change from baseline and change from baseline in CTC counts will be summarised as continuous variables using descriptive statistics and presented graphically using box plots over time.

Change in PSA and CTC counts and best change in these parameters during the study will be summarised and presented graphically.

Summary statistics (n/%) will be presented for ERG fusion positive/negative results, and/or ERG expression categories (0 to 3), by treatment group at each visit. Sample quantity may mean that only one ERG measure can be performed.

Summary statistics (n/%) will also be presented for patients who have BRCA mutations compared with those who are BRCA wildtype or information is missing.

Proportion of patients achieving an ERG fusion positive response will be presented with 80% CIs.

12.2.3 Patient reported outcomes (PRO)

The exploratory endpoints in this section are defined in Section 11.3.

For analysis of the PRO endpoints, BPI-SF, bone pain item and FACT-P, the following analysis will be performed.

Summary statistics for mean score, standard deviation, median and range will be presented by treatment group for visits until there are less than one third of patients with evaluable data. Box plots will also be presented.

The proportion of patient with best responses of 'Improved', 'No Change' and "Worsened" will be compared between treatments using logistic regression with the same methods and covariates as for the analysis of ORR.

Time to worsening will be assessed by a Cox proportional hazards model using the same methods and covariates as for the primary analysis. The effect of treatment will be estimated by the HR together with its corresponding 80% CI. Kaplan-Meier plots will also be presented by treatment.

In addition the time to worsening for the subscales of the FACT-P (TOI, FAPSI-8, PCS and FWB) will be presented on a forest plot.

12.2.4 Safety data

Safety analyses will be presented using the Safety Analysis Sets and will be done by means of descriptive statistics. Safety profiles will be assessed in terms of AEs, vital signs (including BP and pulse rate), ECG, laboratory data (clinical chemistry and haematology), and physical examination.

All data will be summarised and listed appropriately.

Adverse events will be summarised separately for Parts A and B of the study, and also by dose within Part A. Laboratory data, vital signs, physical examination, body temperature and ECG will be summarised separately for Parts A and B by dose group and by study day. Summaries

will be presented for scheduled visits only. Any unscheduled assessments will be listed. The baseline value is defined as the latest result obtained prior to the start of IP.

The impact of any major protocol deviations, missing data, and the use of rescue or concomitant medication on the robustness of study results will be investigated and any methods employed to deal with these will be documented.

Additional tables, figures, or listings may be produced to aid interpretation.

Further details of summaries of the safety data will be given in the SAP.

12.2.4.1 Adverse events

The number of patients experiencing AEs following administration of olaparib as well as the number of AEs experienced will be summarised. Adverse events will be classified using the MedDRA® system of nomenclature (preferred term and system organ class [SOC]). Adverse events reported before administration of olaparib will be listed only and be referred to as 'pre-treatment.'

Similarly, the number of patients experiencing SAEs, OAEs, AEs that led to withdrawal, AEs that led to death and treatment-related AEs and the number of such events will be summarised by part, as applicable.

All AE data will be listed for all patients. In addition, SAEs, OAEs, and AEs that led to withdrawal or death, and treatment-related AEs will be listed.

12.2.4.2 Dose-limiting toxicities

Dose-limiting toxicities will be summarised by treatment cohort for Part A.

12.2.4.3 Laboratory data

Laboratory data (clinical chemistry and haematology) will be summarised and listed. Shift tables will be provided for select tests, where shift from baseline to the worst value within each part of the study and overall will be summarised. Laboratory data outside the reference ranges should be indicated in the listings.

12.2.4.4 Concomitant medications

Concomitant medications will be summarised by the coded terms. The number of patients receiving a medication will be summarised overall and for each part of the study. A medication taken during the course of the study is considered concomitant. A patient is only counted once if receiving the medication more than once.

Disallowed medications will be listed.

12.2.4.5 Vital signs

Vital signs, including BP (mmHg), heart rate (beats/min), body temperature (°C) and weight (kg), will be summarised at baseline and each scheduled visit. In addition, a summary of vital signs changes from baseline to each visit will be presented by treatment. The baseline value is the last pre-dose assessment.

A listing of all vital sign data will also be produced.

12.2.4.6 Other safety variables

The remaining safety variables will be presented using summary statistics for quantitative data and frequency counts for qualitative parameters.

12.2.4.7 Exposure and compliance

Listings and summaries of exposure and compliance will be produced for olaparib and abiraterone, by treatment cohorts, for Part A and treatment groups in Part B.

The number of patients who discontinued study drug, and the reasons, will be summarised by treatment group for Part A and B separately. These data will also be listed.

12.2.5 PK data (Part A only)

The sample bioanalysis for olaparib and abiraterone will be performed by Covance. The merging of PK concentration data with actual PK sampling times will be performed by Quintiles Data Management. The PK analysis will be the responsibility of the pharmacokineticist at AstraZeneca. The PK summaries, figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of the Quintiles biostatistician.

All data received for olaparib and abiraterone will be presented in data listings. Pharmacokinetic summaries will be presented for patients in the PK analysis set, as defined in Section 12.1. Data from patients excluded from the PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in patient listings.

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (%CV), median, minimum, and maximum values. Additionally, geometric means and geometric %CV (%GCV) will be reported for PK variables (concentrations and all PK parameters, except for $t_{max\ ss}$). The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The %GCV is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Mean, SD, CV%, geometric mean, and %GCV will not be calculated for $t_{max\ ss}$; $t_{max\ ss}$ will be summarised by median, minimum and maximum values.

For all data, descriptive statistics except for %CV and %GCV will follow the rounding convention of the individual data. Coefficients of variation (%CV and %GCV) will always be reported to 1 decimal place. Ratios and any corresponding CIs that are obtained during inferential statistical analysis shall be reported as a percent with 2 decimal places (eg, 99.88).

The plasma concentrations for olaparib and abiraterone will be reported to the same precision as the source data. For descriptive statistics of concentrations, non-quantifiable (NQ) values of plasma concentrations will be handled as follows:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the mean, SD, geometric mean, %CV, and %GCV will be calculated by substituting the LOQ for values which are NQ.

- If more than 50%, but not all, of the concentrations are NQ, the mean, geometric mean, SD, %CV, and %GCV will be reported as not calculable (NC).

- If all the concentrations are NQ, the geometric mean and mean will be reported as NQ and the SD, %CV, and %GCV as NC.

The PK parameters will be rounded for reporting purposes both in the summary tables and by-patient listings. For the calculation of descriptive statistics and the statistical analysis, rounded values as presented in the data listings will be used. Except for raw measurements (such as $C_{max\ ss}$ and $t_{max\ ss}$), all other derived PK parameters will be reported to 3 significant digits.

The PK data will be presented by treatment group (ie, Group 1 [olaparib alone first, then olaparib with abiraterone] and Group 2 [abiraterone alone first, then olaparib with abiraterone]).

The goal of Part A of the study is to determine whether there is any marked evidence of any drug interaction between olaparib and abiraterone by determination of steady state exposure to olaparib in the presence and absence of abiraterone, and determination of steady state exposure to abiraterone in the presence and absence of olaparib. $C_{max\ ss}$, AUC_{ss} and $C_{min\ ss}$ ratios will be calculated for olaparib from Group 1 patients (PK parameter from 'olaparib alone' profile: PK parameter from 'olaparib in combination' profile) and for abiraterone from Group 2 patients (PK parameter from 'abiraterone alone' profile: PK parameter from 'abiraterone in combination' profile). These ratios will be summarised for each group and displayed graphically. No statistical analysis of the data will be performed.

12.2.6 Health economics data

12.2.6.1 Utilities: EQ-5D-5L

Descriptive statistics, graphs and listings will be reported for health state utility index values and visual analogue scale by visits as well as change in these scores from baseline. To support future economic evaluations of olaparib, additional appropriate analyses may be

undertaken, for example, mean health state utility pre- and post-treatment, and pre- and post-progression. Further details will be outlined in the payer analysis plan.

12.2.6.2 Resource use

An exploratory health economic analysis of the frequency of metastatic prostate cancer related palliative interventions, time to interventions, and reason for the intervention will be undertaken. In addition, length of stay, ICU use, concomitant medications and analgesic use will be examined.

These analyses will examine the impact of disease and treatment on resource use to primarily support the economic evaluation of olaparib in castrate resistant metastatic prostate cancer.

12.2.7 Interim analyses (Not applicable)

12.3 Determination of sample size

12.3.1 Part A

The primary objective of Part A of this study is to assess the safety and tolerability of olaparib when combined with abiraterone and to recommend a dose of olaparib for study in Part B. Hence the number of patients has been based on the desire to obtain adequate tolerability, safety and PK data while exposing as few patients as possible to the IP and procedures.

Cohorts of 3 to 6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations/reductions necessary.

The cohort sizes are based upon accepted methodology for Phase I oncology studies.

12.3.2 Part B

The sample size for Part B of this study was selected to be consistent with the research hypothesis as described in Section 1.2. The sample size calculation is based on the primary outcome variable, rPFS.

In total, 100 rPFS events in the study would have 80% power to show a statistically significant rPFS at the 1-sided 10% level if the assumed true treatment effect was HR 0.65; this translates to a 3.75 month benefit in median rPFS on olaparib/abiraterone combination over 7 months (based on the mean of 2 trials: Antonarakis and Eisenberger 2011 and Scher et al 2012) on abiraterone monotherapy if rPFS is exponentially distributed. Approximately 140 patients will be recruited (1:1 ratio) so that data maturity for the rPFS analysis is approximately 70%. Assuming 12 months non-linear recruitment, 100 rPFS events are expected to occur approximately 24 months after the first patient is enrolled in the study (FPI) (12 month accrual + 12 months follow-up). This will be the primary analysis of rPFS. With 100 events, the smallest treatment difference that would be statistically significant is rPFS HR = 0.77 (which translates to approximately a 2.1 months median difference).

Overall survival will be analysed after approximately 60% deaths have occurred. Assuming 12 months' non-linear recruitment, 84 death events are expected to occur approximately

37 months after FPI. With 80% power, an improvement in median time to death of 10 months on olaparib/abiraterone combination over 17 months on abiraterone alone (HR=0.63) could be detected (1-sided, 10% alpha).

The primary and all secondary efficacy endpoints will be analysed in the full analysis set unless otherwise stated. The safety endpoints will be analysed in the safety analysis set.

For sample size information relating to the pharmacogenetic component of the study, please see Appendix D ('Pharmacogenetics research').

12.4 Data monitoring committee (Not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

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

13.2 Overdose

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

There is currently no specific treatment in the event of overdose of olaparib and possible symptoms of overdose are not established.

The primary anticipated complications of olaparib over dosage would consist of bone marrow suppression, peripheral neuropathy and mucositis. Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

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

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

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

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

13.3 Pregnancy

13.3.1 Maternal exposure

Women are not included in this study.

13.3.2 Paternal exposure

Patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of olaparib/placebo, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of any conception (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) from the date of the first dose until 3 months after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information on the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant ECs/IRBs prior to use.

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Clinical Study Protocol Appendix B	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2103

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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Clinical Study Protocol Appendix C	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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Clinical Study Protocol Appendix D	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
BRCA	Breast cancer genes
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the olaparib clinical development programme to explore how genetic variations may affect the clinical parameters associated with olaparib and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to olaparib and/or abiraterone used in combination or as a comparator, and the disease under study within the current Clinical Study Protocol. BRCA genes (genes encoding cancer susceptibility proteins involved in DNA repair) and other genes associated with DNA damage repair may be studied. No other research will be performed on the samples.

BRCA data may be available at the end of the study and sites may request individual patient BRCA results to be provided as required. Sites are responsible for ensuring compliance with all associated local procedures for genetic testing if a patient BRCA result is provided.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the pharmacogenetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion within 120 days of the date of the pharmacogenetic sample collection.

3.1.4 Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 2. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE); such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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 is 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 person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the patient may participate in other components of 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 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 from the genetic aspect of the study at any time.

4.2 Patient data protection

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. BRCA genotype results may be available at the end of the study and can be provided to the investigator if requested by the patient.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse the samples.

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 CRF and database.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients that will agree to participate in the genetic research 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.

7. LIST OF REFERENCES

None

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Clinical Study Protocol Appendix E	
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Study Code	D081DC00008
Edition Number	3
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Appendix E
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥3xULN

- AST ≥3xULN
- TBL ≥2xULN

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6)
- Notify the AstraZeneca representative who will then inform the central Study Team.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to

determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2 of this Appendix.

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

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

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

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

If Yes:

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

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

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

8. REFERENCES

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

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

AstraZeneca

Clinical Study Protocol Appendix F	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

Appendix F
Guidelines for Tumour Assessment: RECIST soft tissue and PCWG2 bone lesions

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TUMOUR ASSESSMENTS

Image based tumour response assessment will be determined by evaluation of soft tissue lesions by modified RECIST v1.1 (Response Evaluation Criteria in Solid Tumours) (Eisenhauer et al 2009) and a separate bone lesions assessment using bone scans, as described in Prostate Cancer Trials Working Group 2 (PGWG2) recommendations (Scher et al 2008, Scher et al 2011).

Note: same method of examination

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is therefore not acceptable to interchange different modalities throughout this study.

1. ASSESSMENT OF MALIGNANT SOFT TISSUE DISEASE BY MODIFIED RECIST CRITERIA

This section details the implementation of modified RECIST v1.1 guidelines for the study with regards to investigator assessment of malignant soft tissue tumour burden.

Note: In this study, bone lesions will not be included in the RECIST assessment as target lesions, non-target-lesions (NTL) or new lesions. The guidelines for bone lesion assessments are defined in Section 2 of this appendix document.

1.1 Definition of measurable, non-measurable, target and non-target lesions

Patients with at least one soft lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computerised tomography (CT) or magnetic resonance imaging (MRI) will be assessed in accordance with the following guidelines.

1.1.1 Measurable lesions

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

1.1.2 Non-measurable lesions

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis) at baseline. Nodes with <10 mm short axis are considered non-pathological and should not be recorded as NTL

- Truly non-measurable lesions include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic

involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI

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

- Skin lesions assessed by clinical examination

- Brain metastasis.

1.1.3 Special cases

- Soft tissue lesion that derives from a lytic bone lesion and meets the definition of measurability on CT/MRI can be considered measurable and recorded as a target lesion. The guidelines for bone lesion assessments are defined in Section 2 of this appendix document.

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

1.1.4 Target lesions

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

1.1.5 Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline (except bone lesions which will be assessed as defined in Section 2 of this appendix document).

1.2 Methods of measurement

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

The methods to be used for RECIST assessment are summarised in Table 1 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 1 Summary of methods of assessment

Target lesions	Non target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Chest X-ray	Chest X-ray
	Clinical examination	Ultrasound

1.2.1 CT and MRI

Computerised tomography and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In this study it is recommended that CT examinations be used to assess tumour burden. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

1.2.2 Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT or MRI.

1.2.3 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs (eg, pleural effusion) and to identify the presence of new lesions.

1.2.4 Ultrasound

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

1.2.5 Endoscopy and laparoscopy

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

1.2.6 Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST v1.1.

In this study PSA and CTC biomarkers are being collected for separate analysis. However the results will not contribute to tumour response based on RECIST v1.1 assessment.

1.2.7 Cytology and histology

Histology will not be used as part of the tumour response assessment per RECIST v1.1.

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

1.3 Tumour response evaluation

1.3.1 Schedule of evaluation

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 4 weeks (28 days) before the start of study treatment. On-study assessments should be performed every 12 weeks (±1 week) until progression, death or withdrawal of consent.

Please refer to the study plan in Section 3.1 of the Clinical Study Protocol for the tumour assessment schedule.

Any other sites at which new disease is suspected should also be adequately imaged after baseline.

1.3.2 Target lesions

1.3.2.1 Documentation of target lesions

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

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

as the baseline sum of diameters. At subsequent assessment visits the sum of diameters for all TLs will be calculated and reported as the sum of diameters at that visit.

Special cases:

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

1.3.2.2 Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 2 Visit response for target soft tissue lesions

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

1.3.3 Non-target lesions

1.3.3.1 Evaluation of non-target lesions

Note: In this study, bone lesions will not be included in the RECIST assessment as NTL. The guidelines for all other bone lesion assessments are defined in Section 2 of this appendix document.

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 3 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 3 Visit response for non-target soft tissue lesions

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

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

1.3.4 New lesions

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

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

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

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

1.3.5 Symptomatic deterioration

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

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

1.3.6 Evaluation of RECIST visit response for soft tissue lesions

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

Table 4 Overall visit response for soft tissue lesions

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

CR complete response; NA not applicable (relevant when no TLs/NTLs at baseline); NE not evaluable; NED no evidence of disease; PD progressive disease; PR partial response; SD stable disease

2. ASSESSMENT OF BONE LESIONS

In this study, bone lesions will be assessed by bone scintigraphy (bone scans). Whole body anteroposterior (AP) and posteroanterior (PA) bone scans should be performed.

2.1 Schedule of evaluation

A baseline bone scan should be performed a maximum of 4 weeks (28 days) before the start of study treatment.

On-study assessments should be performed every 12 weeks (±1 week) until disease progression, discontinuation of study treatment or withdrawal of consent.

Scans for confirmation of progression will be performed preferably at the next scheduled visit and at least 6 weeks after the initial scan where possible progression is identified.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 3.1 of the Clinical Study Protocol for the tumour assessment schedule.

2.2 Assessment of progression in bone lesions

Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment.

- Positive hot spots on a bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions.

Progression on a bone scan is assessed as:

At the 12 week scan:

If 2 or more new metastatic bone lesions are observed on the first 12-week scan, the confirmatory scan performed, preferably at the next scheduled visit for a bone scan (ie, Week 24) and at least 6 weeks later, must show 2 or more additional new metastatic bone lesions (for a total of 4 or more new metastatic bone lesions since the baseline assessment) for progression to be documented.

After the 12 week scan:

If 2 or more new metastatic bone lesions are observed on scans obtained after the first 12-week assessment, confirmatory scan performed preferably at the next scheduled visit for a bone scan (eg, Week 36) and at least 6 weeks later needs to show the persistence of or an increase in the number of metastatic bone lesions compared to the prior scan.

The date of progression is the date of the first scan that shows the change.

2.3 Evaluation of PCWG2 response for bone lesions

Table 5 provides the definitions of the criteria to determine tumour visit response for bone lesions.

Table 5 Overall PCWG2 response for bone lesions

Non –Progressive Disease (non-PD)	Persistence of one or more bone lesions.
Progressive Disease (PD)	Bone lesions fulfilling the requirements for new lesions and confirmation of progression
Non Evaluable (NE)	Only relevant if a bone scan is not performed at that visit.

3. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

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

3.1 CT scans

Computerised tomography scans of the chest, abdomen and pelvis should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST v1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

3.1.1 Anatomic coverage

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

3.1.2 Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on subsequent

examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations.

3.1.3 Slice thickness and reconstruction material

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

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

3.2 MRI scans

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

3.3 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST v1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

4. REFERENCES

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Clinical Study Protocol Appendix G	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

Appendix G
Eastern Cooperative Oncology Group (ECOG) Performance Status

1. ECOG PERFORMANCE STATUS

Patient ability	**Score**
Fully active, able to carry on all pre-disease performance without restriction	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work	**1**
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours	**2**
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	**3**
Completely disabled, unable to carry out any self-care and confined totally to bed or chair	**4**

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Clinical Study Protocol Appendix H	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

Appendix H
Brief Pain Inventory (Short Form)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

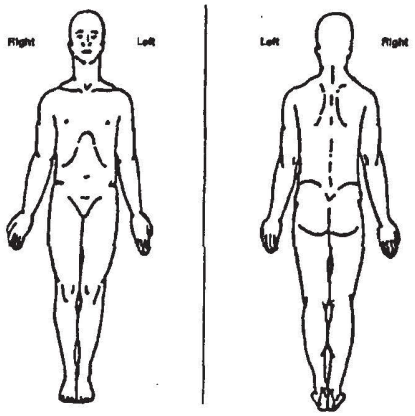
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

_____

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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Clinical Study Protocol Appendix I	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

Appendix I
Bone Pain Item

Please rate your **bone pain** by circling the one number that best describes your **bone pain** at its **worst** in the last 24 hours.										
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
No Bone Pain										**Bone pain as bad as you can imagine**

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Clinical Study Protocol Appendix J	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

Appendix J
FACT-P (Version 4)

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

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

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

FACT-P (Version 4)

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

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

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

FACT-P (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

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Clinical Study Protocol Appendix K	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	2
Date	11 December 2013

Appendix K
EQ-5D-5L Health Questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

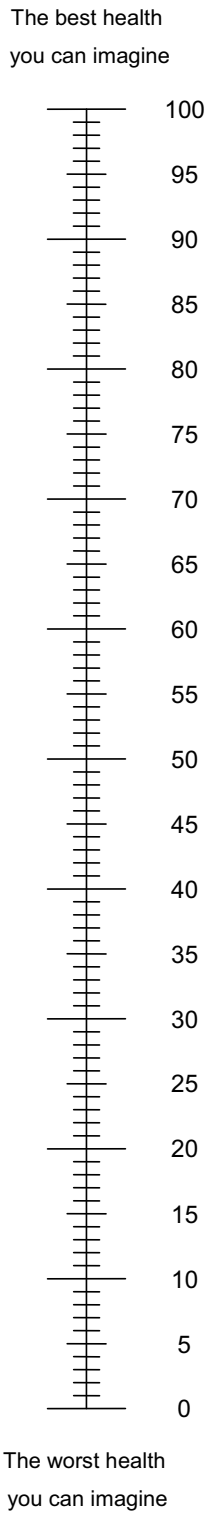
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Revised Clinical Study Protocol Appendix L	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number 2	
Date	20 October 2015

Appendix L
Acceptable Birth Control Methods

ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high foetal risk

Patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination (as listed below), throughout the period of taking study treatment and for 3 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below), when this is in line with their preferred and usual lifestyle. Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug(s).

Acceptable non-hormonal birth control methods include

- Total sexual abstinence (when this is in line with the preferred and usual lifestyle). Abstinence must continue for the total duration of study treatment and for at least 3 months after the last dose. Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom.
- Intra-uterine device (IUD) PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal birth control methods include

- Normal and low dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom
- Etonogestrel implants (eg., Implanon, Norplant) PLUS male condom.
- Norelgestromin / Ethinyl Estradiol (EE) transdermal system PLUS male condom.
- Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (eg., EE and etonogestrel) PLUS male condom

Clinical Study Protocol Amendment	
Amendment Number	2
Drug Substance	Olaparib (AZD2281, KU 0059436)
Study Code	D081DC00008
Date	13 October 2015
Protocol Dated	11 December 2013

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

All centres

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

Summary of changes:

Change 1: Synopsis, Objectives, Secondary Part B

Change 2: Synopsis, Study design, Part B: Randomised part

Change 3: Synopsis, Secondary outcome variables Part B

Change 4: List of Abbreviations and Definitions of Terms

Change 5: Section 1.1.3, Rationale for olaparib in prostate cancer

Change 6: Section 2.2, Secondary objectives, Table 2

Change 7: Table 8, Study Plan Part B, Randomised Part

Change 8: Section 5.1, Restrictions during the study, Contraception

Change 9: Section 5.5.4, Additional study drug abiraterone and prednisone/prednisolone

Change 10: Section 5.6.1, Olaparib and CYP3A4

Change 11: Section 5.8.1.1, Discontinuation of olaparib/placebo only

Change 12: Section 5.8.1.2, Discontinuation of abiraterone only

Change 13: Section 5.10.1, Dose reduction and toxicity management

Change 14: Section 5.10.1.2, Management of anaemia

Change 15: Section 6.7.1.3, Archival tumour samples for biomarker analysis

Change 16: Section 11.5.3, ERG expression/fusion status

Change 17: Section 12.2.1.1, Radiological progression-free survival

Change 18: Section 14, References

Change 19: Appendix A, Signatures, Medical Science Director

Change 20: Appendix A, Signatures, Global Product Statistician

Change 21: Appendix L, Acceptable birth control methods

Key:

~~Strikethrough~~ deletion of text
Bold – additional/changed text

Change 1

Section of protocol affected:

Synopsis, Objectives, Secondary Part B

Previous text:

[...]

To investigate ERG expression/fusion status and BRCA mutation as candidate predictors of response to olaparib. Note: This objective is dependent upon the number of evaluable samples obtained from the study.

Revised text:

[...]

To investigate ~~ERG expression/fusion status and~~ **BRCA and ATM** mutation**s** as candidate predictors of response to olaparib. Note: This objective is dependent upon the number of evaluable samples obtained from the study.

Reason for Amendment:

Change in the study secondary objectives to reflect the scientific knowledge which came from the TOPARP trial (Mateo et al 2015), which has shown olaparib activity (> 80% response rate) in the subgroup of patients who displayed DNA damage response defect gene signature. This finding suggests that olaparib activity in prostate cancer is supposed to rely on synthetic lethality with the concept of BRCAness such as in other tumour types.

Persons who initiated the Amendment:

AstraZeneca

Change 2

Section of protocol affected:

Synopsis, Study design, Part B: Randomised part

Previous text:

[...]

An archival tumour sample will be collected, where available, to measure ERG expression/fusion status and BRCA mutation other biomarkers such as androgen receptor (AR) and phosphatase and tensin homolog (PTEN) may also be measured.

[...]

Revised text:

[...]

An archival tumour sample will be collected, where available, to measure ~~ERG expression/fusion status and~~ **BRCA and ATM mutation status;** other biomarkers such as **ERG expression/fusion status, homologous recombination related gene mutations**, androgen receptor (AR) and phosphatase and tensin homolog (PTEN) may also be measured.

[...]

Reason for Amendment:

To reflect changes in the study secondary objectives.

Persons who initiated the Amendment:

AstraZeneca

Change 3

Section of protocol affected:

Synopsis, Secondary outcome variables Part B

Previous text:

- **Biomarkers**

  Percentage change from baseline in PSA levels and PSA response

  Change in CTC numbers

  ERG expression/fusion and BRCA status; if the number of events in these groups is sufficient then the primary analysis of rPFS will be repeated in all ERG expression/fusion-positive and BRCA mutation patients.

Revised text:

- **Biomarkers**

  Percentage change from baseline in PSA levels and PSA response

  Change in CTC numbers

  ~~ERG expression/fusion and~~ **BRCA and ATM mutation status**; if the number of events in these groups is sufficient then the primary analysis of rPFS will be repeated in all ~~ERG expression/fusion~~ **BRCA and ATM mutation positive patients.**

Reason for Amendment:

To reflect changes in the study secondary objectives.

Persons who initiated the Amendment:

AstraZeneca

Change 4

Section of protocol affected:

List of Abbreviations and Definitions of Terms

Previous text:

None

Revised text:

Abbreviation or special term	Explanation
[…]	**[…]**
ATM	**Ataxia telangiectasia mutated gene**
[…]	**[…]**
BRCP	**Breast cancer resistance protein**
[…]	**[…]**
MATE	**Multidrug and toxin extrusion protein**
mCRPC	**Metastatic Castration Resistant Prostate Cancer**
[…]	**[…]**
OAT	**Organic anion transporter**
[…]	**[…]**
Pgp	**P-glycoprotein**
[…]	**[…]**
UGT	**UDP-glucuronosyltransferase**

Reason for Amendment:

To update list of abbreviations or special terms used in protocol.

Persons who initiated the Amendment:

AstraZeneca

Change 5

Section of protocol affected:

Section 1.1.3, Rationale for olaparib in prostate cancer

Previous text:

[...]

Although only a small number of patients have germline mutations (Castro et al 2013), the number with somatic mutations may be significantly higher (Beltran et al 2013).

Revised text:

[...]

Although only a small number of patients have germline mutations (Castro et al 2013), the number with somatic mutations may be significantly higher (Beltran et al 2013). **Recent clinical data suggest that PTEN and TEMPRSSERG are not key determinants of PARP**

inhibitor sensitivity in mCRPC but do strongly suggest that mutations in DNA repair genes, in particular BRCA2 and ATM, are associated with response to, and duration of therapy on, olaparib (Mateo et al 2015).

Reason for Amendment:

To update study rationale based on the recent scientific findings.

Persons who initiated the Amendment:

AstraZeneca

Change 6

Section of protocol affected:

Section 2.2, Secondary objectives, Table 2

Previous text:

Table 2 Secondary objectives

Secondary objective	Secondary outcome variables
To investigate ERG expression/fusion status and BRCA mutation as candidate predictors of response to olaparib. Note: This objective is dependent upon the number of evaluable samples obtained from the study.	ERG expression/fusion and BRCA status; if the number of events in these groups is sufficient then the primary analysis of rPFS will be repeated in all patients with BRCA and ATM mutations.

Revised text:

Table 2 Secondary objectives

Secondary objective	Secondary outcome variables
To investigate ~~ERG expression/fusion status and~~ **BRCA and ATM** mutation**s** as candidate predictors of response to olaparib. Note: This objective is dependent upon the number of evaluable samples obtained from the study.	~~ERG expression/fusion and~~ **BRCA and ATM** mutation status; if the number of events in these groups is sufficient then the primary analysis of rPFS will be repeated in all ~~ERG expression/fusion positive and BRCA patients~~ **patients with BRCA and ATM mutations**.

Reason for Amendment:

To reflect changes in the study secondary objectives.

Persons who initiated the Amendment:

AstraZeneca

Change 7

Section of protocol affected:

Table 8, Study Plan Part B, Randomised Part

Previous text:

Visit	**[…]**	**7+[o]**
Blood samples for haematology and clinical chemistry (local)[j]	**[…]**	X (from Week 64)

Revised text:

Visit	**[…]**	**7+[o]**
Blood samples for haematology and clinical chemistry (local)[j]	**[…]**	X (from Week ~~64~~**60**)

Reason for Amendment:

To correct discrepancy in numbering visits and weeks.

Persons who initiated the Amendment:

Quintiles

Change 8

Section of protocol affected:

Section 5.1, Restrictions during the study, Contraception

Previous text:

Patients should be asked to avoid unprotected sex with women of child-bearing potential during the trial and for a washout period of 3 months. Where there are effects on spermatogenesis, patients should avoid procreation for 3 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 3 months after discontinuing study treatment. If patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

See Appendix L for details of acceptable birth control methods to be used within the study.

Revised text:

~~Patients should be asked to avoid unprotected sex with women of child-bearing potential during the trial and for a washout period of 3 month. Where there are effects on spermatogenesis, patients should avoid procreation for 3 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 3 months after discontinuing study treatment.~~

Patients and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination, throughout the period of taking study treatment and for 3 months after last dose of study drugs due to the unknown effects of the study drugs on the sperm, or they must totally/truly abstain from any form of sexual intercourse when this is in line with their preferred and usual lifestyle. Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drugs.

If patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

See Appendix L for details of acceptable birth control methods to be used within the study.

Reason for Amendment:

To reflect changes in AstraZeneca's acceptable birth control methods for clinical trial purposes.

Persons who initiated the Amendment:

AstraZeneca

Change 9

Section of protocol affected:

Section 5.5.4, Additional study drug abiraterone and prednisone/prednisolone

Previous text:

[...]

Dose interruptions and reductions will not be permitted for abiraterone, prednisone or prednisolone.

Revised text:

[...]

Dose interruptions and reductions will not be permitted for abiraterone, prednisone or prednisolone **only during part A**. **Dose modifications strategies of abiraterone and prednisone or prednisolone during part B are detailed in section 5.10.1.9.**

Reason for Amendment:

To clarify dose interruptions and reductions strategy and to be consistent with other sections of protocol.

Persons who initiated the Amendment:

AstraZeneca

Change 10

Section of protocol affected:

Section 5.6.1, Olaparib and CYP3A4

Previous text:

5.6.1 Olaparib and CYP3A4

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin, and nelfinavir

For patients taking any of the above, the required washout period prior to starting olaparib is 1 week.

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers should be avoided:

- phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil, and St. John's Wort

For patients taking any of the above, the required washout periods prior to starting olaparib in Part A are:

- phenobarbitone, 5 weeks
- for any of the others, 3 weeks.

If the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare during Part B, the Investigator must contact the AstraZeneca Physician or their designated Medical Monitor. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Long term use of potent inducers and inhibitors of CYP3A4 should be avoided. If a decision is made to allow patients to use a potent inducer or inhibitor then they must be monitored carefully for any change in efficacy or safety of olaparib.

Revised text:

5.6.1 Olaparib and ~~CYP3A4~~ **drug-drug interactions**

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in eCRF.

~~Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.~~

Effect of Other Drugs on Olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Clinical studies to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a potent CYP3A inhibitor increased olaparib Cmax 1.42-fold (90% CI: 1.33-1.52) and increased mean AUC 2.70-fold (90% CI: 2.44-2.97) and that co-administration of a potent CYP inducer decreased Cmax by 71% (Treatment ratio: 0.29; 90% CI: 0.24-0.33) and mean AUC by 87% (Treatment ratio: 0.13; 90% CI: 0.11-0.16). It is therefore recommended that known strong inhibitors or inducers of these isozymes should be avoided with olaparib.

While this is not an exhaustive list, it covers the known potent **CYP3A4/5** inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, **boosted protease inhibitors (**ritonavir, indinavir, saquinavir, telithromycin, nelfinavir, **boceprevir, telaprevir**) and clarithromycin

For patients taking any of the above, the required washout period prior to starting olaparib is 1 week.

In addition, to avoid potential reductions in exposure due to drug interactions, the following **CYP3A4/5** inducers should be avoided:

- phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbit~~one~~**al**, nevirapine, modafinil, and St. John's Wort

For patients taking any of the above **CYP3A4/5 inducers**, the required washout periods prior to starting olaparib in Part A are:

- phenobarbit~~one~~**al**, 5 weeks
- for any of the others, 3 weeks.

If the use of any potent inducers or inhibitors of **CYP3A4/5** are considered necessary for the patient's safety and welfare during Part B, the Investigator must contact the AstraZeneca Physician or their designated Medical Monitor. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Long term use of potent inducers and inhibitors of **CYP3A4/5** should be avoided. If a decision is made to allow patients to use a potent inducer or inhibitor then they must be monitored carefully for any change in efficacy or safety of olaparib.

In vitro olaparib is a substrate for the efflux transporter Pgp. Clinical studies to evaluate the impact of known Pgp inhibitors and inducers have not been conducted.

Effect of Olaparib on Other Drugs

Olaparib can inhibit CYP3A4 and UGT1A1 *in vitro*. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP3A4 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and Pgp is unknown. It cannot be excluded that olaparib upon co administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

In vitro olaparib has been shown to be an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. It cannot be excluded that olaparib may increase the exposure to substrates of P gp (eg, statins, digoxin, dabigatran, colchicine), OATP1B1 (eg, bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (eg, metformin), OCT2 (eg, serum creatinine), OAT3, MATE1 and MATE2K. In particular, caution should be exercised if olaparib is administered in combination with any statin.

Reason for Amendment:

To reflect recent findings on olaparib drug-drug interactions.

Persons who initiated the Amendment:

AstraZeneca

Change 11

Section of protocol affected:

Section 5.8.1.1, Discontinuation of olaparib/placebo only

Previous text:

If a patient discontinues olaparib/placebo but remains on abiraterone, procedures should be followed for the discontinuation and follow-up visit.

Revised text:

If a patient discontinues olaparib/placebo but remains on abiraterone, procedures should be followed for the discontinuation and follow-up visits. **For randomised part B see Table 9.**

[a]Reason for Amendment:

To clarify patient management after olaparib/placebo discontinuation.

Persons who initiated the Amendment:

AstraZeneca

Change 12

Section of protocol affected:

Section 5.8.1.2, Discontinuation of abiraterone only

Previous text:

Patients who discontinue abiraterone and remain on olaparib/placebo should continue to be seen and have assessments performed as outlined in the study plans (see Table 4, Table 5 and Table 8). Once olaparib/placebo treatment is permanently discontinued, procedures should be followed for the discontinuation and follow-up visits.

Revised text:

Patients who discontinue abiraterone and remain on olaparib/placebo should continue to be seen and have assessments performed as outlined in the study plans (see Table 4, Table 5 and Table 8). Once olaparib/placebo treatment is permanently discontinued, procedures should be followed for the discontinuation and follow-up visits. **For randomised part B see Table 9.**

[a]Reason for Amendment:

To clarify patient management after abiraterone discontinuation.

Persons who initiated the Amendment:

AstraZeneca

Change 13

Section of protocol affected:

Section 5.10.1, Dose reduction and toxicity management strategy

Previous text:

Dose interruptions are not permitted in Part A of the study until after all PK assessments are complete.

If a patient's dose is reduced or interrupted at the time of a scheduled study visit, they should still attend the clinic for the scheduled assessments.

Revised text:

Dose interruptions are not permitted in Part A of the study until after all PK assessments are complete.

If a patient's dose is reduced or interrupted at the time of a scheduled study visit, they should still attend the clinic for the scheduled assessments.

For olaparib/placebo, once dose is reduced escalation is not permitted.

Reason for Amendment:

To clarify olaparib/placebo dose reduction management.

Persons who initiated the Amendment:

AstraZeneca

Change 14

Section of protocol affected:

Section 5.10.1.2, Management of anaemia

Previous text:

Adverse events of anaemia CTCAE Grade 1 or 2 (Hb >8 g/dL) should be investigated and managed as deemed appropriate by the Investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia.

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases, management of anaemia may require blood transfusions. However, if a patient develops anaemia CTCAE Grade 3 (Hb <8 g/dL) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to >9 g/dL. Any subsequently required anaemia related interruptions considered likely to be dose related, or coexistent with newly developed neutropenia and/or thrombocytopenia, will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by the Investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

Revised text:

Adverse events of anaemia CTCAE Grade 1 or 2 (Hb~~>~~ ≥ 8 g/dL) should be investigated and managed as deemed appropriate by the Investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. **For reference see Table 12.**

~~However, if a patient develops anaemia CTCAE Grade 3 (Hb <8 g/dL) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to >9 g/dL. Any subsequently required anaemia related interruptions considered likely to be dose related, or coexistent with newly developed~~

~~neutropenia and/or thrombocytopenia, will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.~~

~~If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by the Investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.~~

Table 12 Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 *but* **≥ 8 g/dl (CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb**< 10** *but* **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dl	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be ~~excluded~~ **investigated and appropriately managed**. In some cases management of anaemia may require blood transfusions.

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE Grade 3 (Hb <8 g/dL) or worse anaemia and/or development of blood transfusion dependence), refer to section 5.10.1.5 for the management of this.

[a]Reason for Amendment:

To reflect changes in AstraZeneca's anaemia management for olaparib trials.

Persons who initiated the Amendment:

AstraZeneca

Change 15

Section of protocol affected:

Section 6.7.1.3, Archival tumour samples for biomarker analysis

Previous text:

Tumour samples (where available) will be assessed for ERG expression/fusion status and BRCA mutation, and possibly other exploratory biomarkers such as AR and PTEN. Where validated assays are available, other study samples may be used as surrogates of tumour to increase the numbers of patients within molecularly defined subgroups.

Revised text:

Tumour samples (where available) will be assessed for ~~ERG expression/fusion status and~~ **BRCA and ATM mutations**, and possibly other exploratory biomarkers such as AR and PTEN. Where validated assays are available, other study samples may be used as surrogates of tumour to increase the numbers of patients within molecularly defined subgroups.

Reason for Amendment:

To reflect changes in the study secondary objectives.

Persons who initiated the Amendment:

AstraZeneca

Change 16

Section of protocol affected:

11.5.3 ERG expression/fusion status

Previous text:

11.5.3 ERG expression/fusion status

Samples will be assessed for the expression of ERG/ERG fusion. Full details of categorisation will be given in the statistical analysis plan (SAP).

Revised text:

11.5.3 ~~ERG expression/fusion status~~ **ATM mutation**

Samples will be assessed for ~~the expression of ERG/ERG fusion~~ **ATM mutation**. Full details of categorisation will be given in the statistical analysis plan (SAP).

Reason for Amendment:

To reflect changes in the study secondary objectives.

Persons who initiated the Amendment:

AstraZeneca

Change 17

Section of protocol affected:

Section 12.2.1.1, Radiological progression-free survival

Previous text:

Separate log-rank tests of rPFS will be undertaken using patients who are positive for ERG expression/fusion status and also for patients who have BRCA mutations, using the same model as for the primary analysis. If the number of patients in each subgroup is small, consideration will be given to merging the subgroups prior to analysis.

Revised text:

Separate log-rank tests of rPFS will be undertaken using patients ~~who are positive for ERG expression/fusion status and also for patients~~ **who have BRCA or ATM mutations**, using the same model as for the primary analysis. If the number of patients in each subgroup is small, consideration will be given to merging the subgroups prior to analysis.

Reason for Amendment:

To reflect changes in the study secondary objectives.

Persons who initiated the Amendment:

AstraZeneca

Change 18

Section of protocol affected:

Section 14, References

Previous text:

None

Revised text:

[...]

Mateo et al 2015
Mateo J, Sandhu S, Miranda S, Carreira S, Suneil J, Christy R, et al. DNA repair defects and antitumor activity with PARP inhibitors: TOPARP, a phase II trial of olaparib in metastatic castration resistant prostate cancer. Proceedings: AACR 106th Annual Meeting 2015; April 18-22, 2015; Philadelphia, PA

[...]

Reason for Amendment:

A new reference has been added to protocol to support the change in the secondary objectives.

Persons who initiated the Amendment:

AstraZeneca

Change 19

Section of protocol affected:

Appendix A, Signatures, Medical Science Director

Previous text:

AstraZeneca Research and Development site representative

Jane Robertson, MD MRCP FRCPath Medical Science Director AstraZeneca R&D Alderley Park Macclesfield Cheshire, SK10 4TG UK PPD	Date (Day Month Year)

Revised text:

AstraZeneca Research and Development site representative

Mika Sovak MD **Medical Science Director** **AstraZeneca** **Gaithersburg, MD** **USA** PPD	Date (Day Month Year)

Reason for Amendment:

To reflect a change in study personnel.

Persons who initiated the Amendment:

AstraZeneca

Change 20

Section of protocol affected:

Appendix A, Signatures, Global Product Statistician

Previous text:

AstraZeneca Research and Development site representative

Helen Mann MSc Global Product Statistician AstraZeneca R&D Alderley Park, Macclesfield Cheshire, SK10 4TG UK PPD	Date (Day Month Year)

Revised text:

AstraZeneca Research and Development site representative

Antony Sabin **Global Product Statistician** **AstraZeneca R&D** **Da Vinci Building** **Cambridge** **UK** PPD	Date (Day Month Year)

Reason for Amendment:

To reflect a change in study personnel.

Persons who initiated the Amendment:

AstraZeneca

Change 21

Section of protocol affected:

Appendix L, Acceptable birth control methods

Previous text:

ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high foetal risk

If a patient is sexually active and their partner is of childbearing potential, then they and their partner must agree to the use of 2 highly effective forms of contraception in combination throughout their participation in the study and for 3 months after their last dose of study treatment(s):

Acceptable non-hormonal birth control methods include

- Total sexual abstinence. Abstinence must be for the total duration of the trial and 3 months after the last dose of study treatment.
- Male condom + vasectomy (with post-vasectomy confirmation of azoospermia).
- Male condom with spermicide + tubal occlusion.
- Male condom with spermicide + intra-uterine device (IUD) (eg, copper banded coil); your Study Doctor will advise if your partner's current IUD is acceptable.

Acceptable hormonal birth control methods include

- Male condom with spermicide + normal and low dose combined oral pills
- Male condom with spermicide + Cerazette (desogestrel). Cerazette is currently the only highly efficacious progesterone based pill.
- Male condom with spermicide + Etonogestrel implants (e.g., Implanon, Norplan)
- Male condom with spermicide + Norelgestromin / Ethinyl Estradiol transdermal system
- Male condom with spermicide + Intravaginal device eg, ethinyl estradiol and etonogestrel.

Revised text:

~~If a patient is sexually active and their partner is of childbearing potential, then they and their partner must agree to the use of 2 highly effective forms of contraception in combination throughout their participation in the study and for 3 months after their last dose of study treatment(s):~~

Patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for 3 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below), when this is in line with their preferred and usual lifestyle. Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug(s).

- Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence **(when this is in line with the preferred and usual lifestyle).** Abstinence must ~~be for the total duration of the trial and 3 months after the last dose of study treatment~~ **continue for the total duration of study treatment and for at least 3 months after the last dose. Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.**

- ~~Male condom + vasectomy (with post-vasectomy confirmation of azoospermia).~~**Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia**.

- ~~Male condom with spermicide + tubal occlusion.~~**Tubal occlusion PLUS male condom.**

- ~~Male condom with spermicide + intra-uterine device (IUD) (eg, copper banded coil); your Study Doctor will advise if your partner's current IUD is acceptable~~ **Intra-uterine device (IUD) PLUS male condom. Provided coils are copper-banded.**

- Acceptable hormonal methods:

- ~~Male condom with spermicide + normal and low dose combined oral pills.~~ **Normal and low dose combined oral pills PLUS male condom.**

- ~~Male condom with spermicide + Cerazette (desogestrel). Cerazette is currently the only highly efficacious progesterone based pill.~~ **Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.**

- **Hormonal shot or injection (eg., Depo-Provera) PLUS male condom**

- ~~Male condom with spermicide + Etonogestrel implants (e.g., Implanon, Norplan)~~ **Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom.**

- ~~Male condom with spermicide + Norelgestromin / Ethinyl Estradiol transdermal system~~ **Norelgestromin / Ethinyl Estradiol (EE) transdermal system PLUS male condom**

- **Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom**

- ~~Male condom with spermicide + Intravaginal device eg, ethinyl estradiol and etonogestrel~~ **Intravaginal device (e.g., EE and etonogestrel) PLUS male condom**

Reason for Amendment:

To reflect changes in AstraZeneca's acceptable birth control methods for clinical trial purposes.

Persons who initiated the Amendment:

AstraZeneca

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

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

AstraZeneca Research and Development site representative

PPD

Mika Sovak MD
Medical Science Director

Date
(Day Month Year) 10/20/15

AstraZeneca
Gaithersburg, MD
USA

PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

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

AstraZeneca Research and Development site representative

PPD

PPD
Study Leader

16 Oct 2015
Date
(Day Month Year)

Quintiles Srl
Cassina Plaza
Via Roma, 108
20060 Cassina dé Pecchi (MI)

PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

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This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

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

AstraZeneca Research and Development site representative

PPD

16/10/15
Date
(Day Month Year)

Antony Sabin
Global Product Statistician

AstraZeneca R&D
Da Vinci Building
Cambridge
UK

PPD

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

Centre No.: 2801

Signature: PPD

20/10/15.

Date
(Day Month Year)

Professor Noel Clarke
Professor of Urological Oncology

The Christie NHS Foundation Trust
Wilmslow Road
Withington
Manchester M20 4BX
PPD

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Olaparib (AZD2281, KU 0059436)
Study Code	D081DC00008
Date	15 August 2014
Protocol Dated	11 December 2013

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

Centres affected by the Amendment:

All centres.

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

Change 1.1: Synopsis, Study design

Change 1.2: Synopsis, Statistical methods

Change 1.3: Section 1.1.3, Rationale for olaparib in prostate cancer

Change 1.4: Section 3.1.1, Part A: Safety run-in/dose escalation

Change 1.5: Section 3.1.2, Part B: Randomised part

Change 1.6: Section 3.1, Overall study design and flow chart, Figure 2

Change 1.7: Section 3.1, Overall study design and flow chart, Figure 3

Change 1.8: Section 3.1, Overall study design and flow chart, Figure 4

Change 1.9: Section 3.1, Overall study design and flow chart, Figure 5

Change 1.10: Section 3.1, Overall study design and flow chart, Table 4

Change 1.11: Section 3.1, Overall study design and flow chart, Table 5

Change 1.12: Section 3.1, Overall study design and flow chart, Table 8

Change 1.13: Section 3.1, Overall study design and flow chart, Table 9

Change 1.14: Section 6.2.1, Post-treatment

Change 1.15: Section 6.4.3, Recording of adverse events

Change 1.16: Section 6.4.5.2, Clinical chemistry assessments for safety

Change 1.17: Section 7.1, Volume of blood, Table 14 to 16

Change 1.18: Section 9.5, Study timetable and end of study

Change 1.19: Section 12.2.1.1, Radiological progression-free survival

Change 1.20: Section 12.2.1.2, Time to second progression (PFS2)

Change 1.21: Section 12.2.1.3, Overall survival (OS)

Change 1.22: Section 13.3.2, Paternal exposure

Change 1.23: Section 14, References

Change 1.24: Appendix A, Signatures, Medical Science Director

Change 1.25: Appendix A, Signatures, Global Product Statistician

Change 1.26: Appendix E, Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law, Section 2

Change 1.1

Section of protocol affected:

Synopsis, Study design

Previous text:

Part A: Safety run-in/dose escalation

Patients will attend the clinic on the first day of study treatment, then at 1, 2, 4, 8 and 12 weeks, and every 12 weeks thereafter.

[...]

Part B: Randomised part

Patients who have been dosed in Part A of the study may not participate in Part B.

Patients will receive olaparib or placebo (randomisation ratio 1:1), at the dose determined by Part A of the study, and abiraterone 1000 mg once daily. They will attend the clinic on the first day of study treatment, then at 4, 8 and 12 weeks, and every 12 weeks thereafter (every 24 weeks after Week 72).

Revised text:

Part A: Safety run-in/dose escalation

Patients will attend the clinic on the first day of study treatment, at 1 **and** 2 **weeks, then every 4 weeks up to Week 52,** and every 12 weeks thereafter.

[...]

Part B: Randomised part

Patients who have been dosed in Part A of the study may not participate in Part B.

Patients will receive olaparib or placebo (randomisation ratio 1:1), at the dose determined by Part A of the study, and abiraterone 1000 mg once daily. They will attend the clinic on the first day of study treatment, then **every 4 weeks up to Week 52,** and every 12 weeks thereafter.

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

Change 1.2

Section of protocol affected:

Synopsis, Statistical methods

Previous text:

The primary endpoint of Part B is rPFS. The sample size of 140 patients will have 80% power to detect a significant difference at the 1-sided 10% level after 100 events have occurred in the full analysis set, if the assumed true treatment effect was hazard ratio (HR) 0.65. This translates to a 3.75 month benefit in median rPFS on olaparib given with abiraterone compared to placebo given with abiraterone. Cox proportional hazards model and Kaplan-Meier summaries will be undertaken for the primary and sensitivity analyses of rPFS, and all other secondary and exploratory time-to endpoints.

Revised text:

The primary endpoint of Part B is rPFS. The sample size of 140 patients will have 80% power to detect a significant difference at the 1-sided 10% level after 100 events have occurred in the full analysis set, if the assumed true treatment effect was hazard ratio (HR) 0.65. This translates to a 3.75 month benefit in median rPFS on olaparib given with abiraterone compared to placebo given with abiraterone. **A log-rank test** and Kaplan-Meier summaries will be undertaken for the primary and sensitivity analyses of rPFS, and all other secondary and exploratory time-to endpoints.

Reason for Amendment:

A log-rank test has replaced the Cox proportional hazard model as the primary analysis for the time-to-event endpoints, based on recommendations from the United States (US) Food and Drug Administration (FDA).

Persons who initiated the Amendment:

AstraZeneca

Change 1.3

Section of protocol affected:

Section 1.1.3, Rationale for olaparib in prostate cancer

Previous text:

This study will evaluate the investigational drug olaparib when given on a background of the approved drug abiraterone in patients with metastatic CRPC. Part A of this study will provide an initial assessment of safety/tolerability and potential for pharmacokinetic (PK) interaction

between the drugs. For the randomised phase of this study, only post-chemotherapy CRPC patients will be studied (chemotherapy-naive CRPC patients will be recruited in another study). This therefore facilitates a robust assessment of the primary endpoint of radiologic progression-free survival (radiologic PFS, rPFS) within a reasonable timeframe for a Phase II study.

Revised text:

This study will evaluate the investigational drug olaparib when given on a background of the approved drug abiraterone in patients with metastatic CRPC. Part A of this study will provide an initial assessment of safety/tolerability and potential for pharmacokinetic (PK) interaction between the drugs. For the randomised phase of this study, only post-chemotherapy CRPC patients will be studied. This therefore facilitates a robust assessment of the primary endpoint of radiologic progression-free survival (radiologic PFS, rPFS) within a reasonable timeframe for a Phase II study.

Reason for Amendment:

Text referring to a separate study to be run in chemotherapy-naive CRPC patients has been removed as this study is not currently planned.

Persons who initiated the Amendment:

AstraZeneca

Change 1.4

Section of protocol affected:

Section 3.1.1, Part A: Safety run-in/dose escalation

Previous text:

Patients will attend the clinic for assessments on the first day of study treatment, then at 1, 2, 4, 8 and 12 weeks, and every 12 weeks thereafter. They will also attend for study treatment supplies at 16 weeks and every 4 weeks thereafter.

Revised text:

Patients will attend the clinic for assessments on the first day of study treatment, at 1 and 2 weeks, **then every 4 weeks up to Week 52,** and every 12 weeks thereafter. They will also attend for study treatment supplies at 16 weeks and every 4 weeks thereafter.

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

Change 1.5

Section of protocol affected:

Section 3.1.2, Part B: Randomised part

Previous text:

Patients will receive olaparib/placebo 300 mg bid (or 200 mg bid, if 200 mg bid is the maximum tolerated dose in Part A) and abiraterone 1000 mg once daily. They will attend the clinic for assessments on the first day of study treatment, then at 4, 8 and 12 weeks, and every 12 weeks thereafter (every 24 weeks after Week 72). They will also attend for study treatment supplies at 16 weeks and every 4 weeks thereafter.

Revised text:

Patients will receive olaparib/placebo 300 mg bid (or 200 mg bid, if 200 mg bid is the maximum tolerated dose in Part A) and abiraterone 1000 mg once daily. They will attend the clinic for assessments on the first day of study treatment, then **every 4 weeks up to Week 52,** and every 12 weeks thereafter. They will also attend for study treatment supplies at 16 weeks and every 4 weeks thereafter.

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

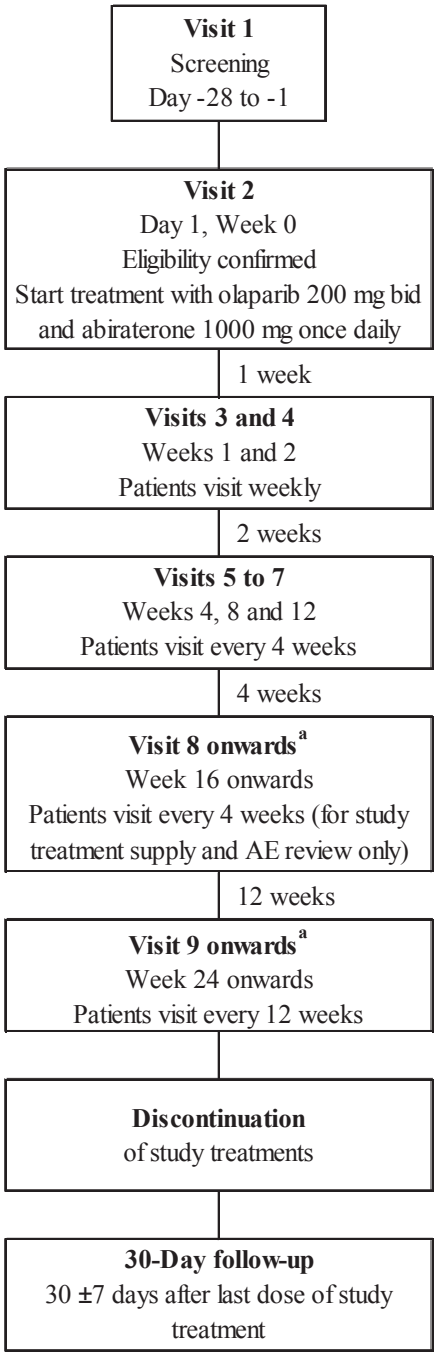
Change 1.6

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Figure 2

Previous text:

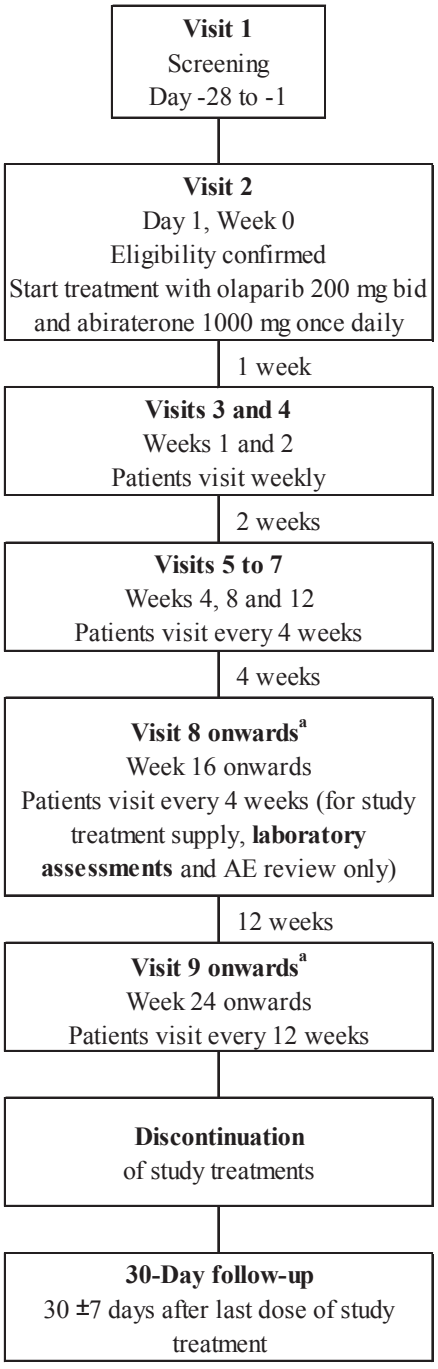
Figure 2 Flow chart for Part A, Cohort 1



[a] Unless patients discontinue study treatment, they will remain in the study and be assessed every 12 weeks until the database for Part A of the study is closed.

Revised text:

Figure 2 Flow chart for Part A, Cohort 1



[a] Unless patients discontinue study treatment, they will remain in the study and be assessed every 12 weeks. **Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.**

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Text referring to patients being assessed every 12 weeks **until the database for Part A of the study is closed** was removed as it was incorrect.

Persons who initiated the Amendment:

AstraZeneca

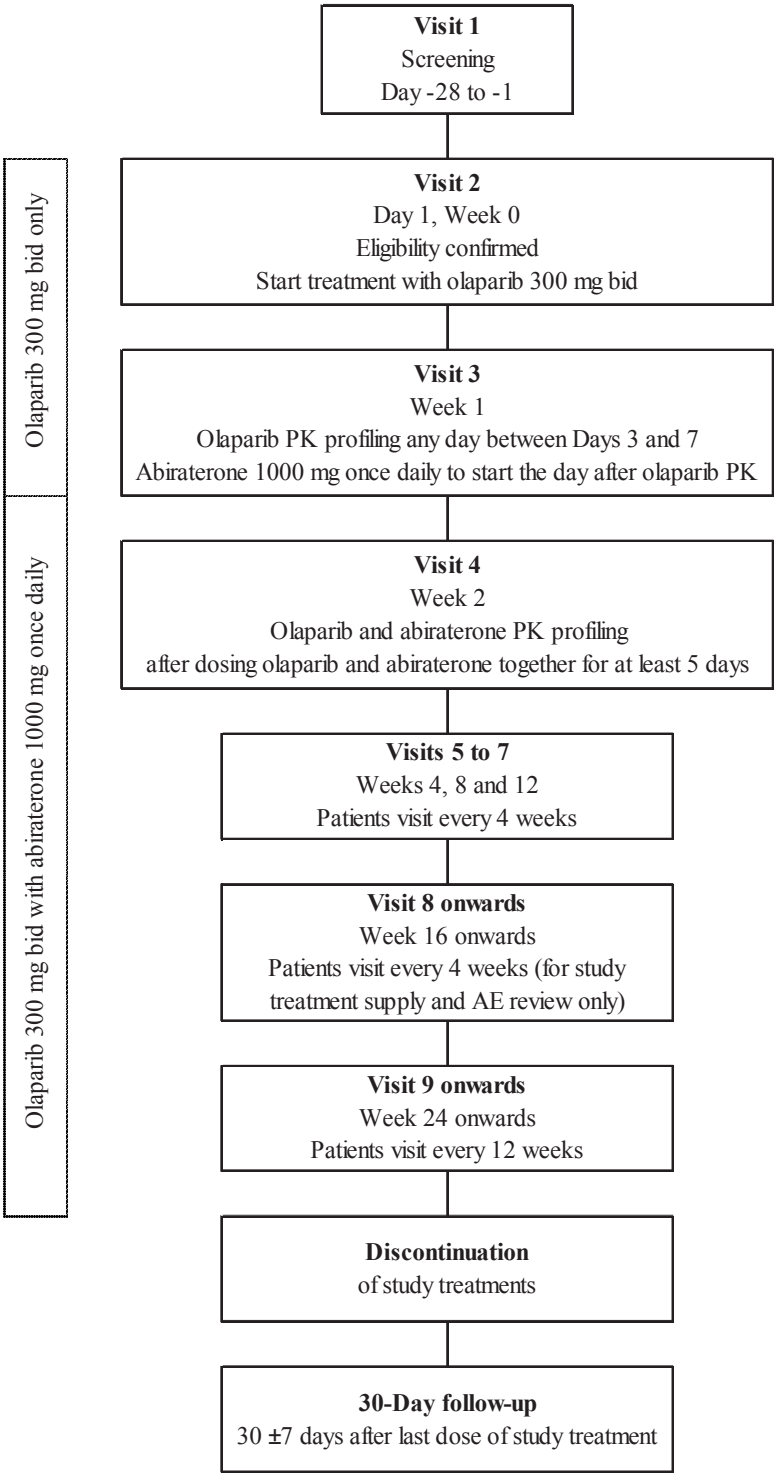
Change 1.7

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Figure 3

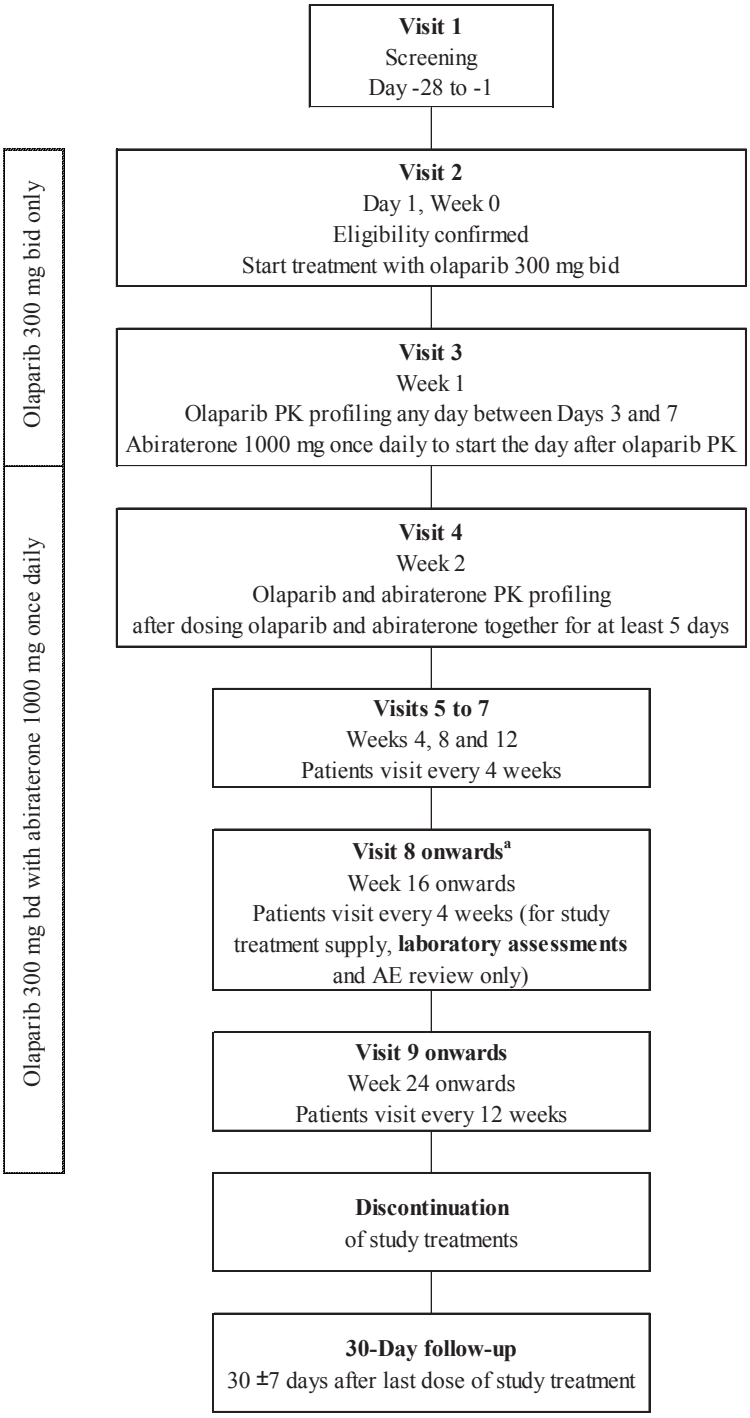
Previous text:

Figure 3 Flow chart for Part A, Cohort 2, Group 1



Revised text:

Figure 3 Flow chart for Part A, Cohort 2, Group 1



[a] **Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.**

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

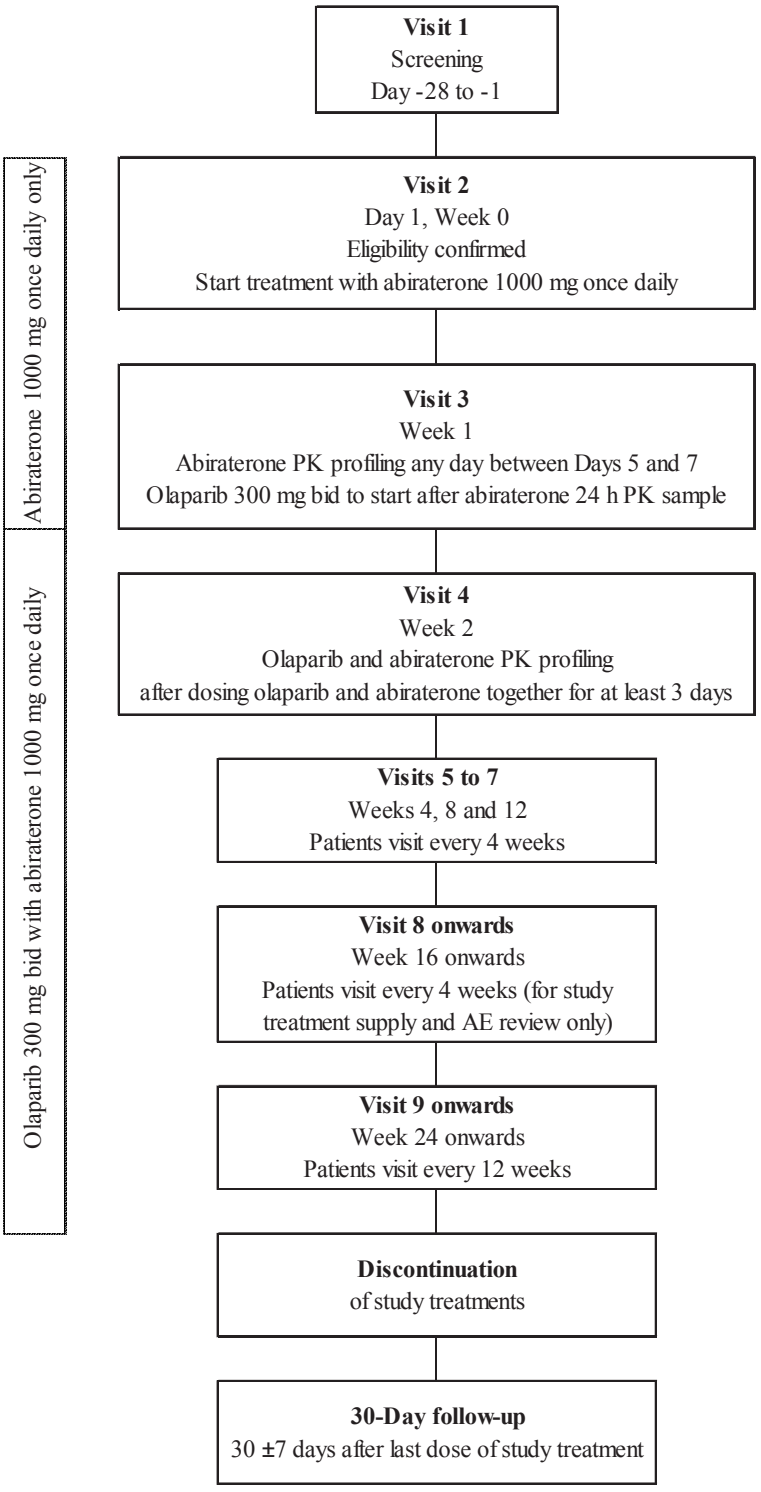
Change 1.8

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Figure 4

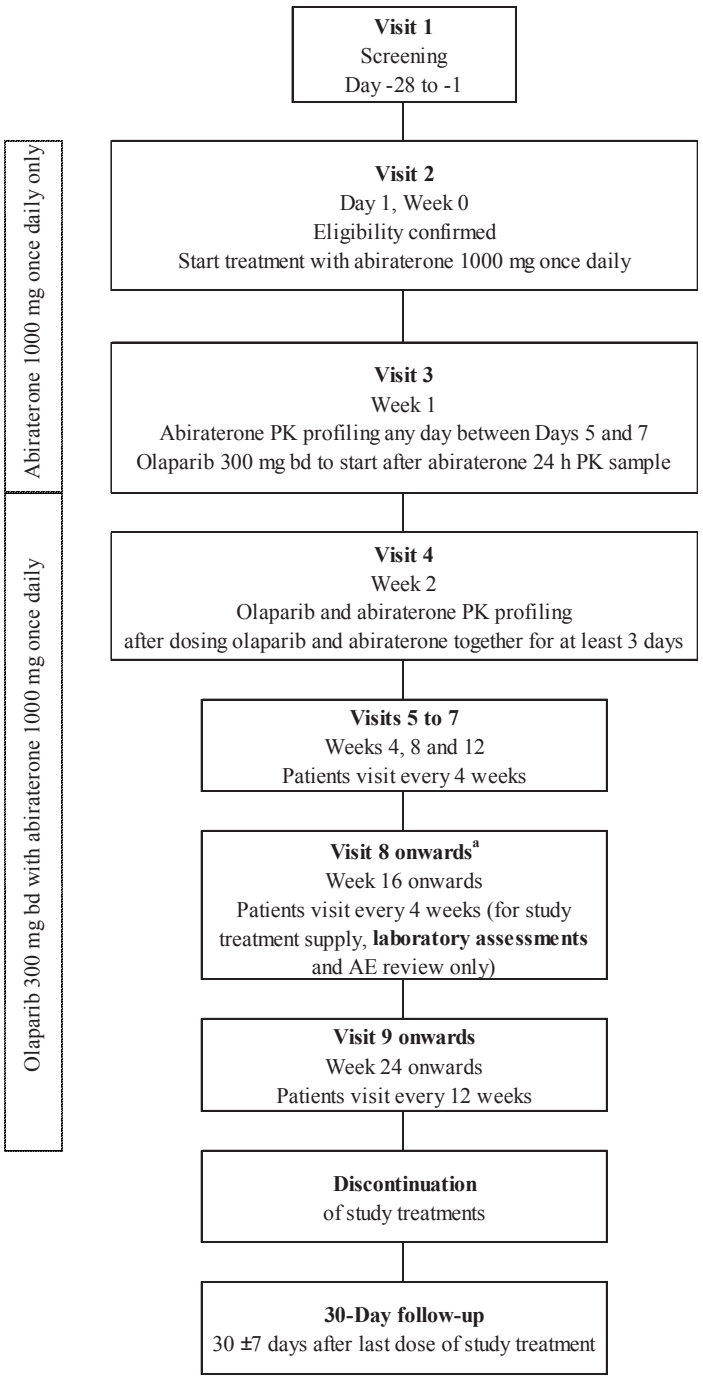
Previous text:

Figure 4 Flow chart for Part A, Cohort 2, Group 2



Revised text:

Figure 4 Flow chart for Part A, Cohort 2, Group 2



[a] **Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.**

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

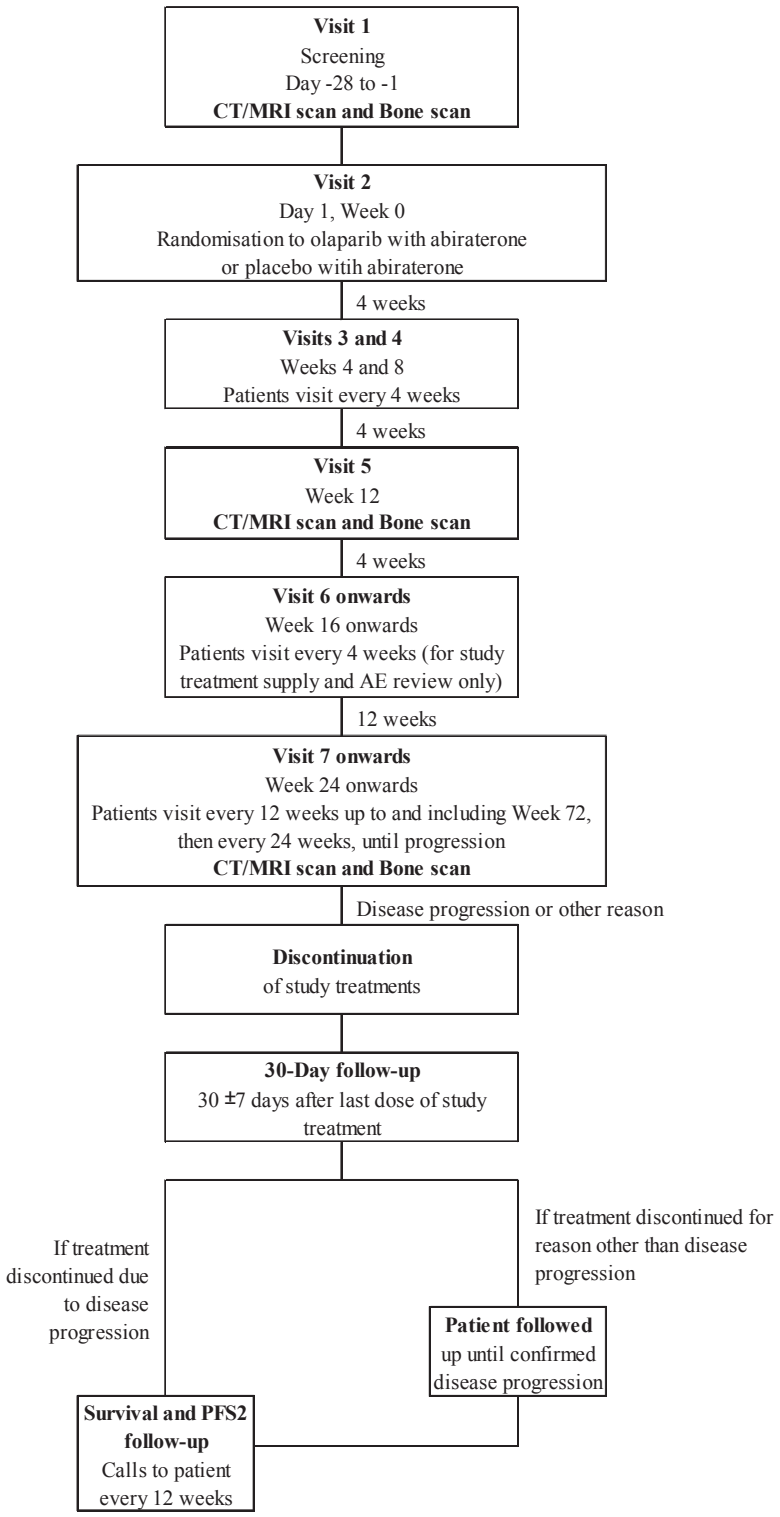
Change 1.9

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Figure 5

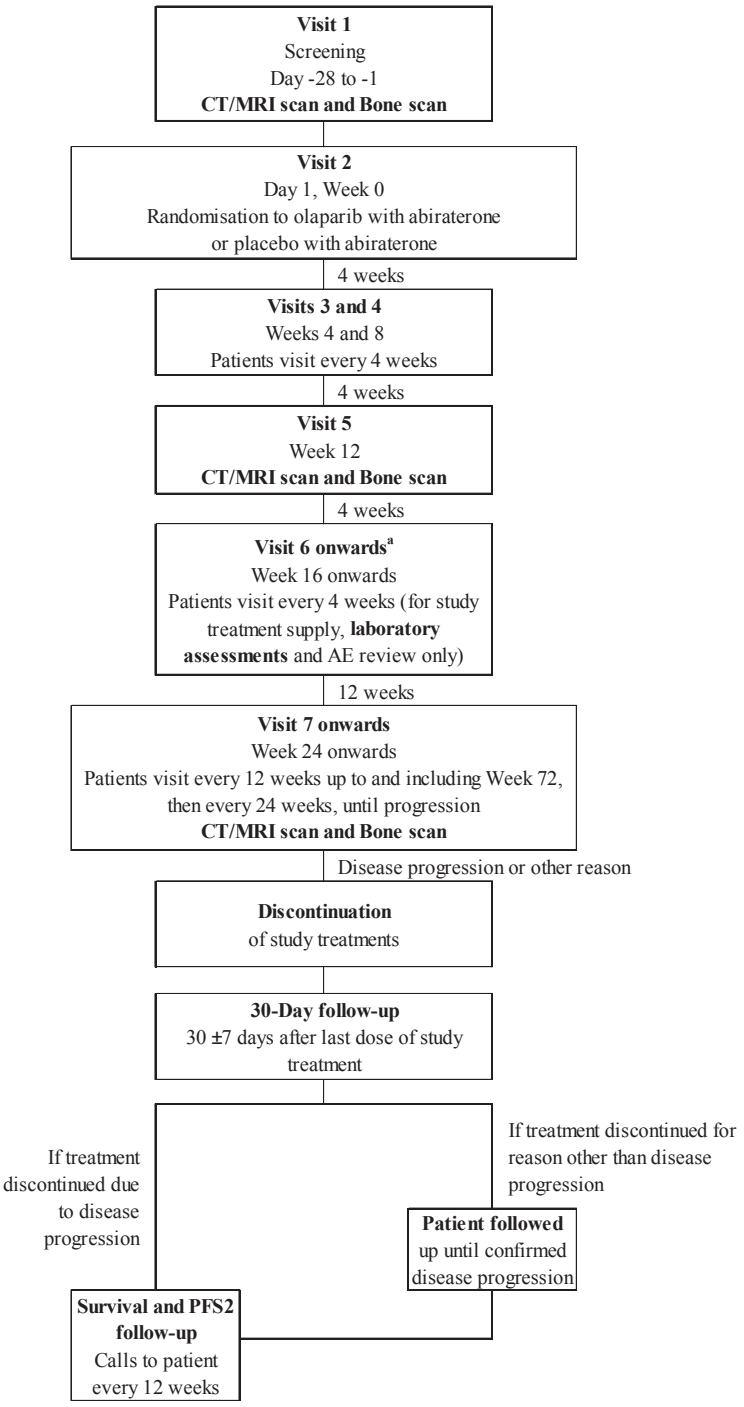
Previous text:

Figure 5 Flow chart for Part B



Revised text:

Figure 5 Flow chart for Part B



[a] **Laboratory assessments will be performed every 4 weeks up to Week 52 while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.**

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

Change 1.10

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Table 4

Previous text:

Table 4 Study Plan – Part A, Cohort 1 (Olaparib 200 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+**	**Discontin-uation of IP**	**30-day follow-up[j]**
Visit window (days)	**–28 to -1**	**±0**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**8**	**15**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Written informed consent	X										
Demographics[a]	X										
Physical examination, height and weight[b]	X										X
Medical/surgical history	X										
ECOG Performance status	X										
Inclusion/exclusion criteria	X	X									
Collect PSA and BRCA status data (local)[c]	X										
12-lead ECG[d]	X										
Vital signs[e]	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication[f]	X	X	X	X	X	X	X		X	X	X
AE and SAE review[g]	X	X	X	X	X	X	X	X	X	X	X
Haematology, clinical chemistry (local)[h]	X	X	X	X	X	X	X		X	X	X

Table 4 Study Plan – Part A, Cohort 1 (Olaparib 200 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+**	**Discontin-uation of IP**	**30-day follow-up[j]**
Visit window (days)	**–28 to -1**	**±0**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**8**	**15**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
PGx blood sample (optional)[i]		X									
Treatment dispensed/returned		X	X	X	X	X	X	X	X	X	

AE adverse event; BRCA Breast cancer gene; ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; IP investigational product; PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race, and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[d] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[e] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[f] Concomitant medication should include all medications taken by the patient before and during the study.

[g] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[h] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). See Section 6.4.5 for a complete list of haematology and chemistry assessments.

[i] Sample will only be collected if separate PGx informed consent has been signed.

[j] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

Revised text:

Table 4 Study Plan – Part A, Cohort 1 (Olaparib 200 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+[j]**	**Discontin-uation of IP**	**30-day follow-up[k]**
Visit window (days)	**–28 to -1**	**±0**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**8**	**15**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Written informed consent	X										
Demographics[a]	X										
Physical examination, height and weight[b]	X										X
Medical/surgical history	X										
ECOG Performance status	X										
Inclusion/exclusion criteria	X	X									
Collect PSA and BRCA status data (local)[c]	X										
12-lead ECG[d]	X										
Vital signs[e]	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication[f]	X	X	X	X	X	X	X		X	X	X
AE and SAE review[g]	X	X	X	X	X	X	X	X	X	X	X
Haematology, clinical chemistry (local)[h]	X	X	X	X	X	X	X	**X (up to Week 52)**	X **(from Week 64)**	X	X

Table 4 Study Plan – Part A, Cohort 1 (Olaparib 200 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+[j]**	**Discontin-uation of IP**	**30-day follow-up[k]**
Visit window (days)	**–28 to -1**	**±0**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**8**	**15**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
PGx blood sample (optional)[i]		X									
Treatment dispensed/returned		X	X	X	X	X	X	X	X	X	

AE adverse event; BRCA Breast cancer gene; ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; IP investigational product; PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race, and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[d] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[e] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[f] Concomitant medication should include all medications taken by the patient before and during the study.

[g] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[h] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). **From Visit 8 (Week 16) onwards, laboratory assessments will be performed every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.** See Section 6.4.5 for a complete list of haematology and chemistry assessments.

[i] Sample will only be collected if separate PGx informed consent has been signed.

[j] **Assessments apply to Visit 9 and subsequent visits occurring every 12 weeks thereafter.**

[k] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

The footnote '**Assessments apply to Visit 9 and subsequent visits occurring every 12 weeks thereafter**' was added to correct an omission in the protocol.

Persons who initiated the Amendment:

AstraZeneca

Change 1.11

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Table 5

Previous text:

Table 5 Study Plan – Part A, Cohort 2 (Olaparib 300 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+[j]**	**Discontin-uation of IP**	**30-day follow-up[k]**
Visit window (days)	**–28 to -1**	**±0**	**±0**	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**3-7**	**12-14**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Written informed	X										
Demographics[a]	X										
Physical examination, height and weight[b]	X										X
Medical/surgical history	X										
ECOG Performance Status	X										
Inclusion/exclusion criteria	X	X									
Collect PSA and BRCA status data (local)[c]	X										
12-lead ECG[d]	X										
Vital signs[e]	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication[f]	X	X	X	X	X	X	X		X	X	X
AE and SAE review[g]	X	X	X	X	X	X	X	X	X	X	X

Table 5 Study Plan – Part A, Cohort 2 (Olaparib 300 mg bid + Abiraterone)

Visit	1 Screening	2	3	4	5	6	7	8+	9+[j]	Discontin-uation of IP	30-day follow-up[k]
Visit window (days)	**–28 to -1**	**±0**	**±0**	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**3-7**	**12-14**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Haematology, clinical chemistry (local)[h]	X	X	X	X	X	X	X		X	X	X
PK profile			X[l,m,n]	X[l,m,n]							
PGx blood sample (optional)[i]		X									
Olaparib/abiraterone dispensed/returned		X	X[l]	X[l]	X	X	X	X	X		
Patient complicance questionnaire[o]		X	X	X							

AE Adverse event; BRCA Breast cancer gene; ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; IP investigational product; PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race, and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[d] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[e] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[f] Concomitant medication should include all medications taken by the patient before and during the study.

[g] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[h] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). See Section 6.4.5 for a complete list of haematology and chemistry assessments.

[i] Sample will only be collected if separate PGx informed consent has been signed.

[j] Assessments apply to Visit 9 and subsequent visits occurring every 12 weeks thereafter.

[k] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

[l] **Group 1:** Olaparib (300 mg bid) dosing starts Day 1. Olaparib steady state PK profile collected any day between Days 3 and 7 after morning dose.
Abiraterone (1000 mg) dosing to start the day after the olaparib PK profile has been collected.
Continue dosing both drugs together for at least 5 days then collect both olaparib and abiraterone PK profiles. See Table 6
Group 2: Abiraterone (1000 mg) dosing starts Day 1. Abiraterone steady state PK profile collected any day between Days 5 and 7 after morning dose.
Olaparib dosing (300 mg bid) to start after the abiraterone PK profile has been collected (immediately after the 24-hour sample).
Continue dosing both drugs together for at least 3 days then collect both olaparib and abiraterone PK profiles. See Table 7.

[m] Blood samples for determination of olaparib to be collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after morning dose on each sampling day.

[n] Blood samples for determination of abiraterone to be collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after morning dose on each sampling day.

[o] Patients will be asked to complete a questionnaire to assess their study treatment compliance from Day 1 until after the PK profiling has been completed.

Revised text:

Table 5 Study Plan – Part A, Cohort 2 (Olaparib 300 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+[j]**	**Discontin-uation of IP**	**30-day follow-up[k]**
Visit window (days)	**–28 to -1**	**±0**	**±0**	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**3-7**	**12-14**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Written informed	X										
Demographics[a]	X										
Physical examination, height and weight[b]	X										X
Medical/surgical history	X										
ECOG Performance Status	X										
Inclusion/exclusion criteria	X	X									
Collect PSA and BRCA status data (local)[c]	X										
12-lead ECG[d]	X										
Vital signs[e]	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication[f]	X	X	X	X	X	X	X		X	X	X
AE and SAE review[g]	X	X	X	X	X	X	X	X	X	X	X

Table 5 Study Plan – Part A, Cohort 2 (Olaparib 300 mg bid + Abiraterone)

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**9+[j]**	**Discontin-uation of IP**	**30-day follow-up[k]**
Visit window (days)	**–28 to -1**	**±0**	**±0**	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**		
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks)**		
Day	**-**	**1**	**3-7**	**12-14**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Haematology, clinical chemistry (local)[h]	X	X	X	X	X	X	X	X **(up to Week 52)**	X **(from Week 64)**	X	X
PK profile			X[l,m,n]	X[l,m,n]							
PGx blood sample (optional)[i]		X									
Olaparib/abiraterone dispensed/returned		X	X[l]	X[l]	X	X	X	X	X		
Patient complicance questionnaire[o]		X	X	X							

AE Adverse event; BRCA Breast cancer gene; ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; IP investigational product; PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race, and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[d] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[e] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[f] Concomitant medication should include all medications taken by the patient before and during the study.

[g] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[h] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). **From Visit 8 (Week 16) onwards, laboratory assessments will be performed every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.** See Section 6.4.5 for a complete list of haematology and chemistry assessments.

[i] Sample will only be collected if separate PGx informed consent has been signed.

[j] Assessments apply to Visit 9 and subsequent visits occurring every 12 weeks thereafter.

[k] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

[l] **Group 1:** Olaparib (300 mg bid) dosing starts Day 1. Olaparib steady state PK profile collected any day between Days 3 and 7 after morning dose.
Abiraterone (1000 mg) dosing to start the day after the olaparib PK profile has been collected.
Continue dosing both drugs together for at least 5 days then collect both olaparib and abiraterone PK profiles. See Table 6.
Group 2: Abiraterone (1000 mg) dosing starts Day 1. Abiraterone steady state PK profile collected any day between Days 5 and 7 after morning dose.
Olaparib dosing (300 mg bid) to start after the abiraterone PK profile has been collected (immediately after the 24-hour sample).
Continue dosing both drugs together for at least 3 days then collect both olaparib and abiraterone PK profiles. See Table 7.

[m] Blood samples for determination of olaparib to be collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after morning dose on each sampling day.

[n] Blood samples for determination of abiraterone to be collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after morning dose on each sampling day.

[o] Patients will be asked to complete a questionnaire to assess their study treatment compliance from Day 1 until after the PK profiling has been completed.

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

Change 1.12

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Table 8

Previous text:

Table 8 Study Plan – Part B, Randomised Part

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6+**	**7+[o]**	**Discontin-uation of IP**	**30-day follow-up[p]**
Visit window	**-28 to -1**	**±0**	**±3**	**±3**	**±3**	**±7**	**±7**		
Week		**0**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks[o])**		
Day	**-**	**1**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Written informed consent including consent for archival tissue sample provision	X								
Demographics[a]	X								
Physical examination, height and weight[b]	X								X
Medical/surgical history	X								
ECOG Performance Status	X								
Inclusion/exclusion criteria	X	X							
CT or MRI scan of the chest, abdomen and pelvis (RECIST 1.1)[c]	X				X		X		
Bone scan[d]	X				X		X		
Collect PSA and BRCA status data (local)[e]	X								
12-lead ECG[f]	X								
Vital signs[g]	X	X	X	X	X		X	X	X

Table 8 Study Plan – Part B, Randomised Part

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6+**	**7+[o]**	**Discontin-uation of IP**	**30-day follow-up[p]**
Visit window	**-28 to -1**	**±0**	**±3**	**±3**	**±3**	**±7**	**±7**		
Week		**0**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks[o])**		
Day	**-**	**1**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Prior and concomitant medication[h]	X	X	X	X	X		X	X	X
AE and SAE review[i]	X	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (local)[j]	X	X	X	X	X		X	X	X
CTC blood sample (Veridex assay, central)[k]	X	X	X		X			X	
CTC blood sample (EPIC assay, central)[k]		X			X				
PSA blood sample (local)		X	X	X	X		X		
PGx blood sample (optional)[l]		X							
Blood biomarker sample (mandatory)		X						X	
Urine biomarker sample (mandatory)		X						X	
Archival tumour sample (where available)		X							

Table 8 Study Plan – Part B, Randomised Part

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6+**	**7+[o]**	**Discontin-uation of IP**	**30-day follow-up[p]**
Visit window	**-28 to -1**	**±0**	**±3**	**±3**	**±3**	**±7**	**±7**		
Week		**0**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks[o])**		
Day	**-**	**1**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
BPI-SF instrument and individual bone pain item[m]		X	X	X	X		X	X	X
FACT-P[m,n]		X	X	X	X		X	X	X
EQ-5D-5L questionnaire[n]		X	X	X	X		X	X	X
Oncology resource use[n]		X	X	X	X		X	X	X
Randomisation to study treatment		X							
Treatment dispensed/returned		X	X	X	X	X	X	X	

AE Adverse event; BPI-SF Brief Pain Inventory – Short Form; BRCA Breast cancer gene; CT Computed tomography;
ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; EQ-5D-5L EuroQuol-5 Dimensions, five-level;
FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer; IP investigational product; MRI magnetic resonance imaging;
PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Baseline assessments should be performed no more than 28 days before the date of randomisation, and ideally should be performed as close to the date of randomisation as possible.
Follow up assessments will be performed every 12 weeks (±1 week) relative to the date of randomisation up to and including Week 72. Thereafter, assessments will be conducted every 24 weeks until objective progression.
Bone lesion PCWG-2 assessments will be performed using bone scan (preferably whole body).
Malignant soft tissue RECIST v1.1 assessments will be performed using CT or MRI scans of chest, abdomen, pelvis.

[d] Bone scan required to confirm progression due to new bone lesions, preferably at the next scheduled visit for a bone scan and at least 6 weeks later.

[e] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[f] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[g] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[h] Concomitant medication should include all medications taken by the patient before and during the study.

[i] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[j] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). See Section 6.4.5 for a complete list of haematology, chemistry assessments.

[k] Visit 2 (Day 1) sample to be collected pre-dose.

[l] Sample will only be collected if separate PGx informed consent has been signed.

[m] The patient should complete the PRO questionnaires in a quiet place before any investigations have been carried out. Site personnel should not influence the patient's answers to the questions. Please refer to Section 6.5.

[n] If the patient discontinues study treatment for reasons other than RECIST or PCWG-2 progression, the 'Oncology Hospital Admission' form, FACT-P and EQ-5D-5L should continue to be administered until progression has been confirmed. After progression, see Table 9.

[o] Assessments apply to Visit 7 and subsequent visits occurring every 12 weeks up to and including Week 72, and every 24 weeks thereafter.

[p] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

Revised text:

Table 8 Study Plan – Part B, Randomised Part

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6+**	**7+[o]**	**Discontin-uation of IP**	**30-day follow-up[p]**
Visit window	**-28 to -1**	**±0**	**±3**	**±3**	**±3**	**±7**	**±7**		
Week		**0**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks[o])**		
Day	**-**	**1**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Written informed consent including consent for archival tissue sample provision	X								
Demographics[a]	X								
Physical examination, height and weight[b]	X								X
Medical/surgical history	X								
ECOG Performance Status	X				**X**		**X**	**X**	
Inclusion/exclusion criteria	X	X							
CT or MRI scan of the chest, abdomen and pelvis (RECIST 1.1)[c]	X				X		X		
Bone scan[d]	X				X		X		
Collect PSA and BRCA status data (local)[e]	X								
12-lead ECG[f]	X								

Table 8 Study Plan – Part B, Randomised Part

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6+**	**7+[o]**	**Discontin-uation of IP**	**30-day follow-up[p]**
Visit window	**-28 to -1**	**±0**	**±3**	**±3**	**±3**	**±7**	**±7**		
Week		**0**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks[o])**		
Day	**-**	**1**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Vital signs[g]	X	X	X	X	X		X	X	X
Prior and concomitant medication[h]	X	X	X	X	X		X	X	X
AE and SAE review[i]	X	X	X	X	X	X	X	X	X
Blood samples for haematology and clinical chemistry (local)[j]	X	X	X	X	X	X **(up to Week 52)**	X **(from Week 64)**	X	X
CTC blood sample (Veridex assay, central)[k]	X	X	X		X			X	
CTC blood sample (EPIC assay, central)[k]		X			X				
PSA blood sample (local)		X	X	X	X		X		
PGx blood sample (optional)[l]		X							
Blood biomarker sample (mandatory)		X						X	
Urine biomarker sample (mandatory)		X						X	

Table 8 Study Plan – Part B, Randomised Part

Visit	**1 Screening**	**2**	**3**	**4**	**5**	**6+**	**7+[o]**	**Discontin-uation of IP**	**30-day follow-up[p]**
Visit window	**-28 to -1**	**±0**	**±3**	**±3**	**±3**	**±7**	**±7**		
Week		**0**	**4**	**8**	**12**	**16+ (every 4 weeks)**	**24+ (every 12 weeks[o])**		
Day	**-**	**1**	**29**	**57**	**85**	**113+**	**169+**	**-**	**-**
Archival tumour sample (where available)		X							
BPI-SF instrument and individual bone pain item[m]		X	X	X	X		X	X	X
FACT-P[m,n]		X	X	X	X		X	X	X
EQ-5D-5L questionnaire[n]		X	X	X	X		X	X	X
Oncology resource use[n]		X	X	X	X		X	X	X
Randomisation to study treatment		X							
Treatment dispensed/returned		X	X	X	X	X	X	X	

AE Adverse event; BPI-SF Brief Pain Inventory – Short Form; BRCA Breast cancer gene; CT Computed tomography;
ECOG Eastern Cooperative Oncology Group; ECG electrocardiogram; EQ-5D-5L EuroQuol-5 Dimensions, five-level;
FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer; IP investigational product; MRI magnetic resonance imaging;
PSA prostate specific antigen; PGx pharmacogenetics; SAE serious adverse event

[a] Demographics include date of birth (if allowed by local regulations), race and ethnic group.

[b] Height and weight will be recorded at the first examination only.

[c] Baseline assessments should be performed no more than 28 days before the date of randomisation, and ideally should be performed as close to the date of randomisation as possible.
Follow up assessments will be performed every 12 weeks (±1 week) relative to the date of randomisation up to and including Week 72. Thereafter, assessments will be conducted every 24 weeks until objective progression.
Bone lesion PCWG-2 assessments will be performed using bone scan (preferably whole body).
Malignant soft tissue RECIST v1.1 assessments will be performed using CT or MRI scans of chest, abdomen, pelvis.

[d] Bone scan required to confirm progression due to new bone lesions, preferably at the next scheduled visit for a bone scan and at least 6 weeks later.

[e] Collect any locally available PSA data for the 12 months prior to study entry, and any locally available BRCA mutation data.

[f] At screening, a 12-lead ECG will be performed to ensure a QTc value of ≤470 ms for eligibility. If the QTc value is >470, the screening ECG may be repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) must be ≤470 ms to confirm patient eligibility. If the screening ECG is obtained within 3 days before Day 1 (Visit 2), then the screening ECG will be considered the baseline, and an ECG will not be necessary on Day 1. Failing to meet this time frame, a baseline ECG must be performed on Day 1 (Visit 2). After baseline, ECGs are only required if clinically indicated.

[g] Including blood pressure (BP), pulse and temperature. Measurements at Visit 2 must take place before first dose of study drug.

[h] Concomitant medication should include all medications taken by the patient before and during the study.

[i] When an AE of nausea or vomiting occurs, there is an additional eCRF for completion.

[j] The Visit 2 (Day 1) laboratory assessments need only be taken if the screening assessments were collected more than 7 days before Day 1 (Visit 2). **From Visit 6 (Week 16) onwards, laboratory assessments will be performed every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.** See Section 6.4.5 for a complete list of haematology, chemistry assessments.

[k] Visit 2 (Day 1) sample to be collected pre-dose.

[l] Sample will only be collected if separate PGx informed consent has been signed.

[m] The patient should complete the PRO questionnaires in a quiet place before any investigations have been carried out. Site personnel should not influence the patient's answers to the questions. Please refer to Section 6.5.

[n] If the patient discontinues study treatment for reasons other than RECIST or PCWG-2 progression, the 'Oncology Hospital Admission' form, FACT-P and EQ-5D-5L should continue to be administered until progression has been confirmed. After progression, see Table 9.

[o] **With the exception of laboratory assessments (see Footnote j for details)**, assessments apply to Visit 7 and subsequent visits occurring every 12 weeks up to and including Week 72, and every 24 weeks thereafter.

[p] 30-day follow-up visit for post-study drug assessment of AEs and concomitant medications as required. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow up period must be followed to resolution.

Reason for Amendment:

To correct an omission in the original protocol, and to bring the protocol in line with project standards, additional ECOG assessments have been added in Table 8 (Part B Randomised Part).

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

Change 1.13

Section of protocol affected:

Section 3.1, Overall study design and flow chart, Table 9

Previous text:

Table 9 Study plan – Randomised part (follow-up post discontinuation of study treatment)

Visit	**Off treatment follow-up for:** Patients who have discontinued study treatment due to reasons other than disease progression **Visits every 12 weeks** **Follow up for 1st progression**	**Time to second progression (PFS2) and survival for:** Patients who have discontinued study treatment due to disease progression Patients who have progressed off treatment **Patients followed up by telephone every 12 weeks post discontinuation of study treatment**
Visit window	±7 days	±7 days
CT or MRI scan of the chest, abdomen and pelvis (RECIST 1.1)[a]	X	
Bone scan (PCWG-2)[a]	X	
BPI-SF and bone pain item	X	
BPI-SF worst pain item and worst bone pain item[b]		X
PSA blood sample (local)[c]	X	
Subsequent cancer therapy following discontinuation of study treatment[d]	X	X
EQ-5D-5L questionnaire	X	
FACT-P	X	
Oncology resource use[e]	X	X[b]
Time to second progression		X
Survival[f,g]	X	X

BPI-SF Brief Pain Inventory – Short Form; CT CT Computed tomography; MRI magnetic resonance imaging;

PCWG-2 Prostate Cancer Working Group 2; PFS2 second progression; PSA prostate specific antigen

[a] Patients will continue to be assessed by objective tumour assessments every 12 weeks (±1 week) relative to date of randomisation up to and including Week 72, then every 24 weeks until progression, via RECIST 1.1 and PCWG-2.

[b] Administered by the Investigator over the telephone.

[c] Scheduled PSA samples will not be collected during the PFS2 and OS follow-up, but a standard of care local PSA value should be collected at the time of PFS2 and included on the database.

[d] All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

[e] The full 'Oncology Hospital Admission' form will be completed until rPFS; thereafter, an abridged version will be completed.

[f] The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 3.1.5).

[g] In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis.

Revised text:

Table 9 Study plan – Randomised part (follow-up post discontinuation of study treatment)

Visit	**Off treatment follow-up for:** Patients who have discontinued study treatment due to reasons other than disease progression **Visits every 12 weeks** **Follow up for 1st progression**	**Time to second progression (PFS2) and survival for:** Patients who have discontinued study treatment due to disease progression Patients who have progressed off treatment **Patients followed up by telephone every 12 weeks post discontinuation of study treatment**
Visit window	±7 days	±7 days
ECOG Performance Status	**X**	**X**
CT or MRI scan of the chest, abdomen and pelvis (RECIST 1.1)[a]	X	
Bone scan (PCWG-2)[a]	X	
BPI-SF and bone pain item	X	
BPI-SF worst pain item and worst bone pain item[b]		X
PSA blood sample (local)[c]	X	
Subsequent cancer therapy following discontinuation of study treatment[d]	X	X
EQ-5D-5L questionnaire	X	
FACT-P	X	
Oncology resource use[e]	X	X[b]
Time to second progression		X
Survival[f,g]	X	X

BPI-SF Brief Pain Inventory – Short Form; CT CT Computed tomography; MRI magnetic resonance imaging;
PCWG-2 Prostate Cancer Working Group 2; PFS2 second progression; PSA prostate specific antigen

[a] Patients will continue to be assessed by objective tumour assessments every 12 weeks (±1 week) relative to date of randomisation up to and including Week 72, then every 24 weeks until progression, via RECIST 1.1 and PCWG-2.

[b] Administered by the Investigator over the telephone.

[c] Scheduled PSA samples will not be collected during the PFS2 and OS follow-up, but a standard of care local PSA value should be collected at the time of PFS2 and included on the database.

[d] All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

[e] The full 'Oncology Hospital Admission' form will be completed until rPFS; thereafter, an abridged version will be completed.

[f] The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 3.1.5).

[g] In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis.

Reason for Amendment:

To correct an omission in the original protocol, and to bring the protocol in line with project standards, additional ECOG assessments have been added in Table 9 (Randomised Part, follow-up discontinuation of study treatment).

Persons who initiated the Amendment:

AstraZeneca

Change 1.14

Section of protocol affected:

Section 6.2.1, Post-treatment

Previous text:

For patients who discontinue study treatment in Part A, there will be no further follow-up or data collection after their 30-day follow-up visit.

The database for Part A of the study will be closed after the decision has been made whether or not to proceed with Part B of the study. Patients are permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib/placebo and abiraterone (see Sections 5.5.2 and 9.5).

Patients who discontinue study treatment in Part B will be followed up until disease progression. Thereafter, they will be followed up for PFS2 and survival in accordance with the study plan (see Table 8).

Dispensing and accountability records will continue to be collected after follow-up for as long as patients continue to receive IP.

Revised text:

For patients who discontinue study treatment in Part A, there will be no further follow-up or data collection after their 30-day follow-up visit.

Patients who discontinue study treatment in Part B will be followed up until disease progression. Thereafter, they will be followed up for PFS2 and survival in accordance with the study plan (see Table 8).

Dispensing and accountability records will continue to be collected after follow-up for as long as patients continue to receive IP.

Reason for Amendment:

Text relating to the closure of the Part A database has been removed because there is no plan to close the database for Part A after the decision on Part B dose is taken, and text is

contradictory to text in Section 3.1.2. The remainder of this paragraph is not needed as it duplicates text in Section 5.5.2.

Persons who initiated the Amendment:

AstraZeneca

Change 1.15

Section of protocol affected:

Section 6.4.3, Recording of adverse events

Previous text:

[...]

NB. Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN may need to be reported as SAEs, please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Revised text:

[...]

NB. Cases where a patient shows **elevations in liver biochemistry may require further evaluation and occurrences of** AST **or** ALT ≥3xULN **together with** total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law'for further instructions **on cases of increases in liver biochemistry and evaluation of Hy's Law.**

Reason for Amendment:

To reflect a change in AstraZeneca's operating procedure on Hy's Law

Persons who initiated the Amendment:

AstraZeneca

Change 1.16

Section of protocol affected:

Section 6.4.5.2, Clinical chemistry assessments for safety

Previous text:

[...]

NB. In case a patient shows an AST or ALT ≥3xULN total bilirubin ≥2xULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Revised text:

[...]

NB. In case a patient shows an AST **or** ALT ≥3xULN **together with** total bilirubin ≥2xULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Reason for Amendment:

To reflect a change in AstraZeneca's operating procedure on Hy's Law.

Persons who initiated the Amendment:

AstraZeneca

Change 1.17

Section of protocol affected:

Section 7.1, Volume of blood, Table 14 to 16

Previous text:

Table 14 Volume of blood to be drawn from each patient in Cohort 1, Part A

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	10[a]	27
	Haematology	2.7	10[a]	27
Pharmacogenetics (optional)		9	1	9
Total				**63**[b]

[a] 10 samples taken at: Visits 1 to 9, discontinuation and follow-up.
[b] For every additional 12 weeks that patients remain in the study after Visit 9, a further 5.4 mL blood will be collected (for safety analyses).

[...]

Table 15 Volume of blood to be drawn from each patient in Cohort 2, Part A

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	10[a]	27
	Haematology	2.7	10[a]	27
Pharmacokinetic	Olaparib (Group 1)	2.0	18	36
	Abiraterone (Group 1)	2.0	10	20
	Olaparib (Group 2)	2.0	9	18
	Abiraterone (Group 2)	2.0	20	40
Pharmacogenetics	(Optional)	9	1	9
Total	Group 1			**119**[b]
	Group 2			**121**[b]

[a] 10 samples taken at: Visits 1 to 9, discontinuation and follow-up.
[b] For every additional 12 weeks that patients remain in the study after Visit 9, a further 5.4 mL blood will be collected (for safety analyses).

[...]

Table 16 Volume of blood to be drawn from each patient in Part B

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	8[a]	21.6
	Haematology	2.7	8[a]	21.6
Biomarker	PSA	5	5[b]	25
	CTC (enumeration)	10	5	50
	CTC (biomarkers)	10	2	20
	Exploratory	11	2	22
Pharmacogenetics	(Optional)	9	1	9
Total				**169.2**[c]

[a] 8 samples taken at: Visits 1 to 7, discontinuation and follow-up.
[b] 5 samples taken at: Visits 1, 3, 4, 5 and 6.
[c] For every additional visit where blood samples are collected after Visit 7, a further 10.4 mL blood will be collected (for safety and PSA analyses).

Revised text:

Table 14 Volume of blood to be drawn from each patient in Cohort 1, Part A

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	**12**[a]	**32.4**
	Haematology	2.7	**12**[a]	**32.4**
Pharmacogenetics (optional)		9	1	9
Total				**73.8**[b]

[a] **12** samples taken at: Visits 1 to 9, discontinuation and follow-up.
[b] **From Visit 8 (Week 16) onwards, a further 5.4 mL blood will be collected (for safety analyses) every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.**

[...]

Table 15 Volume of blood to be drawn from each patient in Cohort 2, Part A

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	**12**[a]	**32.4**
	Haematology	2.7	**12**[a]	**32.4**
Pharmacokinetic	Olaparib (Group 1)	2.0	18	36
	Abiraterone (Group 1)	2.0	10	20
	Olaparib (Group 2)	2.0	9	18
	Abiraterone (Group 2)	2.0	20	40
Pharmacogenetics	(Optional)	9	1	9
Total	Group 1			**129.8**[b]
	Group 2			**131.8**[b]

[a] **12** samples taken at: Visits 1 to 9, discontinuation and follow-up.
[b] **From Visit 8 (Week 16) onwards,** a further 5.4 mL blood will be collected (for safety analyses) **every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment.**

[...]

Table 16 Volume of blood to be drawn from each patient in Part B

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.7	**10**[a]	**27**
	Haematology	2.7	**10**[a]	**27**
Biomarker	PSA	5	5[b]	25
	CTC (enumeration)	10	5	50
	CTC (biomarkers)	10	2	20
	Exploratory	11	2	22
Pharmacogenetics	(Optional)	9	1	9
Total				**180**[c]

[a] **10** samples taken at: Visits 1 to 7, discontinuation and follow-up.
[b] 5 samples taken at: Visits 1, 3, 4, 5 and 6.
[c] **From Visit 6 (Week 16) onwards, a further 5.4 mL blood will be collected (for safety analyses) every 4 weeks up to Week 52, while the patient is on treatment, whichever comes first, and then every 12 weeks for as long as the patient is on treatment. In addition, from Visit 7 (Week 24) a 5 mL blood sample will be taken every 12 weeks for PSA analysis.**

Reason for Amendment:

To enhance the safety of patients receiving this novel combination therapy, the visit frequency is increased to every 4 weeks for the first 52 weeks on the trial, to allow more frequent laboratory safety assessments.

Persons who initiated the Amendment:

AstraZeneca

Change 1.18

Section of protocol affected:

Section 9.5, Study timetable and end of study

Previous text:

The database for Part A of the study will be closed after the decision has been made whether or not to proceed with Part B of the study.

Revised text:

The database for Part A **and Part B are one database, and therefore the data will be analysed at the same time. Part A patients continue beyond their initial 14 days treatment as specified in Section 5.5.2.**

Reason for Amendment:

Text has been revised to correct erroneous wording and to clarify wording.

Persons who initiated the Amendment:

AstraZeneca

Change 1.19

Section of protocol affected:

Section 12.2.1.1, Radiological progression-free survival

Previous text:

The primary endpoint of Part B, rPFS (weeks), is defined in Section 11.1.3. Once approximately 100 progression events have occurred, the primary analysis will be performed. Radiological progression-free survival will be analysed using a Cox proportional hazards model with a factor for treatment group. The hazard ratio (HR) and 80% confidence interval (CI) will be estimated from the model (using ties=Efron). The CI will be calculated using a profile likelihood approach. The p-value will be based on twice the change in log-likelihood resulting from the addition of treatment factor to a model that contains no factors.

[...]

[...]

[...]

Separate Cox proportional hazards models of rPFS will be undertaken using patients who are positive for ERG expression/fusion status and also for patients who have BRCA mutations, including the same factors as for the primary analysis. If the number of patients in each subgroup is small, consideration will be given to merging the subgroups prior to analysis.

As an exploratory analysis, a Cox proportional hazards model of rPFS may be undertaken including some or all of the following factors: PTEN, AR status, disease related biomarkers, demographic and disease characteristics.

If there are too few events available for a meaningful analysis (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), only descriptive statistics will be provided.

Revised text:

The primary endpoint of Part B, rPFS (weeks), is defined in Section 11.1.3. Once approximately 100 progression events have occurred, the primary analysis will be performed. Radiological progression-free survival will be analysed using **a log-rank test**. The hazard ratio (HR) and 80% confidence interval (CI) will be estimated **from the U and V statistics**

obtained directly from the LIFETEST model with inclusion of STRATA terms for the stratification variables (and using the Breslow approach for handling ties). A HR less than 1 will favour Olaparib.

The HR and its confidence interval can be estimated from the log-rank as follows (Berry et al 1999, Sellke et al 1983):

$$HR = exp(U/V)$$

$$80\%\ CI\ for\ HR = (exp\{U/V - 1.28/\sqrt{V}\}, exp\{U/V + 1.28/\sqrt{V}\})$$

Where $U = \sum_i (d_{1i} - e_{1i})$ **is the log-rank test statistic(with d_{1i} and e_{1i} the observed and expected events in group 1) and $\sqrt{V}$ the standard deviation of the log-rank test statistic as produced in the LIFETEST output.**

The HR (Olaparib vs. placebo) together with its corresponding 80% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour Olaparib).

[...]

[...]

[...]

Separate **log-rank tests** of rPFS will be undertaken using patients who are positive for ERG expression/fusion status and also for patients who have BRCA mutations, **using the same model** as for the primary analysis. If the number of patients in each subgroup is small, consideration will be given to merging the subgroups prior to analysis.

Reason for Amendment:

A log-rank test has replaced the Cox proportional hazard model as the primary analysis for the time-to-event endpoints, based on recommendations from the US FDA.

Persons who initiated the Amendment:

AstraZeneca

<u>Change 1.20</u>

Section of protocol affected:

Section 12.2.1.2, Time to second progression (PFS2)

Previous text:

The secondary endpoint of PFS2 (weeks), as defined in Section 11.1.3.1, will be analysed using the same time-to analysis as rPFS: Cox proportional hazard model, Kaplan-Meier and summary statistics.

Revised text:

The secondary endpoint of PFS2 (weeks), as defined in Section 11.1.3.1, will be analysed using the same time-to analysis as rPFS: **log-rank test**, Kaplan-Meier and summary statistics.

Reason for Amendment:

A log-rank test has replaced the Cox proportional hazard model as the primary analysis for the time-to-event endpoints, based on recommendations from the US FDA.

Persons who initiated the Amendment:

AstraZeneca

Change 1.21

Section of protocol affected:

Section 12.2.1.3, Overall survival (OS)

Previous text:

The secondary efficacy endpoint for Part B, OS (months), as defined in Section 11.1.4, will be performed when approximately 60% of patients have died; patients who have not died at that point will be censored.

The same time-to analyses will be undertaken as for rPFS: Cox proportional hazard model, Kaplan-Meier and summary statistics. A listing of OS time per patient will also be produced.

Revised text:

The secondary efficacy endpoint for Part B, OS (months), as defined in Section 11.1.4, will be performed when approximately 60% of patients have died; patients who have not died at that point will be censored.

The same time-to analyses will be undertaken as for rPFS: **log-rank test**, Kaplan-Meier and summary statistics. A listing of OS time per patient will also be produced.

Reason for Amendment:

A log-rank test has replaced the Cox proportional hazard model as the primary analysis for the time-to-event endpoints, based on recommendations from the US FDA.

Persons who initiated the Amendment:

AstraZeneca

Change 1.22

Section of protocol affected:

Section 13.3.2, Paternal exposure

Previous text:

Patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of olaparib/placebo, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of any conception (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) from the date of the first dose until 3 months after the last dose should, if possible, be followed up and documented.

Revised text:

Patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of olaparib/placebo, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of any conception (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) from the date of the first dose until 3 months after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information on the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant ECs/IRBs prior to use.

Reason for Amendment:

To provide clarification on when and how to use the consent form for pregnant partners of male participants.

Persons who initiated the Amendment:

AstraZeneca

Change 1.23

Section of protocol affected:

Section 14, References

Previous text:

None

Revised text:

[...]

Berry et al 1999
Berry G, Kitchin RM & Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Statistics in Medicine 1991; 10:749-755.

[...]

Sellke et al 1983
Sellke, T. and Siegmund, D. Sequential analysis of the proportional hazards model. Biometrika 70: 315-326, 1983.

Reason for Amendment:

Two new references have been added to the protocol to support the change in statistical methodology to be used in the primary analysis for the time-to-event endpoints.

Persons who initiated the Amendment:

AstraZeneca

Change 1.24

Section of protocol affected:

Appendix A, Signatures, Medical Science Director

Previous text:

AstraZeneca Research and Development site representative

PPD

Date
(Day Month Year)

AstraZeneca R&D
Alderley Park, Macclesfield
Cheshire, SK10 4TG
UK

PPD

Revised text:

AstraZeneca Research and Development site representative

Jane Robertson, MD MRCP FRCPath
Medical Science Director

Date
(Day Month Year)

AstraZeneca R&D Alderley Park
Macclesfield
Cheshire, SK10 4TG
UK

PPD

Reason for Amendment:

To reflect a change in study personnel.

Persons who initiated the Amendment:

AstraZeneca

Change 1.25

Section of protocol affected:

Appendix A, Signatures, Global Product Statistician

Previous text:

AstraZeneca Research and Development site representative

PPD

Date
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Alderley Park, Macclesfield
Cheshire, SK10 4TG
UK

PPD

Revised text:

AstraZeneca Research and Development site representative

Helen Mann MSc
Global Product Statistician

Date
(Day Month Year)

AstraZeneca R&D
Alderley Park, Macclesfield
Cheshire, SK10 4TG
UK

PPD

Reason for Amendment:

To reflect a change in study personnel.

Persons who initiated the Amendment:

AstraZeneca

Change 1.26

Section of protocol affected:

Appendix E, Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law, Section 2

Previous text:

2 DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

Revised text:

2 DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2xULN at any point during the study **following the start of study medication** irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST **or** ALT ≥3x ULN **together with** TBL ≥2xULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

AstraZeneca

Clinical Study Protocol Amendment No 1 Appendix A	
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D081DC00008
Edition Number	1
Date	15 August 2014
Protocol Dated	11 December 2013

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

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

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

AstraZeneca Research and Development site representative

PPD

21-Aug-2014

Carsten Goessl, MD
Senior Medical Director

Date
(Day Month Year)

Signing on behalf of:

Jane Robertson, MD MRCP FRCPath
Medical Science Director

AstraZeneca R&D
Alderley Park, Macclesfield
Cheshire, SK10 4TG
UK

PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

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

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

AstraZeneca Research and Development site representative

PPD

PPD

Study Leader

21 Aug 2014

Date
(Day Month Year)

Quintiles S.p.A.
Cassina Plaza
Via Roma, 108
20060 Cassina dé Pecchi (MI)

PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

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

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

AstraZeneca Research and Development site representative

PPD

Helen Mann MSc
Global Product Statistician

21/08/2014
Date
(Day Month Year)

AstraZeneca R&D
Alderley Park, Macclesfield
Cheshire, SK10 4TG
UK

PPD

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.:

Signature: PPD

22-8-14

Professor Noel Clarke
Professor of urological oncology

Date
(Day Month Year)

The Christie NHS Foundation Trust
Wilmslow Road
Withington
Manchester M20 4BX

PPD