Clinical Study Protocol	
Drug Substance	Olaparib
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A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 4.0, 07 March 2019

Changes to the protocol are summarized below.

- Protocol Synopsis (Study site(s) and number of Subjects planned; Study design; Statistical methods), Section 1.4 (Study Design), Figure 1 (Study design) and Figure 2 (Study flow chart) – [redacted]
- Protocol Synopsis (Study design) – clarification that the study is the PROfound study.
- Protocol synopsis (Duration of treatment), Section 3.9.1 (Procedures for discontinuation of a subject from investigational product), Section 4 (Study Schedule – Screening (Part 1 and 2)/Table 2), Section 4 (Study Schedule – On Study Treatment and Discontinuation/Table 3), Section 4 (Study schedule and timing of procedures/Table 4), Section 4 (Study Schedule – Subjects switching to olaparib/Table 5), Section 4.2 (Treatment period), Section 4.2.1 (Subjects who switch to olaparib), Section 4.3 (Follow-up period), Section 5.1.1 (Imaging tumor assessments), Section 5.3.3.1 (Assessment of Healthcare Resource Use), Section 7.2 (Dose and treatment regimens), Section 8.4.1.1 (Radiological Progression Free Survival (rPFS)) and Appendix E (Tumor response evaluation) – updated to clarify that after the date of DCO for primary analysis, there is no plan for BICR to read scans, and the investigator-assessed radiographic progression will prevail.
- Protocol Synopsis (Study design; Investigational product, dosage and mode of administration), Section 7.1 (Identity of investigational product and comparators/Table 12) and Section 7.2 (Dose and treatment regimens) – updated to clarify use of 'enzalutamide capsules/tablets'.
- [redacted]
- Protocol synopsis (Target subject population, Biomarker selection) – updated since study may use more than one tissue testing laboratory [redacted]
- [redacted]
- Section 1.2.1 (Rationale for developing the Lynparza Homologous Recombination Repair (HRR) Assay) and Section 5.7.6 (Exploratory use of residual biomarker samples and data

generated from tumor testing (Optional)) – updated the language for genes analyzed in the Lynparza HRR Assay.

- Section 1.3 (Benefit/risk and ethical assessment) – revised Section link from 6.9.2 to Section 6.10.2.
- [redacted]
- Table 2 (Study schedule - screening (Part 1 and 2)) and Section 5.7.3.1 (Screening part 1: optional blood sample for germline testing) – added clarification that optional blood samples for germline testing will not be collected in China.
- [redacted]
- Table 3 (Study Schedule – On Study Treatment and Discontinuation) and Section 5.6.1 (Collection of pharmacogenetics samples) – added clarification that pharmacogenetics samples will not be collected in China.
- Table 3 (Study Schedule – On Study Treatment and Discontinuation) and Section 5.1.5 (PSA Assessments) – clarified that the PSA results will not be available for the sites prior to final analysis.
- Section 4.2 (Treatment period) – clarified the access to olaparib for subjects randomized to the comparator group.
- Section 4.2.1 (Subjects who switch to olaparib) – updated wording for continuing olaparib treatment.
- Section 4.3 (Follow-up period) – updated text since the subject's decision has not been captured on the eCRF to date, and clarified that discontinuation is based on BICR and post primary analysis by investigator.
- Section 5.1.1 (Imaging tumor assessments/Figure 3) – title updated to reflect that the schematic applies for before the primary (rPFS) analysis.
- Section 5.1.2 (Tumor evaluation) – added clarification that scans will not be required after primary analysis.
- [redacted]

- Section 5.7.2 (Collection, Analysis and Reporting of Tumor Samples) – [redacted] Add added clarity on the subject population for the confirmed deleterious or suspected deleterious mutation biomarker testing.
- Section 5.7.3.2 (Screening Part 2: Mandatory Blood Sample for Germline Testing) – removed the phrase 'clinical-grade' describing mandatory HRR germline blood sample, and clarified that the retrospective germline testing results are in accordance with the procedures for research use
- [redacted]
- Section 5.7.7 (Storage, re-use and destruction of biological sample) – revised wording to include local regulation.
- [redacted]
- Section 6.9 (Safety Reporting and Medical Management) – inserted a new sub-section for Medication Errors with the reporting description.
- Section 7.7 (Concomitant and other treatments/Palliative radiotherapy) – added clarity that the treatment is olaparib.
- Section 8.1 (Statistical considerations) – added clarification of the blinding requirements.
- Section 8.3.1 (Efficacy analysis set) – added clarification on the efficacy analysis sets.
- Section 8.3.2 (Safety analysis set) – clarified the definition of the global [redacted] safety analysis set, and that safety data for subjects switching from investigator choice to olaparib will be reported in a separate section.
- Section 8.3.4 (Table 13) – included DoR and patient population as part of the efficacy data variable.
- Section 8.4.1.1 (Radiological Progression Free Survival (rPFS)) – revised wording on the 2 missed visit rule (details will be included in the SAP).
- Section 8.4.2.5 (Duration of Response) – added clarity that DoR is based on subjects with confirmed DoR.
- Section 8.4.4.1 (Adverse events) – for accuracy, the description of treatment emergent AE (TEAE) has been revised.
- Section 8.5.4 (Subgroup analysis) – added clarification for the analysis.
- [redacted]
- Section 9.3 (Study timetable and end of study) – revised language for clarity.
- Appendix A (Additional Safety Information) – inserted text for the definition of Medication Errors.
- Version 3.0, 04 June 2018 – summary of changes for Section 8.5.3.3 has been clarified.
- Minor editorial and formatting updates performed for consistency but not tracked or noted as changes to the protocol.

Version 3.0, 04 June 2018

Changes to the protocol are summarized below.

- Protocol Synopsis, Section 7.1 (Identity of investigational product and comparators) and Section 7.2 (Dose and treatment regimens) – Abiraterone acetate 500mg tablets added
- Protocol Synopsis and Section 7.2 (Dose and treatment regimens) – Abiraterone acetate dosing instructions clarified
- Section 1.3 (Benefit/risk assessment) - Revised risk-benefit assessment section
- Section 1.4 (Study Design) – Update to screening numbers
- Section 2.4 (Exploratory Objectives) - Added additional Exploratory objectives for ctDNA
- Section 3.1 (Inclusion Criteria) – Updated inclusion criteria #5 and #10
- Section 3.2 (Exclusion Criteria) – Updated exclusion criteria #5 and #8
- Section 3.8.1 (Grapefruit Juice) – Wording strengthened from 'not recommended' to 'prohibited'
- Section 5.1.2 (Tumor Evaluation) – Added clarification for if unscheduled bone scan occurs prior to week 8
- Section 5.3.1.5 (Analgesic Log) – Clarification that ERT is not integrated with EDC
- Section 5.4.2 (Determination of drug concentration) – Clarification of the lab used
- Section 5.4.3 (Storage and destruction of pharmacokinetic samples) – Change to wording as samples cannot be both destroyed and anonymized by pooling.
- Section 5.7.2 (Collection, Analysis and Reporting of Tumor Samples) – Minor edits to reference the 'pathology and genomics manual'
-
- Section 6.1.1 (Olaparib adverse events of special interest) – Removed requirement to report non-serious AESI to Patient Safety function
- Section 7.5 (Compliance) – Clarified instructions for drug accountability of locally supplied drug.
- Section 8.4.4 (Safety Endpoints) and Section 8.5.8 (Safety Analyses) – reference to ECG removed
- Section 8.5.3.3 (Overall Survival) – Correction to final OS analysis alpha level taking into account the correlation between the planned interim and final analyses.
- Table 2 (Study Schedule – Screening (Part 1 and 2)) and Section 5.7.3.1 – Added optional blood sample for exploratory germline testing to Screening Part 1 and clarified mandatory blood sample for germline testing at Screening Part 2 in Section 5.7.3.2
- Table 2 (Footnote g), Table 3 (Footnote j), Table 4 (Footnote b), Table 5 (Footnote c) – removed requirement for additional eCRF page for nausea and vomiting
- Table 2 (Study Schedule – Screening (Part 1 and 2)) and Section 8.5.8.4 (Concomitant medications) – clarification regarding concomitant medication collection.
- Table 3 (Footnote c) – update to wording of "approximately 50 subjects assigned to olaparib treatment", to "at least 50 subjects assigned to olaparib treatment"
- Table 3 (Footnote o), Table 4 (Footnote f) and Table 5 (Footnote d) – Clarification regarding collection of anti-cancer treatments
- Table 4 (Footnote i), Section 5.3.1.1 (BPI-SF) and Section 5.3.2 (Administration of PRO questionnaires) – Clarified instructions for completion of BPI-SF and analgesic log
- Table 4 (Footnote k) – Clarified requirements for collection of opioids after treatment discontinuation
- Table 9 (Management of anemia) – updated actions
- Appendix E (Tumor progression evaluation - Schedule of the evaluation) – correction of baseline assessment window and clarified footnote in Table 19 and 21

Version 2.0, 09 March 2017 Changes to the protocol are summarized below.
• Abbreviation of MGUS was added • Section 6.3.1 (Time period for collection of adverse events) and Table 2 Study Schedule – Screening (Part 1 and 2) footnote g: added the clarification: In screening part 1 only SAEs related to study procedures must be reported (AEs do not require reporting). From screening part 2 onwards - all AEs/SAEs must be reported. • Section 7.7 (Concomitant and other treatments)-Administration of other anti-cancer agents: delete "corticosteroids for the symptomatic control of brain metastases" because subjects with known brain metastases are excluded from the study according to exclusion criteria #13. • Section 8.4.4.3 (Concomitant medications) and Section 9.4 (Data management by AstraZeneca or delegate): updated that medications will be classified according to WHO Drug Dictionary. • Reference: added one reference Sun and Chen, 2010 (referred in section 8.5.6.1 Sensitivity analyses for rPFS) • Appendix F: updated wording related to abstinence

Version 1.0, 19 Oct 2016
Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

AstraZeneca

PROTOCOL SYNOPSIS

A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations

International Co-ordinating Investigator

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Study site(s) and number of Subjects planned

Approximately 340 subjects will be randomized at study sites worldwide. [redacted]

Study period		Phase of development
Estimated date of first subject enrolled	Q1 2017	3
Estimated date of last subject completed	Q1 2021	3

Study design

PROfound is a prospective, multicenter, randomized, open-label, phase 3 trial evaluating the efficacy and safety of olaparib versus enzalutamide or abiraterone acetate in subjects with metastatic castration-resistant prostate cancer (mCRPC) who have failed prior treatment with a new hormonal agent (NHA) and have a qualifying tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway. Subjects will be divided into two cohorts based on HRR gene mutation status.

Subjects with mutations in either *BRCA1*, *BRCA2*, or *ATM* will be in Cohort A whereas subjects with mutations among 12 other genes involved in the HRR pathway (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* or *RAD54L*) will be in Cohort B. The primary endpoint of the study is radiographic progression free survival (rPFS) in subjects with *BRCA1*, *BRCA2* or *ATM* mutations (Cohort A). Given the open label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of rPFS based on blinded independent central review (BICR) of all subject scans. Key secondary endpoints include confirmed objective response rate (Cohort A), rPFS (combined Cohorts A + B), time to pain progression (Cohort A), and overall survival (Cohort A).

Approximately 340 subjects will be randomized 2:1 (olaparib : investigator choice of enzalutamide or abiraterone acetate) into the trial, with ~240 subjects in Cohort A and approximately 100 subjects in Cohort B. [redacted] The treatment groups include olaparib tablets (300 mg bid) or investigator choice of either enzalutamide capsules/tablets (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone). The investigator must declare prior to randomization their choice of either enzalutamide or abiraterone acetate. [redacted]

The randomization scheme will be stratified based on:

- Prior taxane (yes vs no)
- Measurable disease (yes vs no)

Randomized study treatment will be given until objective radiographic progression as assessed by BICR. Upon BICR progression, subjects randomized to the investigator choice arm will be given the option to switch to olaparib.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with mCRPC with *BRCA1*, *BRCA2* or *ATM* qualifying mutations (Cohort A)	• rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

Key Secondary Objective:	**Outcome Measure:**
To determine the efficacy (as assessed by ORR) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Confirmed ORR by BICR assessment in subjects with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying mutations (Cohort A+B). [redacted]	• rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
To determine the efficacy (as assessed by time to pain progression) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Pain progression based on BPI-SF item 3 “worst pain in 24 hours” and opiate analgesic use (AQA score)
To determine the efficacy (as assessed by overall survival) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Overall Survival (OS)

Other Secondary Objectives:	**Outcome Measure:**
To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Time from randomization to the first SSRE • Time from partial or complete response in subjects with measurable disease (RECIST 1.1) to progression by BICR (DoR) • Time from randomization to opiate use for cancer-related pain • Confirmed ORR (RECIST 1.1) in soft tissue by BICR in subjects with measurable disease (Soft tissue response) • Proportion of Subjects achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA_{50} response) • Proportion of Subjects achieving a decline in the number of CTCs from ≥ 5 cells/7.5mL to < 5 cells/7.5mL whole blood (CTC conversion rate) • Time from randomization to second progression by investigator assessment of radiological or clinical progression or death (PFS2)
To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A) on disease-related symptoms and health-related quality of life (HRQoL)	• Pain severity progression based on BPI-SF Pain Severity domain/subscale and opiate analgesic use (AQA score) • Pain interference based on BPI-SF Pain Interference domain/subscale • FACT-P (FACT-P total score, trial outcome index [TOI], functional well-being [FWB], physical well-being [PWB], prostate cancer subscale [PCS], and FACT Advanced Prostate Symptom Index 6 [FAPSI 6]) • Proportion of Subjects with pain (BPI-SF item 3) score ≥ 4 points at baseline who have a decrease of ≥ 2 points in pain (BPI-SF item 3) and without ≥ 1 point increase in analgesic score (AQA score) at 12 weeks, confirmed at least 3 weeks later (Pain palliation)

To assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations other than *BRCA1*, *BRCA2* or *ATM* (Cohort B). [redacted]	• rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria • Confirmed ORR by BICR assessment in subjects with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria • Pain progression based on BPI-SF item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) • OS
To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations (Cohort A+B). [redacted]	• Confirmed ORR by BICR assessment in subjects with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria • Time from randomization to the first SSRE • Time from partial or complete response in subjects with measurable disease (RECIST 1.1) to progression by BICR (DoR) • Time from randomization to opiate use for cancer-related pain • Confirmed ORR (RECIST 1.1) in soft tissue by BICR in subjects with measurable disease (Soft tissue response) • Proportion of Subjects achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA_{50} response) • Proportion of Subjects achieving a decline in the number of CTCs from ≥ 5 cells/7.5mL to < 5 cells/7.5mL whole blood (CTC conversion rate) • Time from randomization to second progression by investigator assessment of radiological or clinical progression or death (PFS2) • OS

To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations (Cohort A+B) on disease-related symptoms and health-related quality of life (HRQoL). [redacted]	• Pain progression based on BPI-SF item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) • Pain severity progression based on BPI-SF Pain Severity domain/subscale and opiate analgesic use (AQA score). • Pain interference based on BPI-SF Pain Interference domain/subscale • FACT-P (FACT-P total score, trial outcome index [TOI], functional well-being [FWB], physical well-being [PWB], prostate cancer subscale [PCS] and FACT Advanced Prostate Symptom Index 6 [FAPSI 6]) • Proportion of Subjects with pain (BPI-SF item 3) score ≥ 4 points at baseline who have a decrease of ≥ 2 points in pain (BPI-SF item 3) and without ≥ 1 point increase in analgesic score (AQA score) at 12 weeks, confirmed at least 3 weeks later (Pain palliation)
To determine the exposure to olaparib in a subset of subjects receiving olaparib. [redacted]	• Olaparib plasma concentration data

Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of olaparib versus investigator choice of enzalutamide or abiraterone acetate	• AEs/SAEs • Collection of clinical chemistry/hematology parameters

Target subject population

All subjects in the study will be selected based on the following 2 criteria:

Biomarker selection: Documented tumor (tissue) qualifying mutation(s) in one of 15 HRR genes that is predicted to be deleterious or suspected deleterious. All subjects must provide a formalin fixed and paraffin embedded (FFPE) tumor sample for tissue-based HRR gene panel mutation testing using the clinical trial assay (CTA) known as the Lynparza HRR Assay. Foundation Medicine, Inc. (FMI) will provide the CTA, a novel next generation sequencing (NGS)-based assay using DNA extracted from Formalin Fixed Paraffin Embedded (FFPE) tissue. Tumor tissue samples can be from either primary tumor (e.g., transrectal biopsies or radical prostatectomy specimen) or metastatic biopsy. The tumor sample will be tested for mutation in 15 pre-specified HRR genes. If the test results indicate that the subject has a qualifying mutation in the *BRCA1, BRCA2*, or *ATM* genes, the subject is eligible for Cohort A of the study. If the results indicate that the subject has a qualifying mutation in any of the

remaining 12 genes (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*), then the subject is eligible for Cohort B. [redacted]

Treatment setting: All subjects must have mCRPC and have received and failed prior treatment with an NHA (e.g., abiraterone acetate or enzalutamide). Prior receipt of other anti-prostate cancer therapies, including docetaxel, cabazitaxel, radium-223, and sipuleucel-T is permitted but not required. Subjects must not have received previous treatment with a DNA-damaging cytotoxic chemotherapy (e.g., prior platinum-based chemotherapy and mitoxantrone are not permitted) or a PARP inhibitor, including olaparib.

Duration of treatment

Until the primary rPFS analysis, all subjects should continue to receive randomized study treatment until radiographic progression as assessed by BICR, or until the subject is unable to tolerate study treatment. After the date of data cut-off (DCO) for the primary analysis, subjects should receive treatment until radiographic progression as assessed by the investigator, or until the subject is unable to tolerate study treatment. [redacted] **Bone progression requires confirmation by a second bone scan at least 6 weeks later.** Radiologic assessments will include both bone scans and CT/MRI and will be scheduled every 8 weeks (±7 days). All imaging assessments (including unscheduled visit scans) will be sent to AstraZeneca appointed central reader on an ongoing basis and analysis by BICR will be triggered upon investigator-assessed progression. Results of BICR will be immediately reported back to sites. Since the primary analysis of the study is based on BICR, it is important that study treatment and scheduled imaging assessments continue until progression by BICR. For this same reason, PSA (Prostate Specific Antigen) rise, without evidence of radiographic progression, is strongly discouraged as a criterion to stop treatment or to start a new systemic anti-prostate cancer therapy.

Upon documentation of radiographic progression by BICR before the primary rPFS analysis, or after the primary rPFS analysis based on investigator-assessed radiographic progression, receipt of subsequent anti-cancer therapies is allowed at the investigator's discretion and will be recorded. Furthermore, upon BICR-assessed progression, subjects randomized to investigator choice arm will be given the option to receive olaparib.

No restrictions are made to prior or concurrent receipt of bone metastases targeting therapies with zoledronic acid or denosumab.

Investigational product, dosage and mode of administration

Subjects will receive either olaparib, enzalutamide, or abiraterone acetate.

Olaparib: Olaparib is available as a film-coated tablet containing 150 mg or 100 mg of olaparib. Subjects will be administered study treatment orally at a dose of 300 mg twice daily (bid). The planned dose of 300 mg bid will be made up of two x 150 mg tablets twice daily, with 100 mg tablets used to manage dose reductions.

Subjects should take doses at a similar time each day, with the twice daily doses taken approximately 12 hours apart. All doses should be taken with a glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Study tablets can be taken with or without food. On the PK sampling day subjects should fast from 1 hour before taking the olaparib dose to two hours after.

Enzalutamide: Enzalutamide is available as capsules/tablets containing 40 mg of enzalutamide. Subjects will be administered study treatment orally at a dose of 160 mg once daily. Subjects should take enzalutamide doses at a similar time each day. Capsules/tablets should be swallowed whole and can be taken with or without food, in full accordance with local prescribing information.

Abiraterone acetate with prednisone: Abiraterone acetate is available as tablets containing 250 mg or 500 mg of abiraterone acetate. Subjects will be administered study treatment orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg administered twice daily orally. Subject should take abiraterone acetate doses at a similar time each day. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate and one hour after the dose of abiraterone acetate. The tablets should be swallowed whole with water and not crushed or chewed, in full accordance with local prescribing information.

Statistical methods

The primary analysis of rPFS primary endpoint will be performed after approximately 143 progression or death events have been accrued in 240 subjects in Cohort A (60% maturity) and would provide 95% power to show a statistically significant difference in rPFS at 2-sided 5% alpha level if the assumed true treatment effect was a HR=0.53 (corresponding to an assumed increase in median rPFS from 5 months (enzalutamide or abiraterone acetate) to 9.5 months (olaparib). [redacted]

It is anticipated that the study accrual period will be approximately 28 months and that 143 progression and death events will occur approximately 35 months after the first subject is randomized in the study. rPFS will be analyzed using a log rank test stratified by previous taxane (yes, no) and measurable disease (yes, no) and the corresponding p value will be generated. The hazard ratio together with its corresponding 95% confidence interval will be estimated using a Cox Proportional Hazards Model.

If the primary analysis of rPFS in Cohort A demonstrates statistical significance, testing of key secondary endpoints ORR (Cohort A), rPFS (Cohort A+B), time to pain progression (Cohort A) and OS (Cohort A) will be performed in a hierarchical manner using the alpha level recycled from the primary endpoint.

Safety analyses will be presented using the Safety Analysis Set and will be done by means of descriptive statistics in Cohorts A, B and A+B. Safety profiles will be assessed in terms of AEs, vital signs (including BP and pulse rate), ECG, laboratory data (clinical chemistry and hematology), and physical examination.

Analyses on Cohorts B and A+B will be performed at the time of primary rPFS analysis in Cohort A.

Pharmacokinetic analysis

The plasma concentration-time data will be analyzed by non-linear mixed effects modelling in order to evaluate the pharmacokinetic characteristics of olaparib, quantify variability in the pharmacokinetics, identify demographic or pathophysiological covariates which may explain the observed variability and explore exposure-response relationships.

TABLE OF CONTENTS PAGE

TITLE PAGE 1
VERSION HISTORY 2
PROTOCOL SYNOPSIS 7
TABLE OF CONTENTS 16
1. INTRODUCTION 27
1.1 Background and rationale for conducting this study 27
1.1.1 Advanced prostate cancer and its treatment 27
1.1.1.1 Standard-of-care therapy in mCRPC failing abiraterone or enzalutamide 28
1.1.1.2 Standard-of-care therapy in mCRPC who have failed abiraterone acetate and/or enzalutamide and docetaxel (+/-cabazitaxel) 29
1.1.2 Research hypothesis 29
1.1.3 PARP inhibition as a target for HRR mutation positive mCRPC 29
1.1.4 Pre-clinical experience 30
1.1.5 Toxicology and safety pharmacology summary 30
1.1.6 Clinical experience 30
1.1.6.1 Preliminary Report of Olaparib Activity in Prostate Cancer (Sandhu et al 2013) 31
1.1.6.2 TOPARP A (Mateo et al 2015) 31
1.2 Rationale for study design, doses and control groups 32
1.2.1 Rationale for developing the Lynparza Homologous Recombination Repair (HRR) Assay 33
1.3 Benefit/risk and ethical assessment 33
1.4 Study Design 34
2. STUDY OBJECTIVES 36
2.1 Primary objectives 36
2.2 Secondary objectives 36
2.3 Safety objectives 39
2.4 Exploratory objectives 39
3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL 41
3.1 Inclusion criteria 41
3.2 Exclusion criteria 43
3.3 Subject enrollment and randomization 46

3.4 Procedures for handling incorrectly enrolled or randomized Subjects 46
3.5 Methods for assigning treatment groups 47
3.6 Methods for ensuring blinding 47
3.7 Methods for unblinding 47
3.8 Restrictions 47
3.8.1 Grapefruit juice 48
3.8.2 Contraception 48
3.8.3 Blood donation 48
3.9 Discontinuation of investigational product 48
3.9.1 Procedures for discontinuation of a subject from investigational product 49
3.10 Criteria for study withdrawal 49
3.10.1 Screen failures 50
3.10.2 Withdrawal of the informed consent 50
3.11 Discontinuation of the study 51
4. STUDY SCHEDULE AND TIMING OF PROCEDURES 52
4.1 Enrollment/screening period 63
4.1.1 Re-Screening 63
4.2 Treatment period 63
4.2.1 Subjects who switch to olaparib 64
4.3 Follow-up period 64
5. STUDY ASSESSMENTS 65
5.1 Efficacy assessments 65
5.1.1 Imaging tumor assessments 65
5.1.1.1 CT and MRI scans tumor assessments (RECIST 1.1) 66
5.1.1.2 Bone scans tumor assessment (based on PCWG3 criteria) 67
5.1.2 Tumor evaluation 67
5.1.3 Second progression 69
5.1.4 Symptomatic skeletal related events (SSRE) 69
5.1.5 PSA Assessments 69
5.2 Safety assessments 69
5.2.1 Laboratory safety assessments 69
5.2.1.1 Coagulation 70
5.2.1.2 Bone marrow or blood cytogenetic samples 70
5.2.2 Physical examination 71
5.2.3 ECG 71
5.2.3.1 Resting 12-lead ECG 71
5.2.4 Vital signs 71
5.2.4.1 Pulse and blood pressure (BP) 71
5.2.4.2 Body temperature 71

5.3 Other assessments 71
5.3.1 Patient reported outcomes 71
5.3.1.1 BPI-SF 72
5.3.1.2 FACT-P 73
5.3.1.3 PRO-CTCAE 73
5.3.1.4 Patient Global Impression of Change (PGIC) 74
5.3.1.5 Analgesic Log 74
5.3.1.6 Analgesic Use Scoring 74
5.3.1.7 EQ-5D-5L 75
5.3.2 Administration of PRO questionnaires 76
5.3.3 Healthcare Resource Use 77
5.3.3.1 Assessment of Healthcare Resource Use 78

5.4 Pharmacokinetics 78
5.4.1 Collection of samples 78
5.4.2 Determination of drug concentration 78
5.4.3 Storage and destruction of pharmacokinetic samples 78

5.5 Pharmacodynamics 79

5.6 Pharmacogenetics 79
5.6.1 Collection of pharmacogenetics samples 79

5.7 Biomarker analysis 79
5.7.1 HRR gene panel testing of tumor biopsy sample 79
5.7.2 Collection, Analysis and Reporting of Tumor Samples 79
5.7.3 Blood Sample for Germline HRR Testing 80
5.7.3.1 Screening Part 1: Optional Blood Sample for Germline Testing 81
5.7.3.2 Screening Part 2: Mandatory Blood Sample for Germline Testing 81
5.7.4 Exploratory blood samples for biomarker analysis (e.g., ctDNA analysis) 81
5.7.5 Circulating tumor cells (CTCs) 81
5.7.6 Exploratory use of residual biomarker samples and data generated from tumor testing (Optional) 82
5.7.7 Storage, re-use and destruction of biological samples 82
5.7.8 Labelling and shipment of biological samples 82
5.7.9 Chain of custody of biological samples 82
5.7.10 Withdrawal of Informed Consent for donated biological samples 83

6. SAFETY REPORTING AND MEDICAL MANAGEMENT 83

6.1 Definition of adverse events 83
6.1.1 Olaparib adverse events of special interest 83

6.2 Definitions of serious adverse event 84

6.3 Recording of adverse events 84
6.3.1 Time period for collection of adverse events 84
6.3.1.1 Adverse events after the 30 day follow up period 84
6.3.2 Follow-up of unresolved adverse events 85
6.3.3 Variables 85

6.3.4 Causality collection 86
6.3.5 Adverse events based on signs and symptoms 86
6.3.6 Adverse events based on examinations and tests 87
6.3.7 Hy's Law 87
6.3.8 Disease progression 87
6.3.9 New cancers 88
6.3.10 Lack of efficacy 88
6.3.11 Deaths 88

6.4 Reporting of serious adverse events 88

6.5 Overdose 89

6.6 Pregnancy 89
6.6.1 Paternal exposure 90

6.7 Management of toxicities related to olaparib 90
6.7.1 Management of hematological toxicity 90
6.7.1.1 Management of anemia 90
6.7.1.2 Management of neutropenia, leukopenia and thrombocytopenia 91
6.7.1.3 Management of prolonged hematological toxicities while on study treatment 92
6.7.2 Management of non-hematological toxicity 92
6.7.2.1 Management of new or worsening pulmonary symptoms 92
6.7.2.2 Management of nausea and vomiting 93
6.7.2.3 Interruptions for intercurrent non-toxicity related events 93

6.8 Management of toxicities related to enzalutamide and abiraterone acetate 94
6.8.1 Dose adjustment recommendations for enzalutamide 94
6.8.2 Dose adjustment recommendations for abiraterone acetate 94

6.9 Medication error 94

6.10 Study governance and oversight 94
6.10.1 Steering Committee 94
6.10.2 Data Monitoring Committee 95

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS 95

7.1 Identity of investigational product and comparators 95

7.2 Dose and treatment regimens 95

7.3 Labelling 97

7.4 Storage 97

7.5 Compliance 97

7.6 Accountability 98

7.7 Concomitant and other treatments 98
7.7.1 Other concomitant treatment 101

8. STATISTICAL ANALYSES BY ASTRAZENECA 101
8.1 Statistical considerations 101
8.2 Sample size estimate 101
8.3 Definitions of analysis sets 102
8.3.1 Efficacy analysis set 102
8.3.2 Safety analysis set 102
8.3.3 PK analysis set 103
8.3.4 PRO analysis set 103
8.4 Outcome measures for analyses 104
8.4.1 Primary Endpoints 104
8.4.1.1 Radiological Progression Free Survival (rPFS) 104
8.4.2 Secondary Endpoints 105
8.4.2.1 Confirmed Overall Objective Response Rate (ORR) 105
8.4.2.2 Time to Pain Progression 105
8.4.2.3 Overall Survival 106
8.4.2.4 Time to first Symptomatic Skeletal –Related Event (SSRE) 106
8.4.2.5 Duration of Response 106
8.4.2.6 Time to Opiate Use for Cancer Pain 107
8.4.2.7 Prostate Specific Antigen (PSA) Response 107
8.4.2.8 Circulating Tumor Cell (CTC) Conversion rate 107
8.4.2.9 Time from randomization to second progression or death (PFS2) 107
8.4.2.10 Pain Severity 107
8.4.2.11 Pain Interference 108
8.4.2.12 FACT-P 108
8.4.2.13 Pain Palliation 110
8.4.2.14 Pharmacokinetic Endpoints 110
8.4.3 Exploratory Endpoints 110
8.4.3.1 PRO-CTCAE 110
8.4.3.2 Patient Global Impression of Change (PGIC) 110
8.4.3.3 Resource Use 110
8.4.3.4 EQ-5D-5L 110
8.4.4 Safety Endpoints 111
8.4.4.1 Adverse Events 111
8.4.4.2 Other significant Adverse Events (OAE) 111
8.4.4.3 Concomitant medications 111
8.4.4.4 Compliance and exposure 112
8.5 Methods for statistical analyses 112
8.5.1 Multiplicity Strategy for Primary Endpoint and Key Secondary endpoints 112
8.5.2 Analysis of the primary variable(s) 113
8.5.2.1 Radiological Progression Free Survival 113
8.5.3 Analysis of the secondary variable(s) 114
8.5.3.1 Confirmed Objective Response Rate (ORR) 114
8.5.3.2 Time to Pain Progression: 115

8.5.3.3 Overall Survival 115
8.5.3.4 Time to first Symptomatic Skeletal-Related Event (SSRE) 116
8.5.3.5 Duration of Response: 116
8.5.3.6 Time to Opiate use for Cancer related Pain 116
8.5.3.7 Prostate Specific Antigen (PSA) Response 116
8.5.3.8 Circulating Tumor Cell (CTC) conversion rate 116
8.5.3.9 Time from randomization to second progression or death 117
8.5.3.10 PK Analysis 117
8.5.4 Subgroup analysis 117
8.5.5 Interim analysis 118
8.5.6 Sensitivity analysis 119
8.5.6.1 Sensitivity analyses for rPFS 119
8.5.7 Supportive analyses 121
8.5.7.1 Patient reported outcomes (PRO) 121
8.5.7.2 EQ-5D-5L 121
8.5.7.3 Resource Use 122
8.5.8 Safety Analyses 122
8.5.8.1 Adverse events 122
8.5.8.2 Dose-limiting toxicities 122
8.5.8.3 Laboratory data 122
8.5.8.4 Concomitant medications 122
8.5.8.5 Vital signs 123
8.5.8.6 Other safety variables 123
8.5.8.7 Exposure and compliance 123

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA 124
9.1 Training of study site personnel 124
9.2 Monitoring of the study 124
9.2.1 Source data 124
9.2.2 Study agreements 124
9.2.3 Archiving of study documents 125
9.3 Study timetable and end of study 125
9.4 Data management by AstraZeneca or delegate 125
10. ETHICAL AND REGULATORY REQUIREMENTS 126
10.1 Ethical conduct of the study 126
10.2 Subject data protection 126
10.3 Ethics and regulatory review 127
10.4 Informed consent 127
10.5 Changes to the protocol and informed consent form 128
10.6 Audits and inspections 128

11. LIST OF REFERENCES 129

LIST OF TABLES

Table 1 Composite response rates (primary endpoint) by biomarker status (Mateo et al 2015) 32
Table 2 Study Schedule – Screening (Part 1 and 2) 53
Table 3 Study Schedule – On Study Treatment and Discontinuation 55
Table 4 Study Schedule – Follow-up Post Discontinuation of Study Treatment 59
Table 5 Study Schedule – Subjects switching to olaparib 61
Table 6 Requirements for documentation of progression 68
Table 7 Laboratory Safety Variables 70
Table 8 Treatment assignment by Tumor Sample Mutation Result 79
Table 9 Management of anemia 90
Table 10 Management of neutropenia, leukopenia and thrombocytopenia 91
Table 11 Dose reductions for olaparib 93
Table 12 Identity of investigational product and comparators 95
Table 13 Summary of Outcome Variables and Analysis Populations 103
Table 14 Definition of visit response for FACT-P, FAPSI-8, TOI, PCS and FWB 109
Table 15 Overall score response criteria 109
Table 16 Summary of Methods of Assessment 148
Table 17 Evaluation of target lesions 151
Table 18 Evaluation of Non-Target Lesions 151
Table 19 Overall Visit Soft Tissue Response 152
Table 20 Bone progression status 154
Table 21 Overall radiological visit response 155
Table 22 Best overall response when confirmation of CR and PR required. 155

LIST OF FIGURES

Figure 1 Study Diagram 35
Figure 2 Study Flow Chart 52
Figure 3 Assessment of Progression by BICR (prior to primary rPFS analysis) 66
Figure 4 Multiplicity Strategy Maintaining Overall Type I Error Rate 113

LIST OF APPENDICES

Appendix A Additional Safety Information 135
Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document 138
Appendix C Pharmacogenetics Research 139
Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law 142
Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors) in Soft Tissue and PCWG3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions 147
Appendix F Acceptable birth control methods 157
Appendix G Patient Reported Outcomes 158
Appendix H Performance Status (ECOG/KARNOFSKY SCALES) 170

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
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboblastin Time
AST	Asparate Aminotransferase
ATM	Ataxia Telangiectasia Mutated
BICR	Blinded Independent Central Review
bid	Twice daily
BP	Blood Pressure
BPI-SF	Brief Pain Inventory- Short Form
BRCA1, BRCA2	Breast Cancer 1 gene or Breast Cancer 2 gene
BUN	Blood Urea Nitrogen
CrCl	Creatinine Clearance
CRF	Case Report Form (electronic/paper)
CRPC	Castration-Resistant Prostate Cancer
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTA	Clinical Trial Assay
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCIS	Ductal Carcinoma *in situ*
DCO	Data cut-off
DNA	Deoxyribonucleic Acid
DoR	Duration of Response

Abbreviation or special term	Explanation
DSB	Double Strand Break
dUCBT	Double Umbilical Cord Blood Transplantation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group: a performance status using scales and criteria to assess how a subject's disease is progressing
EQ-5D-5L	EuroQol 5-dimension, 5-level health state utility index
FACT-P	Functional Assessment of Cancer Therapy- Prostate Cancer
FFPE	Formalin fixed, paraffin embedded
FMI	Foundation Medicine Inc.
FSH	Follicle Stimulating Hormone
FWB	Functional Well-Being
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HRCT	High Resolution Computed Tomography
HR	Hazard Ratio
HRD	Homologous Recombination Repair Deficiency
HRR	Homologous Recombination Repair
ICH	International Conference on Harmonization
ICI	International Coordinating Investigator
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LHRH	Luteinizing Hormone-Releasing Hormone
LSLV	Last Subject Last Visit
LIMS	Laboratory Information Management System
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MCV	Mean Cell Volume
MDS	Myelodysplastic Syndrome

Abbreviation or special term	Explanation
MGUS	Monoclonal Gammopathy of Undetermined Significance
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
NHA	New Hormonal Agent (abiraterone, enzalutamide)
NTL	Non-Target Lesion
OAE	Other Significant Adverse Event
od	Once daily
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase
PCR	Polymerase Chain Reaction
PCS	Prostate Cancer Subscale
PCWG3	Prostate Cancer Working Group 3
PGx	Pharmacogenetic research
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PRO-CTCAE	Patient Reported Outcomes- Common Terminology Criteria for Adverse Events
PSA	Prostate Specific Antigen
PWB	Physical Well-Being
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic Progression-Free Survival
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
SSB	Single Strand Breaks
SSRE	Symptomatic Skeletal Related Event (symptomatic fracture, need for radiation to bone metastasis, need for surgery for bone metastasis, spinal cord compression)
TL	Target Lesion

Abbreviation or special term	Explanation
TOI	Trial Outcome Index
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Advanced prostate cancer and its treatment

Prostate cancer has been associated with over-diagnosis and over-treatment in early stages (Shen and Kumar 2015), where cure rates are high and average long-term clinical outcomes favorable. However, it is a heterogeneous disease and no cure exists for those patients reaching the metastatic castration-resistant (mCRPC) stage of the disease. With an estimated incidence of 233,000 new cases and 29,480 deaths in 2014, it is the most frequently diagnosed non-skin cancer and second most frequent cause of cancer deaths in US males (American Cancer Society 2014). Similar prostate cancer mortality rates are reported for Western Europe (Center et al 2012). Almost all patients dying from prostate cancer will have mCRPC, and 90% of overall mortality in mCRPC patients is attributable to the underlying malignant disease (Scher et al 2015).

While a variety of life prolonging agents are approved for mCRPC, a median overall survival of about 3 years obtained with early treatment initiation such as abiraterone acetate and enzalutamide (Ryan et al 2013 and Beer et al 2014) still constitutes a grossly reduced life expectancy when compared to the about 15 years of life expectancy for age-matched men (~ 70 years) from the general population (US Social Security). Hence a high unmet medical need remains for men with mCRPC for efficacious and well tolerated therapies.

A small percentage of prostate tumors have loss of function mutations in candidate genes involved in homologous recombination repair (HRR) of DNA. *BRCA1, BRCA2*, or *ATM* are the most well-characterized and/or frequently mutated HRR genes in prostate cancer and hence form the basis for selecting a biomarker-defined target mCRPC population in this phase 3 registration study. The overall mutation frequency for these three genes is expected to be less than 15% (Kumar et al 2016, Mateo et al 2015 and Robinson et al 2015); furthermore, assuming a technical failure rate of 25% to determine *BRCA1, BRCA2*, or *ATM* mutations in tumor tissue obtained either by fresh biopsy or using archival tissue, only about 1 out of 10 patients with mCRPC will qualify for Cohort A of the proposed registration trial. It appears that about half of HRR gene mutations detectable in tumor tissue constitute germline mutations (the other half being somatic in nature, i.e., exclusively occurring in tumor tissue; Mateo et al 2015). While an adverse prognostic impact of germline *BRCA2* mutations has been described (Castro et al 2015), it is less clear if other germline or somatic HRR gene mutations are associated with similar adverse clinical outcomes. For patients with mCRPC there are no readily available clinical parameters known (e.g., age and Gleason score at initial diagnosis, metastatic

patterns) to phenotypically differentiate those patients with underlying tumor HRR gene mutations from those without HRR gene mutations (Mateo et al 2015).

However, mCRPC patients with HRR gene mutations have a high propensity to benefit from anti-cancer therapies resulting in an increased number of DNA double-strand breaks, such as the PARP inhibitor olaparib (Mateo et al 2015 and Kaufman et al 2015), and potentially platin compounds (Cheng et al 2015). Notably, in the phase II single arm study reported by Mateo et al. high response rates, including confirmed RECIST responses of > 50%, were observed with olaparib treatment in biomarker-positive patients (tissue HRR mutations) despite these patients having failed both abiraterone acetate and/or enzalutamide as well as docetaxel and the majority of them also having received cabazitaxel. Conversely, almost no responses were seen in biomarker-negative patients. A striking difference in biological activity of olaparib was also seen between biomarker-positive vs. – negative patients on other clinical outcomes such as radiologic progression free survival and overall survival (Mateo et al 2015). This phase 2 study is described in more detail in Section 1.1.6.1. An independent phase 2 clinical study reported by Kaufman et al 2015 included mCRPC patients with germline *BRCA1* or *BRCA2* mutations and found a similar rate (50%) of confirmed RECIST responses following treatment with olaparib.

There are no approved targeted treatments for mCRPC patients with tissue mutations of *BRCA1*, *BRCA2*, *ATM* or other HRR genes and their treatment is not different from non-selected mCRPC patients.

1.1.1.1 Standard-of-care therapy in mCRPC failing abiraterone or enzalutamide

New hormonal agents (NHA) such as abiraterone acetate and enzalutamide are potent, orally available treatment options with a favorable tolerability profile and have replaced docetaxel as preferred choice of first-line therapy for mCRPC (Flaig et al 2016). Both of these agents have demonstrated robust improvements on PFS and OS and have also shown a significantly prolonged time to initiation of cytotoxic chemotherapy (Ryan et al 2013 and Beer et al 2014). However, once mCRPC patients have failed NHA, the benefit from approved therapeutic options appears substantially diminished and no clear single standard of care exists as none of the currently approved agents have been developed for a post-NHA setting:

Taxanes: Unless symptomatic or with high tumor burden, few patients are expected to immediately receive docetaxel. For example, 48% of mCRPC patients never received docetaxel at a major U.S. academic center (Steinberger et al 2015).

Efficacy of docetaxel appears markedly reduced when given after NHA as compared to first line use (Mezynski et al 2012, Schweizer et al 2014), likely attributable to at least partial cross-resistance between taxanes and NHA (van Soest et al 2013).

The efficacy of docetaxel after failure of abiraterone acetate does not appear to be superior to that of enzalutamide (Sun and Chen 2010 and Suzman et al 2014).

Cabazitaxel appears to have a low real-world usage (Flaig et al 2016) and is approved only after failure of docetaxel.

Both docetaxel and cabazitaxel are administered per i.v. infusion and have boxed warnings for hypersensitivity reactions as well as neutropenia/neutropenic deaths.

NHA: Due to at least partial cross-resistance, switching from one NHA to the other is associated with reduced efficacy (Cheng et al 2015), with rPFS outcomes similar to those observed with docetaxel in a post-NHA setting (Sun and Chen 2010 and Suzman et al 2014).

Other agents: Sipuleucel-T and radium-223 are rarely used additional therapeutic options; their use is either limited regionally (sipuleucel-T: U.S.) and/or restricted to certain patient populations such as those with asymptomatic/minimally symptomatic disease (sipuleucel-T) or those with bone-only disease and symptoms (radium-223). Efficacy of these agents in a post-NHA setting is unknown.

In addition to limited efficacy, tolerability issues such as fatigue (Moreira et al 2016) and hematologic toxicity from taxanes may further limit use of available options and contribute to short real-world estimated median treatment durations between 10 weeks (taxane) and 14 to 17 weeks (NHA) in a second line setting (Flaig et al 2016). The median overall survival of patients who have failed NHA but have not previously received taxane chemotherapy appears to be between 8.6 months and 12.5 months (Azad et al 2015 and Mezynski et al 2012) reflecting a high unmet medical need for mCRPC patients who fail NHA.

1.1.1.2 Standard-of-care therapy in mCRPC who have failed abiraterone acetate and/or enzalutamide and docetaxel (+/-cabazitaxel)

Limited data are available for patients who failed both NHA and at least one taxane-based chemotherapy. As expected, in general, responses to treatments decrease with more lines of prior therapies, while differences in prognostic baseline factors still confer heterogeneity in clinical response measured by rPFS and OS (Caffo et al 2015). Additional data by (Mateo et al 2015 and Azad et al 2015) indicate a median overall survival of up to 10 months for these very advanced patients, reflecting a high unmet medical need for mCRPC patients who have failed prior NHA(s) and prior taxane(s).

1.1.2 Research hypothesis

Single agent olaparib at 300 mg bid has superior efficacy and an acceptable tolerability profile as compared with enzalutamide or abiraterone acetate in mCRPC patients with deleterious or suspected deleterious HRR gene mutations and who have previously failed treatment with an NHA such as enzalutamide or abiraterone acetate. The efficacy in this study will be assessed by the primary analysis of rPFS defined as the time from randomization until the date of objective radiological disease progression or death. Radiological assessments (RECIST 1.1 for soft tissue and PCWG3 for bone) will be based upon blinded, independent central review (BICR).

1.1.3 PARP inhibition as a target for HRR mutation positive mCRPC

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP-ribose)] polymerization (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 tumors with deficiencies in 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 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 (HRR). Tumors with homologous recombination deficiencies (HRD), such as mCRPC in patients with *BRCA1, BRCA2, ATM* or other HRR gene mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available taxane-based chemotherapy regimens.

HRR defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al 2009, Tutt et al 2010, Mateo et al 2015, and Kaufman et al 2015). The main mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011 and Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knockout models, either as a stand-alone treatment or in combination with established chemotherapies.

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 e.g., dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anesthetized dog or any behavioral, 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 the 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.

AstraZeneca considers that the advanced prostate cancer patient population involved in this study falls under the advanced cancer, limited life expectancy definition outlined in ICH S9 guideline "Non-clinical Evaluation For Anticancer Pharmaceuticals" and meets the requirements outlined in the guideline. Further information can be found in the current version of the olaparib IB

1.1.6 Clinical experience

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

1.1.6.1 Preliminary Report of Olaparib Activity in Prostate Cancer (Sandhu et al 2013)

The first report of olaparib monotherapy activity in advanced prostate cancer came from 3 patients with advanced prostate cancer and germline *BRCA2* mutations who were treated in Phase I studies. Each patient was castration-resistant before the start of olaparib therapy and 1 of them also received previous docetaxel and abiraterone acetate. Duration of olaparib treatment (300 mg bid tablet) ranged from 11 to 34 months for the 3 patients. The post-NHA post-taxane patient experienced a RECIST partial response and a PSA response (from 63 to 3.8 µg/l) under olaparib and remained on treatment for > 26 months.

1.1.6.2 TOPARP A (Mateo et al 2015)

TOPARP A was a multicenter phase 2 investigator-initiated single arm study (NCT01682772) in mCRPC patients conducted in the United Kingdom. Prior pre-treatment with docetaxel was required and almost all patients had at least one prior NHA, which rendered TOPARP A, a third line and above setting. Olaparib was administered daily at 400 mg bid tablets. The primary endpoint, composite response rate (RR), was defined as either objective response by RECIST 1.1 and/or PSA fall ≥50% and/or circulating tumor cell (CTC) count falls from ≥5 to <5/7.5 ml blood (Veridex™). For these components to each count as a primary endpoint event, confirmation by a second measurement at least 4 weeks later was required. The secondary endpoints for the study included safety, tolerability, progression-free survival (PFS), and overall survival (OS). Exome, transcriptome, targeted next-generation sequencing (NGS) and digital PCR tests were conducted from mandated biopsies (in 43 patients, mCRPC biopsy material was suitable for NGS, in the remaining 6 patients archival tumor tissue obtained at initial diagnosis was analyzed). Overall, 50 patients were enrolled; prior treatments included docetaxel (100%), cabazitaxel (58%), abiraterone acetate (96%), enzalutamide (28%), and palliative radiotherapy (26%).

Efficacy (overall population)

In the full population of evaluable patients (n = 49; one patient was lost to follow-up after 1 week and deemed non-evaluable by DMC, 16 (32.7%) responded to olaparib (95% CI: 20.0-47.5) by the composite response definition with 12 patients on treatment for >6 months. Six of 32 RECIST 1.1 measurable patients had radiological responses (18.8 %), and 11 patients had a biochemical response defined as a ≥50% decrease in PSA levels. Four of these responses lasted more than 1 year.

Efficacy by biomarker status

NGS identified homozygous deletions and/or deleterious mutations in DNA repair genes in 16/49 (32.7%) cases, including eight (8) patients with *BRCA1, BRCA2* and 5 with *ATM* alterations. Of the sixteen patients with DNA repair mutations, 14 (87.5%) responded to olaparib by the composite response definition including all 7/7 patients with *BRCA2* loss (4 bi-allelic somatic loss; 3 germline mutations) and 4/5 patients with *ATM* aberrations. Few responses were observed in biomarker-negative patients (no DNA repair mutations; 2/33 = 6% RR). Table 1 illustrates *composite* response rates by biomarker status.

Table 1 Composite response rates (primary endpoint) by biomarker status (Mateo et al 2015)

Biomarker	Responder		Total (n=49)
	No (n=33)	Yes (n=16)	
Negative	31 (93.9%)	2 (6.1%)	33
Positive	2 (12.5%)	14 (87.5%)	16

Median rPFS of the 16 marker positive patients was 9.8 months with a median OS of 13.8 months, as opposed to a markedly lower median rPFS of 2.7 months with a median OS of 7.5 months in patients without DNA repair gene mutations (Mateo et al 2015**)**.

Time on treatment ranged from 24 to 48 weeks (mean = 39 and median = 40 weeks) among the 7 patients with *BRCA2* mutations and from 11 to 73 weeks (mean = 43 and median = 57 weeks) among the 5 patients with *ATM* mutations. There were 3 patients still being treated with olaparib among the *BRCA2* subgroup at data cut-off.

Safety:

The most frequently observed AEs (all grades; irrespective of causality) were anemia (76%), fatigue (58%), nausea (36%) and arthralgia (30%). The most common grade >3 adverse events were anemia (20%) and fatigue (12%), with 26% of patients requiring a dose reduction.

1.2 Rationale for study design, doses and control groups

Based on data from the TOPARP A study (Mateo et al 2015) a decision was made to require the presence of a qualifying tissue HRR gene mutation as an inclusion criterion for patients with mCRPC who have failed prior therapy with an NHA. The molecular analysis will be performed by a designated central diagnostic provider (Foundation Medicine, Inc.) using an NGS assay, the investigational Lynparza HRR Assay. The rationale for only using *BRCA1, BRCA2* and *ATM* tissue mutations for the primary endpoint (Cohort A) is based upon the prevalence of these mutations and/or how well mutations in these genes are characterized to date. It is expected that qualifying mutations will be detectable in the tissue of about one out of 10 mCRPC patients.

While the TOPARP A trial was limited to patients who had failed both NHA and a taxane, this study will also enroll patient not yet having received taxane chemotherapy for mCRPC as there is a medical need for patients failing NHA both pre- and post-taxane (see Section 1.1.1.1 and Section 1.1.1.2) and as the biological activity of olaparib is expected to be independent of prior taxane therapy.

The randomization will be 2:1 (olaparib vs. enzalutamide or abiraterone acetate). Enzalutamide and abiraterone acetate were chosen as comparators for the following reasons:

- Enzalutamide and abiraterone acetate are broadly approved for the treatment of mCRPC. Switch to the alternate NHA mirrors a relevant real-world scenario for a situation in which no single standard of care exists (Vogelzang et al 2016).

- Similar efficacy compared to docetaxel in post-NHA setting (Sun and Chen 2010 and Suzman et al 2014), but oral availability and superior tolerability compared to taxanes make them the preferred treatment of choice.

- Documented effectiveness both pre and post docetaxel (de Bono et al 2011, Ryan et al 2013, Scher et al 2012 and Beer et al 2014).

Due to the open-label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with the primary analysis of rPFS based on blinded independent central review (BICR) of all scans. Also, acknowledging the bone predominance of mCRPC and the particular challenges of determining bone progression in patients with high skeletal tumor burden (Kluetz et al 2013), progression in bone will require confirmation by a repeat scan at least 6 weeks later as outlined in detail by PCWG3 criteria (Scher et al 2016).

The dose used in TOPARP A (400 mg tablets bid) was chosen at a time when information on the relative clinical activity with the tablet formulation was not fully complete; as a 300 mg bid tablet dose is now considered maximally effective and used across the ongoing olaparib development program, this dose has been chosen for this study.

1.2.1 Rationale for developing the Lynparza Homologous Recombination Repair (HRR) Assay

AstraZeneca has partnered with Foundation Medicine, Inc. (FMI) to develop a novel tumor tissue-based companion diagnostic – the Lynparza HRR Assay – for the detection of mutations in a panel of 15 HRR genes. The 15 genes that comprise the Lynparza HRR Assay are a subset of the genes covered in the FoundationOne® comprehensive cancer panel: a clinical-grade cancer gene profiling test which analyzes the coding sequence of 310 cancer-related genes plus introns from select genes for variants and/or rearrangements.

For each patient that passes tissue sample and sequencing quality control, FMI will generate a report specifying presence or absence of qualifying HRR gene mutations. A patient has a qualifying mutation if any deleterious or suspected deleterious mutation is found in the HRR genes. A mutation is regarded as deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site mutations), or select missense mutations well-known to be deleterious in ClinVar/BIC databases. Furthermore, larger scale alterations such as genomic truncating rearrangements or homozygous deletions will also be classified as qualifying. Patients without qualifying HRR gene mutations as determined by the Lynparza HRR Assay will not be eligible for the study.

1.3 Benefit/risk and ethical assessment

As the proposed study will be limited to biomarker-positive patients (i.e., those with qualifying mutations in *BRCA1*, *BRCA2*, or *ATM* [Cohort A] or other HRR genes [Cohort B]) for which strong clinical activity can be expected (Mateo et al 2015 and Kaufman et al 2015) and as olaparib has been

found to be well tolerated across various cancer entities, a positive benefit/risk profile is expected and no ethical issues are identified from exposing patients to olaparib within the planned registration trial.

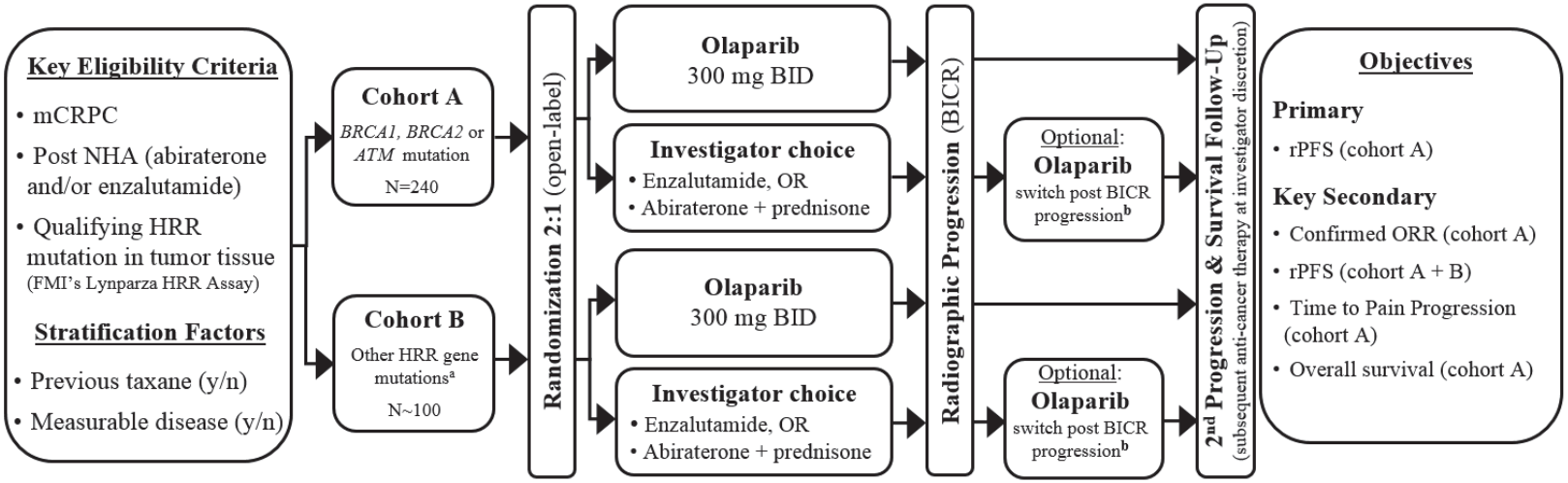
More detailed information about the known and expected benefits and risks of olaparib may be found in the current version of the olaparib IB.

See Section 6.10.2 for information regarding the Data Monitoring Committee.

1.4 Study Design

This is a prospective, multicenter, open-label, randomized phase 3 trial evaluating the efficacy and safety of olaparib (300 mg orally bid) versus investigator choice of either enzalutamide (160 mg orally od) or abiraterone acetate (1,000 mg orally od with 5 mg bid prednisone) in approximately 340 subjects with mCRPC with qualifying HRR gene mutations who have failed prior treatment with an NHA. [redacted] Prior to randomization, approximately 5500 subjects will be centrally screened for eligibility based on tumor tissue testing using the Lynparza HRR assay (FMI, Cambridge MA). Subjects with *BRCA1, BRCA2* or *ATM* qualifying gene mutations will be included in Cohort A whereas subjects with mutations among 12 other genes involved in HRR (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*) will be included in Cohort B. Subjects will be randomized 2:1 to either olaparib or predeclared investigator choice of either enzalutamide or abiraterone acetate in each of the Cohorts A and B. Randomization will be stratified based on prior receipt of taxane chemotherapy (yes vs no) and presence of measurable disease at baseline (yes vs no).

Figure 1 Study Diagram



[a] Cohort B HRR genes include *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L.*
[b] Subjects randomized to investigator choice arm will be given the opportunity to begin treatment with open-label olaparib (300 mg bid) only after objective radiographic progression by blinded independent central reader (BICR). No intervening systemic anti-cancer therapy following discontinuation of randomized treatment will be permitted. Subjects may continue on olaparib as long as they show clinical benefit as judged by the investigator.

[redacted]

2. STUDY OBJECTIVES

2.1 Primary objectives

Primary Objective:	**Outcome Measure:**
To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with mCRPC with *BRCA1*, *BRCA2* or *ATM* qualifying mutations (Cohort A)	• rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

2.2 Secondary objectives

Key Secondary Objective:	**Outcome Measure:**
To determine the efficacy (as assessed by ORR) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Confirmed ORR by BICR assessment in subjects with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying mutations (Cohort A+B). [redacted]	• rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
To determine the efficacy (as assessed by time to pain progression) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Pain progression based on BPI-SF item 3 “worst pain in 24 hours” and opiate analgesic use (AQA score)
To determine the efficacy (as assessed by overall survival) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Overall survival (OS)

Other Secondary Objectives:	**Outcome Measure:**
To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A)	• Time from randomization to the first SSRE • Time from partial or complete response in subjects with measurable disease (RECIST 1.1) to progression by BICR (DoR) • Time from randomization to opiate use for cancer-related pain • Confirmed ORR (RECIST 1.1) in soft tissue by BICR in subjects with measurable disease (Soft tissue response) • Proportion of Subjects achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA_{50} response) • Proportion of Subjects achieving a decline in the number of CTCs from ≥ 5 cells/7.5mL to < 5 cells/7.5mL whole blood (CTC conversion rate) • Time from randomization to second progression by investigator assessment of radiological or clinical progression or death (PFS2)
To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A) on disease-related symptoms and health-related quality of life (HRQoL)	• Pain severity progression based on BPI-SF Pain Severity domain/subscale and opiate analgesic use (AQA score) • Pain interference based on BPI-SF Pain Interference domain/subscale • FACT-P (FACT-P total score, trial outcome index [TOI], functional well-being [FWB], physical well-being [PWB], prostate cancer subscale [PCS], and FACT Advanced Prostate Symptom Index 6 [FAPSI 6]) • Proportion of Subjects with pain (BPI-SF item 3) score ≥ 4 points at baseline who have a decrease of ≥ 2 points in pain (BPI-SF item 3) and without ≥ 1 point increase in analgesic score (AQA score) at 12 weeks, confirmed at least 3 weeks later (Pain palliation)

To assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations other than *BRCA1*, *BRCA2* or *ATM* (Cohort B). [redacted]	• rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria • Confirmed ORR by BICR assessment in subjects with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria • Pain progression based on BPI-SF item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) • OS
To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations (Cohort A+B). [redacted]	• Confirmed ORR by BICR assessment in subjects with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria • Time from randomization to the first SSRE • Time from partial or complete response in subjects with measurable disease (RECIST 1.1) to progression by BICR (DoR) • Time from randomization to opiate use for cancer-related pain • Confirmed ORR (RECIST 1.1) in soft tissue by BICR in subjects with measurable disease (Soft tissue response) • Proportion of Subjects achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA_{50} response) • Proportion of Subjects achieving a decline in the number of CTCs from ≥ 5 cells/7.5mL to < 5 cells/7.5mL whole blood (CTC conversion rate) • Time from randomization to second progression by investigator assessment of radiological or clinical progression or death (PFS2) • OS

To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations (Cohort A+B) on disease-related symptoms and health-related quality of life (HRQoL). [redacted]	• Pain progression based on BPI-SF item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) • Pain severity progression based on BPI-SF Pain Severity domain/subscale and opiate analgesic use (AQA score). • Pain interference based on BPI-SF Pain Interference domain/subscale • FACT-P (FACT-P total score, trial outcome index [TOI], functional well-being [FWB], physical well-being [PWB], prostate cancer subscale [PCS] and FACT Advanced Prostate Symptom Index 6 [FAPSI 6]) • Proportion of Subjects with pain (BPI-SF item 3) score ≥ 4 points at baseline who have a decrease of ≥ 2 points in pain (BPI-SF item 3) and without ≥ 1 point increase in analgesic score (AQA score) at 12 weeks, confirmed at least 3 weeks later (Pain palliation)
To determine the exposure to olaparib in a subset of subjects receiving olaparib. [redacted]	• Olaparib plasma concentration data

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of olaparib versus investigator choice of enzalutamide or abiraterone acetate	• AEs/SAEs • Collection of clinical chemistry/hematology parameters

2.4 Exploratory objectives

These exploratory objective analyses may be reported separately from the clinical study report.

Exploratory Objective:	**Outcome Measure:**
To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate on patient-reported treatment tolerability and overall health status	• PRO-CTCAE • PGIC

To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying mutations (Cohort A) based on prior receipt of taxane	• Subgroup analysis of rPFS in subjects with or without prior taxane
To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with either germline or somatic *BRCA1*, *BRCA2* or *ATM* qualifying mutations (Cohort A).	• Subgroup analysis of rPFS based on whether the qualifying mutation is a germline mutation or only in the tumor (somatic)
To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2*, or *ATM* qualifying mutations as detected by ctDNA analysis. [redacted]	• rPFS analysis in patients with qualifying mutation identified by ctDNA test
To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying mutations as detected by ctDNA analysis. [redacted]	• rPFS analysis in patients with qualifying mutation identified by ctDNA test
To explore methods of estimating OS adjusting for the impact of the control arm receiving subsequent PARP inhibitors (including olaparib), platinum compounds or imbalances between the treatment arms for other potentially active agents	• OS adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents)
To compare the tumour HRR gene mutation status in all screened subjects with evaluable results from plasma. [redacted]	• Comparison of HRR gene mutation status between tumor DNA and plasma derived ctDNA

Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumor samples that were mandatory for entry onto the study or on blood samples. [redacted]	• Evaluate loss of heterozygosity of HRR genes in tumors • Evaluation of ctDNA collected from plasma at baseline and at progression • CTCs (EPIC assay)
To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional)	• Blood sample pharmacogenetics analysis
To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason of hospitalizations and hospital attendances, procedures conducted and hospital length of stay (HOSPAD) • EQ-5D-5L

3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject must 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.

Following written informed consent, all subjects will undergo central HRR gene mutation status assessment using the Lynparza HRR Assay (see Section 5.7.1 and Section 5.7.2) and initial eligibility criteria review, as defined by the marked criteria (*) in Section 3.1 Inclusion criteria and Section 3.2 Exclusion criteria, below.

Subjects should not be pre-screened based on prior germline results since approximately half of subjects are expected to carry mutations only in the tumor and not germline. In addition, subjects may undergo testing using HRR Lynparza Assay before progression on NHA.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfill the following criteria:

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

2. *Male ≥ 18 years of age.

3. *Histologically confirmed diagnosis of prostate cancer.

4. *Candidate for treatment with enzalutamide or abiraterone acetate with documented current evidence of metastatic castration-resistant prostate cancer, where metastatic status is defined as at least one (1) documented metastatic lesion on either bone scan or CT/MRI scan. Subjects whose disease spread is limited to regional pelvic lymph nodes or local recurrence (e.g., bladder, rectum) are not eligible.

5. Subjects must have progressed on prior NHA (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC. Determination of progression is done per local investigator.

6. Serum testosterone levels ≤ 50 ng/dL (≤ 1.75 nmol/L) within (≤) 28 days before randomization.

7. *Subjects without prior surgical castration must be currently taking and willing to continue luteinizing hormone-releasing hormone (LHRH) analog (agonist or antagonist) therapy throughout the duration of study treatment.

8. Radiographic progression at study entry while on androgen deprivation therapy (or after bilateral orchiectomy). Determination of progression is done per local investigator.

9. Qualifying HRR mutation in tumor tissue by the Lynparza HRR Assay (see Section 5.7.1 and Section 5.7.2).

   – Either archival or de novo biopsies are acceptable.

   – If subjects have a mutation in one of the 15 HRR genes based on prior prostate cancer tissue specimen testing by the commercially available FoundationOne ® assay, they must have the mutation confirmed as a qualifying mutation by FMI. Residual DNA (stored at FMI) from the original FoundationOne test will be used for confirmation. Subjects who do not have sufficient residual DNA from their original test will be analysed in-silico for qualifying HRR gene mutations based on their original FoundationOne test data, but these subjects must supply sufficient formalin fixed, paraffin embedded (FFPE) tumor sample to carry out retrospective central confirmation using the Lynparza HRR Assay (see Section 5.7.2). [redacted]

10. Subjects must have normal organ and bone marrow function measured within (≤) 28 days prior to administration of study treatment as defined below:

   – Hemoglobin ≥ 10.0 g/dL with no blood transfusions in the past 28 days.

   – Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.

   – Platelet count ≥ 100 x 10^9/L.

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN).
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN.
- Subjects must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation for males or based on a 24 hour urine test.

$$\text{Estimated creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

11. *Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix H).

12. *Subjects must have a life expectancy ≥ 16 weeks.

13. Must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male subjects should also use a highly effective form of contraception ([see Appendix F for acceptable methods]) if they are of childbearing potential.

14. *Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations at the institution, and completing electronic PRO instruments.

For inclusion in i) the optional exploratory genetic research, subjects must fulfill the following criteria:

- Provision of informed consent for genetic research.

If a subject declines to participate in the optional exploratory genetic research, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study.

3.2 Exclusion criteria

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

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

2. *Previous randomization in the present study.

3. Participation in another clinical study with an investigational product during the last 30 days prior to randomization.

4. *Any previous treatment with PARP inhibitor, including olaparib.

5. *Subjects who have any previous treatment with DNA-damaging cytotoxic chemotherapy, except if for non-prostate cancer indication and last dose > 5 years prior to randomization. For example, subjects who have received prior mitoxantrone or platinum-based chemotherapy for prostate cancer are excluded.

   – Prior estramustine is allowed.

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

7. *Subjects with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

8. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

9. Subjects receiving any systemic anti-cancer therapy (except radiotherapy) within 3 weeks prior to study treatment.

   – Agents to maintain castrate status are authorized as detailed in inclusion criterion #7. Agents such as 5-α reductase inhibitors (finasteride, dutasteride), estrogen compounds (including estramustine) and megesterol are considered as anti-cancer agent and prohibited within 3 weeks prior to study treatment.

   – Bone-targeted therapy with denosumab or zoledronic acid is allowed. If subjects are being treated with these agents, they should be on a stable regimen when entering the study.

10. *Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.

11. *Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents.

12. *Persistent toxicities (> grade 2, per the Common Terminology Criteria for Adverse Event (CTCAE)) caused by previous cancer therapy, excluding alopecia or toxicities related to the use of LHRH agonist or antagonist.

13. *Subjects with known brain metastases. A scan to confirm the absence of brain metastases is not required.

14. *Subjects with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

15. Subjects inevaluable for both bone and soft tissue progression as defined by meeting both of the following criteria:

    (a) A bone scan referred to as a superscan showing an intense symmetric activity in the bones.

    (b) No soft tissue lesion (measurable or non-measurable) that can be assessed by RECIST.

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

17. *Subjects considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

18. *Subjects unable to swallow orally administered medication and subjects with gastrointestinal disorders likely to interfere with absorption of the study medication.

19. *Immunocompromised subjects, e.g., subjects who are known to be serologically positive for human immunodeficiency virus (HIV).

20. *Subjects with a known hypersensitivity to olaparib or any of the excipients of the product.

21. *Subjects with known active hepatitis (i.e., Hepatitis B or C)

    – Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible.

    – Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

22. *Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

23. *Whole blood transfusions in the last 120 days prior to entry into the study (packed red blood cells and platelet transfusions are acceptable, for timing, refer to inclusion criteria no.10).

For procedures for withdrawal of incorrectly enrolled subjects, see Section 3.4.

3.3 Subject enrollment and randomization

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

The Investigator(s) will:

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

2. Assign potential subject a unique enrollment number (i.e., E-code) using the centralized Interactive Voice/Web Response System (IVRS/IWRS). The E-code is sequentially issued and will be used to identify the subject on all study-related documents including the electronic case report form (eCRF).

3. Determine subject eligibility. See Sections 3.1 and 3.2.

4. The investigator must declare their choice of either enzalutamide or abiraterone acetate using the IVRS/IWRS.

5. Assign eligible subject unique randomization code

If the subject is found to be ineligible during screening, the subject must be screen failed in the IVRS/IWRS. Specific directions concerning the use of the IVRS/IWRS will be provided in a separate instruction manual. If a subject withdraws from participation in the study then his assigned codes cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized Subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Subjects in Cohort A and Cohort B will be randomized in a 2:1 ratio to olaparib or investigator choice of enzalutamide or abiraterone acetate.

The randomization codes will be computer generated using a randomization system (AZRand) and loaded into the interactive voice response system/interactive web response system (IVRS/IWRS) database. A blocked randomization list will be generated to ensure an approximate balance between the olaparib and enzalutamide or abiraterone acetate arms in Cohorts A and B (2:1). The randomization will be stratified by previous taxane use (yes, no) and whether subject had measurable disease (yes, no).

Randomization will be done centrally via IVRS/IWRS after subject eligibility is established and prior to treatment. Every effort should be made to minimize the time between randomization and starting the study drug. It is recommended that subjects commence study drug as soon as possible after randomization.

Separate randomization schedules will be generated for Cohorts A and B as follows:

1. Cohort A: Subjects with mCRPC with previous NHA among subjects with either a *BRCA1, BRCA2* or *ATM* qualifying gene mutation. Subjects will be randomized either to olaparib or investigator choice of enzalutamide or abiraterone acetate.

2. Cohort B: This cohort will assess olaparib activity among subjects in the same setting but with qualifying mutations among 12 other genes involved in the HRR pathway (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*). Subjects will be randomized either to olaparib or investigator choice of enzalutamide or abiraterone acetate

For each subject, the IVRS/IWRS will identify a unique kit ID number corresponding to the randomization code matching the treatment arm assigned to the subject. Following treatment allocation, the first dose of study medication should be administered to the subject after completion of study visit procedures. At subsequent dispensing visits, the subject will be dispensed medication with the kit ID as allocated by the IVRS/IWRS.

If a subject receives incorrect treatment at any time during the study, the center must immediately notify the AstraZeneca representative and IVRS/IWRS contact for immediate correction, where possible.

3.6 Methods for ensuring blinding

Not applicable.

3.7 Methods for unblinding

Not applicable.

3.8 Restrictions

For restricted medications please see Section 7.7.

3.8.1 Grapefruit juice

It is prohibited to consume grapefruit juice while on olaparib therapy.

3.8.2 Contraception

Subjects must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male subjects should also use a highly effective form of contraception (as described in Appendix F) if they are of childbearing potential. Subjects should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

For details of acceptable methods of contraception refer to Appendix F Acceptable Birth Control Methods.

3.8.3 Blood donation

Subjects should not donate blood or plasma while participating in this study and for 3 months following the last dose of study treatment.

3.9 Discontinuation of investigational product

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

- Subject decision: The subject is at any time free to discontinue treatment, without prejudice to future treatment
- Adverse Event
- Severe non-compliance with the study protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Objective radiographic progression by blinded independent central review (BICR) as defined in Section 5.1.2.
- Unequivocal clinical progression:
  - Cancer pain requiring initiation of chronic administration of opioids, or
  - Immediate need to initiate cytotoxic chemotherapy, radiation therapy, or surgical intervention for complications due to tumor progression, or
  - Deterioration in ECOG performance status to ≥ Grade 3.
- Initiation of restricted anticancer therapy (see Section 7.7).

The reason for IP discontinuation will be recorded in the eCRF.

3.9.1 Procedures for discontinuation of a subject from investigational product

By discontinuing from IP, the subject is not withdrawn from the study. Subjects should be followed for progression (if discontinuation in the absence of progression) and OS following treatment discontinuation as per the study schedule. If a subject is withdrawn from study, see Section 3.10.

Any subject discontinuing investigational product should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule (see study schedule Table 3). The subject's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the principal Investigator/Sub-Investigator 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 subject. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If subjects discontinue study treatment, the AstraZeneca monitor must be informed immediately. Subjects will be required to attend the treatment discontinuation visit (see study schedule Table 3). The subject should return all study medication.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the subjects underlying disease, or the subject is lost to follow up (see Section 6.3.2). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4) and followed to resolution as above. Subjects should be seen at least 30 days after discontinuing study medication to collect and / or complete AE information. For guidance on reporting adverse events after the 30 day follow up period see Section 6.3.1.1.

After completing the treatment discontinuation visit and the 30 day safety follow-up visit, subjects will proceed directly with follow-up visits as defined in the study schedule (see Table 4). For subjects who discontinue study treatment after BICR progression, the first 12 week follow-up visit will be 12 weeks after the discontinuation of study treatment. Subjects who discontinue therapy prior to radiographic progression will continue with follow-up visits every 8 weeks per the original schedule until documentation of radiographic progression by BICR (see Table 4). There is no plan for BICR to read any scans dated after the date of data cut-off (DCO) for the primary analysis. There will be no need to request confirmation of BICR PD after this time point, and the investigator-assessed radiographic progression will prevail. [redacted] All adverse events occurring after the 30 day safety follow-up visit will be assessed at the first follow-up visit.

While it is preferred that follow-up visits post radiographic progression and discontinuation of study treatment are conducted in-person, subjects may proceed with a modified follow-up (i.e., through regular telephone contacts, every 12 weeks or a contact at study closure, if agreed to by the subject and in compliance with local data privacy laws/practices). All subjects will be followed until death or end of study (see Section 9.3).

3.10 Criteria for study withdrawal

The term withdrawal from the study refers to both discontinuation from study treatment and study assessments.

Reasons for withdrawal from the study:

- Voluntary withdrawal by the subject who is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Incorrectly enrolled subjects i.e., the subject does not meet the required inclusion/exclusion criteria for the study.
- Subject lost to follow-up.
- Death.

All subjects, unless they have refused to participate in any further follow–up, will be followed for survival up until death or end of study. If a subject wishes to withdraw from the study, this should be clearly documented in the eCRF.

3.10.1 Screen failures

Screen failures are subjects who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as 'screen failed' (i.e., subject does not meet the required inclusion/exclusion criteria) in IVRS/IWRS. This reason for study withdrawal is only valid for screen failures (not randomized subject).

In exceptional cases, where a subject has met HRR status and has screened failed eligibility for other criteria, the subject may be re-evaluated for study eligibility, as determined by the AstraZeneca physician, provided that they have not previously been randomized, assigned or received treatment (see Section 4.1.1).

3.10.2 Withdrawal of the informed consent

Subjects are free to withdraw from the study (investigational product and assessments) at any time, without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any adverse events (AE). If the subject prefers not to provide a reason for withdrawal, it should be recorded as such. The Investigator will follow up AEs outside of the clinical study. The subject will return electronic PRO (ePRO) devices.

If a subject withdraws from participation in the study, then his/her enrollment/randomization/treatment code cannot be reused. Withdrawn subjects will not be replaced.

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

- further participation in the study including any further follow up (e.g., survival calls)
- the use of any samples (see Section 5.7.4)

The status of ongoing, withdrawn (from the study) and "lost to follow-up" subjects at the time of an overall survival analysis should be obtained by the site personnel by checking the subject notes, hospital records, contacting the subject's general practitioner and checking publicly available death registries. In the event that the subject has actively withdrawn consent to the processing of their

personal data, the vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.11 Discontinuation of the study

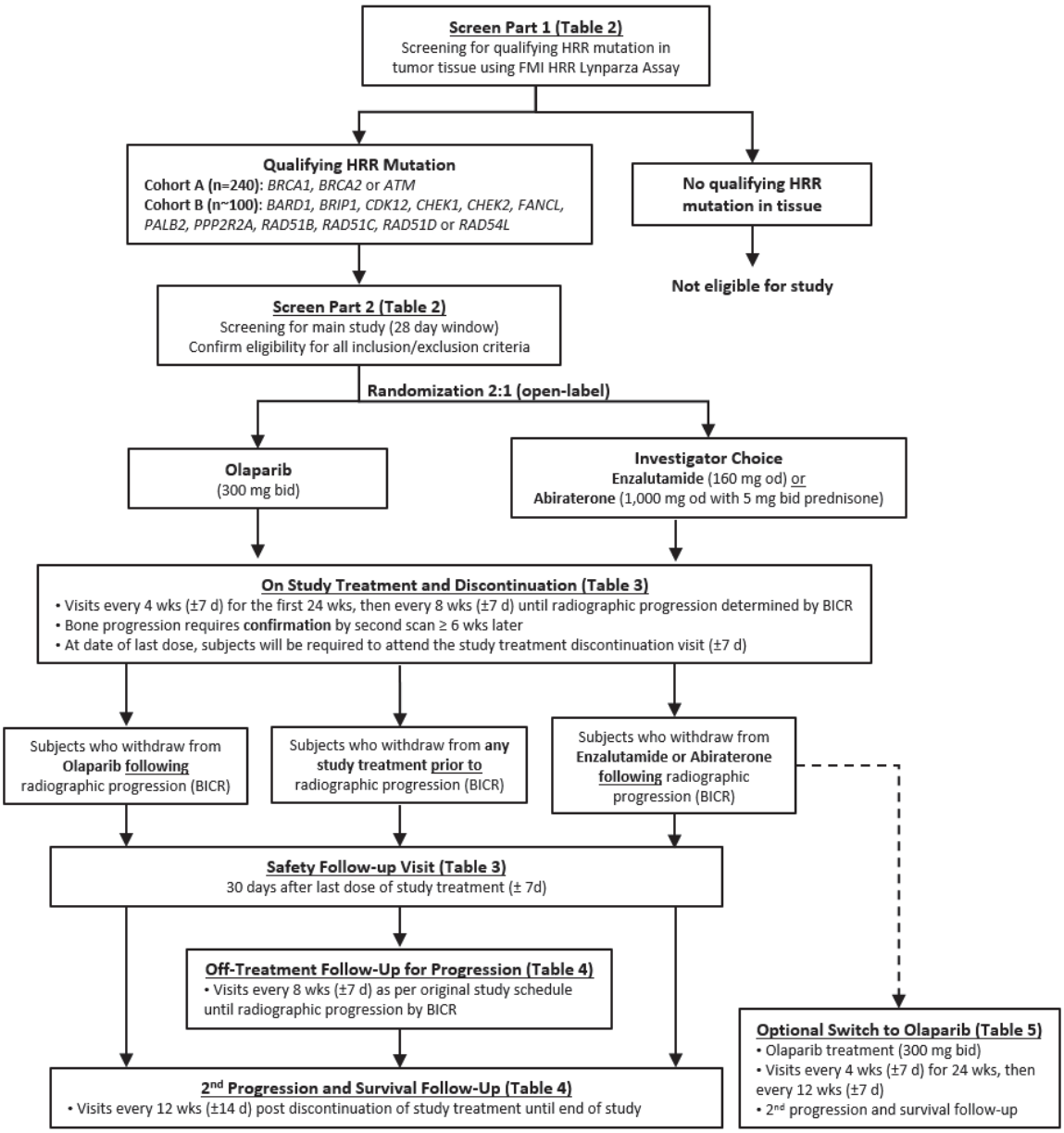
The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the Subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY SCHEDULE AND TIMING OF PROCEDURES

Figure 2 Study Flow Chart



[redacted]

Table 2 Study Schedule – Screening (Part 1 and 2)

	Part 1 All subjects	Part 2
Day		-28 to -1
Informed consent	X	X
Demographics	X	
Medical and surgical history[a]		X
Family history of cancer	X	
Prior cancer therapies including radiotherapy		X
Inclusion/exclusion criteria	X (all * criteria)[h]	X
ECOG Performance status (0-2)		X
BPI-SF, analgesic log (captured in ePRO)[b]		X
Physical examination		X
Vital signs (includes BP, pulse, and temperature), body weight		X
ECG		X
Hematology/clinical chemistry[c]		X
Blood sample for testosterone		X
Urinalysis		X
Tumor tissue sample for HRR status[d, e]	X	
Blood sample for germline HRR status testing		X
Blood sample for biomarker analysis (e.g,. ctDNA)[k]	X	
Blood sample for germline testing (optional, subject consent required) [j]■	X	
Tumor Assessment (Bone scan and CT/MRI)[f]		X
Adverse Events (from time of consent)[g]	X	X
Concomitant medications		X[i]

a Includes history of blood transfusion within previous 120 days from randomization and the reasons e.g., bleeding or myelosuppression.
b Must be completed by subject daily for 7 consecutive days by prior to randomization
c Coagulation test should be performed at screening and if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1.

d Subjects must have a confirmed qualifying HRR status based on the Lynparza HRR Assay to be eligible for the study. Subjects with known HRR status based on FoundationOne® assay may enroll pending documented confirmation of the qualifying mutation by FMI (see Section 5.7.2).

e Tissue submitted for central HRR status testing with the Lynparza HRR Assay only after all (*) eligibility criteria in Part 1 have been met.

f RECIST 1.1 assessments will be performed using CT scans of the chest, abdomen, and pelvis (or MRI where CT is contraindicated). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual subjects. Bone scans will be performed as detailed in Section 5.1.2, consistent with PCWG3 criteria. Baseline assessments should be performed no more than 28 days before the date of randomization, and ideally, should be performed as close as possible to the start of study treatment.

g In screening part 1, only SAEs related to study procedures must be reported (AEs do not require reporting). From screening part 2 onwards - all AEs/SAEs must be reported.

h See Sections 3.1 and 3.2 for marked eligibility (*) criteria.

i Includes all medication being taken from the start of screening part 2 and onwards.

j Optional sample for future germline testing. Sample will be stored for future testing to explore diagnostic test development and thus results will not be available to subjects or their treating physician (see Section 5.7.3.1).

[redacted]

Table 3 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**Visit No. 8 onwards**	**Study treatment discontinued**	**Safety Follow-up**
Week	**0 (Day1)**	**4**	**8**	**12**	**16**	**20**	**24, And every subsequent 8 weeks**	**Last dose of study drug**	**30 days after last dose**
Visit Window		**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**
Randomization	X								
Physical exam [a]	X[b]								
Vital signs, body weight (includes BP, pulse and temperature) [a]	X[b]								
ECOG performance status	X	X	X	X	X	X	X	X	
ECG [a]	X[b]								
Blood samples for PK analysis (subset of subjects)[c]		X							
CTC blood sample (CELLSEARCH® assay)	X		X		X		X	X	
CTC blood sample (EPIC assay)[d]	X						X[e]		
Hematology/clinical chemistry[f]	X[b]	X	X	X	X	X	X	X	X
Urinalysis [a]	X[b]								

Table 3 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**Visit No. 8 onwards**	**Study treatment discontinued**	**Safety Follow-up**
Week	**0 (Day1)**	**4**	**8**	**12**	**16**	**20**	**24, And every subsequent 8 weeks**	**Last dose of study drug**	**30 days after last dose**
Visit Window		**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**
Tumor Assessment (bone scan and CT/MRI)[g h]			X[h]		X[h]		X[h]	X[i]	
SSRE Assessment	X	X	X	X	X	X	X	X	
PSA[j]	X	X	X	X	X	X	X	X	
Adverse Events[k]	X	X	X	X	X	X	X	X	X
Concomitant medications including blood transfusions	X	X	X	X	X	X	X	X	X
Opioid use[l]	X	X	X	X	X	X	X	X	X
BPI-SF, analgesic log (captured in ePRO)	To be completed by subject daily for 7 consecutive days every 4 weeks from the date of randomization (not required to be at site)								
PRO-CTCAE	Every 2 weeks (starting on Day 1) for the first 8 weeks, then every 4 weeks								
EQ-5D-5L	X		X		X		X	X	
FACT-P	X		X		X		X	X	
Patient Global Impression of Change (PGIC)[m]			X		X		X	X	
Healthcare resource use[n]	X		X		X		X	X	X
Study treatment dispensed/returned	X	X	X	X	X	X	X[o]	X	

Table 3 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**Visit No. 8 onwards**	**Study treatment discontinued**	**Safety Follow-up**
Week	**0 (Day1)**	**4**	**8**	**12**	**16**	**20**	**24, And every subsequent 8 weeks**	**Last dose of study drug**	**30 days after last dose**
Visit Window		**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**
Subsequent cancer therapy following discontinuation of study treatment [p]									X
Blood sample for pharmacogenetics (optional, subject consent required)[d]	X								
Blood samples for biomarker analysis at progression[d]							X[e]		

a To be additionally performed if clinically indicated at any other time.

b If assessed within 7 days before randomization and meets the stated eligibility criteria (if applicable), it does not to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

c PK sampling will be performed in a subset of subjects. At least 50 subjects assigned to olaparib treatment at pre-agreed sites will have PK assessment samples taken. Sampling times: Pre-dose (- 30 min ± 15 min), 30 min ± 15 min, 2 ± 0.5 h, 5 ± 0.5 h, 8± 1 h. Subjects should fast from 1 hour before olaparib dosing to 2 hours after.

[redacted]

e Blood samples for biomarker analysis (e.g., ctDNA) and EPIC CTC to be taken at objective BICR-assessed radiological disease progression (i.e., not at every treatment visit), and post primary analysis, to be taken at investigator-assessed radiographic progression.

f Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly. Coagulation test should be performed at screening and if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1.

g Follow-up assessments will be performed every 8 weeks (±7 days) relative to the date of randomization until radiographic progression as assessed by BICR, and post primary analysis, as assessed by investigator. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the subject has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

h Bone progression observed by bone scan requires confirmation by bone scan at least 6 weeks later (see Section 5.1.2). Soft tissue progression observed by CT or MRI, according to RECIST1.1 criteria, does not require a confirmatory scan.

i Bone scan and CT scans of the chest, abdomen, and pelvis (or MRI where CT is contraindicated) should be conducted at the treatment discontinuation visit if radiographic progression has not yet been determined by BICR (including confirmatory scan for bone progression) and it has been ≥ 6 weeks since the last radiologic assessment (bone scan and CT/MRI), and post primary analysis, by investigator.

j PSA values while on the study will not be reported to the site prior to final analysis.

k All ongoing adverse events/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution.

l Opioid use will be captured by the site in the eCRF.

m See Section 5.3.1.4 for more information regarding the Patient Global Impression of Change (PGIC).

n See Section 5.3.3 for more information regarding the healthcare resource use.

o Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to subjects to last longer in accordance with local practice.

p All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigators opinion of response to them, post discontinuation of study treatment need to be recorded.

Table 4 Study Schedule – Follow-up Post Discontinuation of Study Treatment

Visit Number	**Off-Treatment Follow-Up for Progression** For subjects who discontinue therapy prior to BICR progression [a]	**2nd Progression and Survival Follow-Up** Follow-up after BICR radiographic progression
Visit Frequency	**Every 8 weeks per original schedule until radiographic progression**	**Every 12 weeks**
Visit Window	**±7d[a]**	**±14d**
Adverse Events	X[b]	X[b]
Tumor Assessment (bone scan and CT/MRI)	X[c]	
Opioid use [k]	X[k]	X[k]
Blood sample for biomarker analysis at progression (e.g., ctDNA)	X[d]	
Healthcare resource use	X	
Secondary malignancies incl. MDS/AML [e]	X	X
Subsequent cancer therapy following discontinuation of study treatment [f]	X	X
Time to second progression [g]		X[g]
Survival [h]		X
BPI-SF, analgesic log (captured in ePRO) [i j]	Every 4 weeks	Every 4 weeks for 24 weeks[j]
PRO-CTCAE [j]	Every 4 weeks	Every 4 weeks for 24 weeks[j]
FACT-P [j]	X	Every 8 weeks for 24 weeks[j]
EQ-5D-5L [j]	X	Every 8 weeks for 24 weeks[j]

a Visit schedule for subjects who discontinue study treatment prior to radiographic progression determined by BICR. This includes subjects with ≥2 new lesions on a bone scan that has not been confirmed by a second scan ≥6 weeks later (see Section 5.1.2). Visits continue every 8 weeks (±7 days) per original study schedule until documentation of radiographic progression as assessed by BICR. Following radiographic progression subjects move to follow-up for 2nd progression and survival with visits every 12 weeks (±14 days) relative to the randomization date. Until the primary rPFS analysis all imaging assessment and study treatment should continue until objective disease progression as assessed by BICR. There is no plan for BICR to read any scans dated after the date of DCO for the primary analysis. There will be no need to request confirmation of BICR PD after this time point, and the investigator-assessed radiographic progression will prevail.

b All ongoing adverse events/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution.

c Imaging assessments (CT/MRI and bone scan) will be performed as per the original schedule every 8 weeks (±7 days) relative to date of randomization until radiographic progression as assessed by BICR and post primary analysis, by investigator. Bone progression observed by bone scan requires confirmation by bone scan at least 6 weeks later (see Section 5.1.2). Soft tissue progression observed by CT or MRI, according to RECIST1.1 criteria, does not require confirmation.

d Blood samples for biomarker analysis (e.g., ctDNA) and EPIC CTC to be taken at objective radiological disease progression (i.e., not at every treatment visit), and post primary analysis, at investigator-assessed radiographic progression.

e Since some cases of MDS/AML or new primary malignancies develop after discontinuing treatment with olaparib, investigators will be asked during the regular follow-up if the subject has developed MDS/AML or a new primary malignancy and prompted to report any cases as a SAE (or AE if at least one of the criteria for SAE is not met, such as for non-melanoma skin cancers, see Section 6.2) even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm (see Sections 6.1.1 and 6.3.1.1).

f All anti-cancer treatments post discontinuation of study treatment (including, but not limited to, chemotherapy and targeted agents), and the investigators opinion of response need to be recorded.

g Second progression is based on investigator assessment according to local standard clinical practice and includes both radiographic and clinical progression. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (i.e., first progression).

h The status of ongoing, withdrawn (from the study) and "lost to follow-up" subjects at the time of an overall survival analysis should be obtained by the site personnel by checking the subjects notes, hospital records, contacting the subjects general practitioner and checking publicly available death registries, if allowable per local regulations. In the event that the subject has actively withdrawn consent to the processing of their personal data the vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 3.10.2). In addition to their regular 12 weekly contact, subjects will be contacted in the 7 days following a specified date (data cut-off date) for the survival analysis.

i BPI-SF and analgesic log to be completed by the subject on ePRO device daily, for 7 consecutive days every 4 weeks.

j BPI-SF, analgesic log, PRO-CTCAE, FACT-P, and EQ-5D-5L assessments should continue for 24 weeks post discontinuation of randomized study treatment. For subjects who discontinue treatment prior to BICR-assessed radiographic progression or post primary analysis by investigator-assessed radiographic progression, these assessments should continue for 24 weeks post progression.

k Opioid use will be captured by the site in the eCRF. After treatment discontinuation, only patients with no on-treatment opioid use need to be followed until first opioid use. Continued use does not need to be recorded.

[redacted]

Table 5 Study Schedule – Subjects switching to olaparib

Visit Number	Switch to Olaparib Treatment Visits	Treatment Discontinued	Safety Follow-Up	2nd Progression and Survival Follow-Up
Visit Frequency	**Every 4 wks for 24 weeks, then every 12 wks[a]**	**Date last dose of olaparib**	**30 days after last dose of olaparib**	**Every 12 wks after last dose of olaparib**
Visit Window	**±7d**	**±7d**	**±7d**	**±14d**
Switch to Olaparib ICF	X			
Physical exam [b]	X[b]			
Vital signs, body weight (includes BP, pulse and temperature) [b]	X[b]			
ECG [b]	X[b]			
Hematology/clinical chemistry	X	X	X	
Urinalysis [b]	X[b]			
Adverse Events [c]	X	X	X	
Concomitant medications including blood transfusions	X	X	X	
Opioid use [i]	X[i]	X[i]	X[i]	X[i]
Healthcare resource use	X	X		
Study treatment dispensed/returned	X			
Subsequent cancer therapy following discontinuation of randomized treatment [d]	X	X	X	X
Secondary malignancies including MDS/AML [e]	X	X	X	X
Second Progression [f]	X	X		X
Survival [g]	X	X	X	X
BPI-SF, analgesic usage (captured in ePRO) [h]	Every 4 weeks for 24 weeks post discontinuation of randomized treatment			
PRO-CTCAE	Every 4 weeks for 24 weeks post discontinuation of randomized treatment			
FACT-P	Every 8 weeks for 24 weeks post discontinuation of randomized treatment			

EQ-5D-5L	Every 8 weeks for 24 weeks post discontinuation of randomized treatment

a Visit schedule for subjects who switch to olaparib post BICR-assessed radiographic progression, or post primary analysis by investigator-assessed radiographic progression. Visits every 4 weeks (±7 days) for 24 weeks following initiation of olaparib, then visits every 12 weeks (±14 days).

b Only required at initiation of olaparib treatment. To be additionally performed if clinically indicated at any other time.

c All ongoing adverse events/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution.

d All anti-cancer treatments post discontinuation of study treatment (including, but not limited to, chemotherapy and targeted agents), and the investigators opinion of response need to be recorded.

e Since some cases [MDS/AML or new primary malignancies] developed after discontinuing treatment with olaparib, investigators will be asked during the regular follow-up for overall survival if the subject has developed MDS/AML or a new primary malignancy and prompted to report any cases as a SAE (or AE if at least one of the criteria for SAE is not met, such as for non-melanoma skin cancers, see Section 6.2) even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm.

f Second progression is based on investigator assessment according to local standard clinical practice and includes both radiographic and clinical progression. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (i.e., first progression).

g The status of ongoing, withdrawn (from the study) and "lost to follow-up" subjects at the time of an overall survival analysis should be obtained by the site personnel by checking the subjects notes, hospital records, contacting the subjects general practitioner and checking publicly available death registries. In the event that the subject has actively withdrawn consent to the processing of their personal data the vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 3.10.2). In addition to their regular 12 weekly contact, subjects will be contacted in the 7 days following a specified date (data cut-off date) for the survival analysis.

h BPI-SF and analgesic log to be completed by the subject on ePRO device daily, for 7 consecutive days every 4 weeks.

i Opioid use will be captured by the site in the eCRF. After treatment discontinuation, only patients with no on-treatment opioid use need to be followed until first opioid use. Continued use does not need to be recorded.

4.1 Enrollment/screening period

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these eligibility criteria must not be randomized. All screening and enrollment procedures will be performed according the assessment schedules in Table 2.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening and baseline evaluations.

All subjects are required to consent to supply a sample of their tumor (archived or newly biopsied) (see Section 5.7.2) sufficient for testing by the Lynparza HRR Assay, for entry into this study. All subjects will also be required to consent to a blood sample for exploratory biomarker research (see Section 5.7.4).

Screening evaluations (Part 2) may be performed over more than one visit and should be completed within the 28 day period prior to randomization within IVRS/IWRS. The subject will be entered into IVRS/IWRS upon enrollment into Screening (Part 1), prior to any other procedures being performed. At screening Part 2, the subject will be supplied with an electronic hand-held device to record patient reported outcome questionnaires and opiate analgesic use logging (see Section 5.3 for further details). Subjects will be asked to complete ePRO for 7 consecutive days before randomization. All efforts should be made to ensure that all ePRO data is collected.

The subject's eligibility should be evaluated during the screening period with the relevant documentation recorded in the subject source records and eCRF. If the subject is determined to be ineligible for study, during screening Part 1, they may be withdrawn by way of a telephone contact (for collection of SAE information only).

4.1.1 Re-Screening

Subjects who are ineligible for study based on HRR status will be screen failed in the IVRS/IWRS and eCRF, should not continue with any remaining screening evaluations and are not permitted to enter the main study phase or be re-screened for study.

Subjects who meet HRR eligibility at screening and screen fail during screening Part 2 may be considered for re-screening after discussion with the AstraZeneca physician.

Where a subject is permitted to re-screen (by the AstraZeneca study physician), the same E-code initially assigned by the IVRS/IWRS should be used. The rationale and approval will be documented in the investigator study file (ISF).

4.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule (see Table 3).

Until the primary rPFS analysis, following randomization in IVRS/IWRS, subjects should receive assigned study treatment until determined to have objective radiographic progression according to Section 5.1.2 by BICR, or until unable to tolerate study treatment (see Section 7.2). After the date of DCO for the primary analysis, subjects should receive treatment until radiographic progression as

assessed by the investigator. Note that bone progression requires confirmation by a second bone scan ≥ 6 weeks later (see Section 5.1.2).

In the absence of tolerability issues, every effort should be made to keep subjects on assigned study treatment until progression by BICR. If the investigator makes a decision to initiate alternative anti-cancer therapy before BICR-assessed radiological progression, unequivocal clinical progression needs to be documented as per Section 3.9. If study treatment is discontinued due to unequivocal clinical progression (in the absence of BICR-assessed radiographic progression), the investigator should obtain imaging scans at the treatment discontinued visit (see Table 3). This includes confirmatory bone scans. Imaging assessments will continue until documentation of progression by BICR, irrespective of initiation of subsequent anti-cancer therapy (see Table 4).

Access to olaparib for subjects randomized to comparator arm will only be possible upon BICR-assessed progression, or after the date of DCO for the primary analysis, upon investigator-assessed radiographic progression, prior to initiation of subsequent anti-cancer therapy (see Section 4.2.1).

4.2.1 Subjects who switch to olaparib

Once subjects on the investigator choice control arm are determined to have objective radiological progression by BICR, or after the date of DCO for the primary analysis, subjects are determined to have radiographic progression by the investigator, they will be eligible to receive olaparib (300 mg bid) and will follow the study schedule as per Table 5, as well as all safety reporting and medical management guidance (Section 6) and investigational product use and concomitant medication restrictions (Section 7).

If a subject has been deemed to have objective disease progression according to investigator assessment, but not by BICR, he is not eligible to switch to olaparib at that time. Subjects should continue to receive randomized study treatment until progression determined by BICR.

The following criteria must be met in order for a subject to switch to olaparib:

- No intervening anti-cancer therapy following discontinuation of randomized treatment
- Any unresolved toxicities from prior therapy should be controlled, and be no greater than CTCAE grade 1 at the time of starting olaparib treatment

Subjects who switch to olaparib may continue treatment with olaparib as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

If subjects are not eligible to switch to olaparib, or choose not to switch, they will enter into the follow-up phase of the study (see Table 4), and other treatment options should be discussed by the investigator.

4.3 Follow-up period

Descriptions of the procedures for this period are included in the study schedule (see Table 4) with exceptions of the following specific requirements for the follow-up period:

If treatment is discontinued due to BICR-assessed radiographic progression, or after the primary rPFS analysis due to investigator-assessed radiographic progression (see Section 5.1.2), the subject may select from two follow-up options, in order of preferred approach:

1. The subject will return for all regular clinical visits and perform all scheduled assessments until end of study (see Table 4) or,

2. The subject will be followed up every 12 weeks by telephone call until end of study, and continuing ePRO completion for the first 6 months after treatment discontinuation. No further study procedures will be performed.

For option 2, AEs including SAEs and subsequent anti-cancer therapies are the minimum elements to be collected at each contact. Subjects may switch from a higher contact option to a lower contact option, during the follow-up period. Subjects who elect not to undergo follow-up after discontinuing from the initial treatment period will be withdrawn from study.

5. STUDY ASSESSMENTS

The RAVE Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the 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 eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Imaging tumor assessments

All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to an AstraZeneca (AZ) appointed Clinical Research Organization (CRO) to enable independent central review. Upon investigator-assessed objective disease progression as defined in Section 5.1.2, review of all scans will be conducted by BICR. The results will be reported back to the sites. All imaging assessments and study treatment should continue until objective disease progression as assessed by BICR (see Figure 3).

The baseline assessments of all imaging modalities should be performed as close as possible to the start of study treatment and no more than 4 weeks (-28 days) before randomization. Following the baseline assessment, subsequent assessments should be performed every 8 weeks (± 7 days), relative to the date of randomization, until objective radiological disease progression by BICR, even after investigator has deemed objective disease progression, irrespective of treatment decisions or dose interruptions. The assessments by different imaging modalities can be done on different days but should all be performed within assessment schedule. It is important to follow the imaging assessment schedule as closely as possible (see Table 3). If scans are performed outside of scheduled visit window

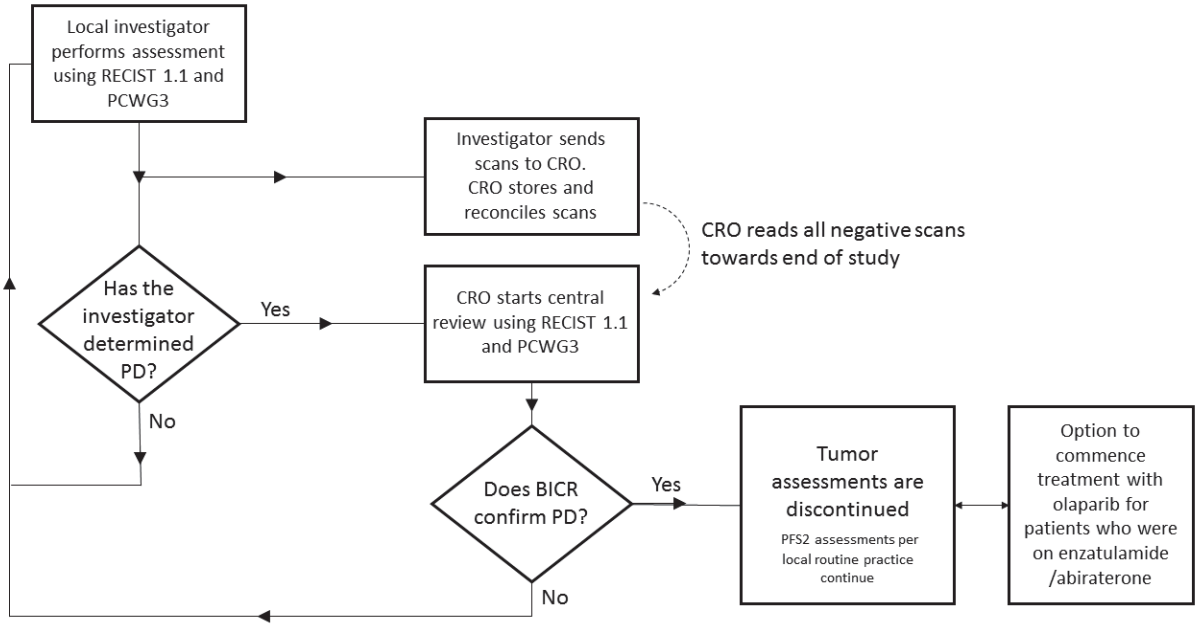
interval, and the subject has not progressed, every attempt should be made to perform the subsequent scans at their originally scheduled time points.

In order for subjects randomized to investigator choice arm to be eligible to switch to olaparib, scheduled tumor assessments must continue until objective radiological disease progression as assessed by BICR, without any intervening systemic anti-cancer therapy following discontinuation of randomized study treatment (see Section 4.2.1).

Until the primary rPFS analysis all imaging assessment and study treatment should continue until objective disease progression as assessed by BICR (see Figure 3). There is no plan for BICR to read any scans dated after the date of DCO for the primary analysis. There will be no need to request confirmation of BICR PD after this time point, and the investigator-assessed radiographic progression will prevail.

Radiological examinations performed during the study should be retained at site as source data.

Figure 3 Assessment of Progression by BICR (prior to primary rPFS analysis)



5.1.1.1 CT and MRI scans tumor assessments (RECIST 1.1)

The imaging modalities used for RECIST assessment will be CT or MRI scans of the chest, abdomen and pelvis. Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of individual subjects. At assessments subsequent to baseline, any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumor burden used at baseline must be used at each subsequent assessment. In this study, bone lesions will not be included in the RECIST soft tissue assessment.

5.1.1.2 Bone scans tumor assessment (based on PCWG3 criteria)

Bone lesions will be assessed by bone scintigraphy commonly performed with Technetium-99 (bone scans). Bone lesions will be assessed by bone scan and will not be part of the RECIST 1.1 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.

5.1.2 Tumor evaluation

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 by bone scan (see Table 6)
- Death.

RECIST 1.1 criteria will be used to assess subject response to treatment by determining progression free survival (PFS) times, objective response rates (ORR), and duration of response (DoR). Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, and SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment. 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 tumor burden at the next scheduled assessment or sooner if clinically indicated. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumor response criteria are presented in Appendix E. For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

Bone lesions will be assessed by bone scan and will not be part of the RECIST 1.1 malignant soft tissue assessment. The definition for bone progression is based on PCWG3 criteria. Positive hot spots on the 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 defined as:

At the 8 week scan:

If **2 or more** new metastatic bone lesions are observed on the first 8-week scan, the confirmatory scan performed (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).

Note - The first bone scan completed after baseline will be considered the '8-week scan' regardless if taken at week 8 or at an unscheduled assessment.

After the 8 week scan:

For subjects **without progression** at the 8 week scan, this scan now serves as new baseline for all subsequent scans, i.e., all bone scans after week 8 are compared to the week 8 scan. If **2 or more** new metastatic bone lesions are observed on scans obtained after the first 8-week assessment (compared to week 8 scan), a confirmatory scan performed **at least 6 weeks later** and preferably no later than the next scheduled visit must 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 documenting the 2 new lesions. 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.

The requirements for determination and confirmation of radiographic progression by either bone scan (bone progression) or CT/MRI (soft tissue progression) are summarized in Table 6:

Table 6 Requirements for documentation of progression.

Visit Date	Criteria for Bone Progression	Criteria for Soft Tissue Progression
Week 8	• 2 or more new lesion compared to baseline bone scan. • Requires confirmation scan at least 6 weeks later with ≥ 2 additional lesions compared to week 8 scan	• Progressive disease on CT or MRI by RECIST 1.1 • No confirmation scan required.
Week 16 or later	• 2 or more new lesions compared to week 8 bone scan. • Requires confirmation scan at least 6 weeks later for persistence or increase in number of lesions	• Progressive disease on CT or MRI by RECIST 1.1 • No confirmation scan required.

It is important to follow the assessment schedule as closely as possible. Please refer to the study schedule in Table 3 and Table 4.

Central reading of scans

All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to an AstraZeneca (AZ) appointed Clinical Research Organization (CRO) to enable blinded independent central review (BICR). Upon documentation of radiographic progression by the investigator, all imaging assessments for the given subject, including unscheduled visit scans, will be reviewed by BICR. Results of this independent review will be communicated to investigators. Subjects should continue imaging assessments until BICR-assessed progression (see Section 5.1.1).

An independent review of all scans used in the assessment of tumors will be conducted prior to the primary analysis of rPFS, including for subjects without investigator-assessed progression.

The primary analysis for this study will be based on the blinded independent central review of all radiological scans (CT/MRI and bone scans).

After the primary rPFS analysis, central review of scans will no longer be required, and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. All treatment decisions will be based on site assessment of scans after rPFS analysis. Ongoing collection of site review tumor assessment is required and must be recorded in the eCRF. [redacted]

5.1.3 Second progression

Following objective radiographic progression by BICR, copies of the patient's radiological scans are no longer required to be sent for central review. Patients will be assessed every 12 weeks for a second progression (using patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve both radiographic and clinical progression (not PSA progression). RECIST 1.1 and PCWG3 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.

5.1.4 Symptomatic skeletal related events (SSRE)

SSREs will be assessed at each visit during the treatment phase, up to and including the study treatment discontinued visit (see Table 3). An SSRE is defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of spinal cord compression, or a tumor related orthopedic surgical intervention.

The occurrence of a SSRE alone, in the absence of disease progression, is discouraged as a reason to discontinue treatment or to initiate new systemic anti-cancer therapy.

5.1.5 PSA Assessments

Blood samples will be collected for PSA assessment at baseline and at each visit during the treatment phase, up to and including the study treatment discontinued visit (see Table 3). The samples will be analyzed by central laboratory. In order to prevent early withdrawal from treatment phase, PSA results will not be sent back to sites prior to final analysis.

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

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the times indicated in the Study schedule (see Table 2, Table 3 and Table 5). All samples unless otherwise indicated will be centrally assessed by central laboratories. Instructions for sample collection, labeling, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites. The volume of blood for collection from each subject for these assessments is presented in the laboratory manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. If applicable, the date, time of collection will be recorded on the appropriate eCRF.

The following laboratory variables will be measured:

Table 7 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Hemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Absolute neutrophil count	S/P-Alkaline phosphatase (ALP)
B-Absolute lymphocyte count	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
B-Mean Cell volume (MCV)	S/P-Albumin
	S/P-Calcium
	S/P-Potassium
Urinalysis (dipstick)	S/P-Sodium
U-Hb/Erythrocytes/Blood	S/P-Urea or Blood Urea Nitrogen (BUN)
U-Protein/Albumin	S/P-Total Protein
U-Glucose	S/P- Lactic dehydrogenase (LDH)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

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

5.2.1.1 Coagulation

Activated partial thromboplastin time (APTT) will be performed at screening and if clinically indicated

International normalized ratio (INR) will be performed at screening and if clinically indicated. Subjects taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

5.2.1.2 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for subjects with prolonged hematological toxicities as defined in Section 6.7.1

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 Patients Safety database. These data are not required to be entered into eCRF.

The Investigator should assess the available results for clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

5.2.2 Physical examination

Performed at screening, baseline and as clinically indicated (see Table 2, Table 3 and Table 5).

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

Twelve-lead ECGs will be obtained after the subject has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed locally as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the subject medical record as source data.

5.2.4 Vital signs

Weight will be assessed at screening and baseline according to the Study Schedule (see Table 2, Table 3 and Table 5) and as clinically indicated at any other time.

Any changes in vital signs should be recorded as an AE, if applicable. For information on how AEs based on changes in vital signs should be recorded and reported, see Section 6.3.

5.2.4.1 Pulse and blood pressure (BP)

Blood pressure and pulse will be assessed at screening and baseline according to the Study Schedule (see Table 2, Table 3 and Table 5) and as clinically indicated at any other time.

Blood pressure and pulse rate will be measured preferably using a semi automatic BP recording device with an appropriate cuff size after 10 minutes rest.

The date of collection and measurement will be recorded on the appropriate eCRF.

5.2.4.2 Body temperature

Body temperature will be measured in degrees Celsius according to local practice at screening, baseline and as clinically indicated (see Table 2, Table 3 and Table 5).

The date of collection and measurement will be recorded on the appropriate eCRF.

5.3 Other assessments

5.3.1 Patient reported outcomes

Patient-reported outcome (PRO) is an umbrella term referring to all outcomes and symptoms that are directly reported by the subject. PROs have become a significant endpoint when evaluating the

effectiveness of treatments in clinical studies. The following five PRO questionnaires will be electronically administered in this study: Brief Pain Inventory- Short Form (BPI-SF), Functional Assessment of Cancer Therapy-Prostate Cancer (FACT-P); patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE); the Patient Global Impression of Change (PGIC); and the EuroQol 5-dimension, 5-level health state utility index (EQ-5D-5L; see Appendix G). Analgesic use will be collected using an electronic analgesic-use log using the ERT Medication Module™ (analgesic log).

Each center must allocate responsibility for monitoring compliance with completion of the PRO questionnaires and the analgesic-use log described in this Section to a specific individual(s) (e.g., a Research Nurse). The Clinical Team will arrange for relevant training in the setup of the electronic device and training subjects in how to self-administer the questionnaires and analgesic-use log using the electronic device. Subjects should complete the questionnaires in accordance with the study schedules (see Table 3, Table 4 and Table 5). Subjects must complete the BPI-SF and analgesic log, the FACT-P, the PGIC and the EQ-5D-5L prior to completing the PRO-CTCAE. The significance and relevance of the data should be explained carefully to participating subjects to ensure they comply with data collection. Subjects should complete all required baseline electronic PRO questionnaires and analgesic log before any treatment is initiated.

5.3.1.1 BPI-SF

The BPI-SF (see Appendix G) is a validated, 15-item domain-specific instrument designed to assess the severity of pain and the impact/interference of pain on daily functions (Cleeland and Ryan 1994). The BPI-SF will be scored according to the user guide (Cleeland 2009). All BPI-SF pain items including “worst pain” is scored on a 0-10 numeric rating scale (NRS) with 0=No Pain and 10=Worst Pain Imaginable. This instrument consists of 2 domains: pain severity and pain interference. The pain severity domain consists of 4 items (item #3. Item #4, item #5, and item #6) which assess pain at its “worst,” “least,” “average,” and “now” (current pain) respectively on the 11-point NRS. These 4 items may be averaged as a composite pain severity score or they may be interpreted individually (Dworkin et al 2005, Turk et al 2006, Dworkin et al 2008 and Food and Drug Administration 2009). In this study, the “worst pain” (item 3) will be used as a single item in assessing pain progression. A composite pain severity score from all the 4 items will also be evaluated as ‘pain severity progression’. A 2- or more point change in the average pain severity or in “worst pain” item is considered clinically meaningful.

The pain interference domain includes 7 items: general activity (item #9A), mood (item #9B), walking ability (item #9C), normal work (item #9D), relations with other people (item #9E), sleep (item #9F), and enjoyment of life (item #9G). The pain interference items are also answered on an 11-point NRS from 0 (Does not interfere) to 10 (Completely interferes). Subjects are asked to recall their symptoms as well as pain interference with daily activities in the past 24 hours. The pain interference domain is scored as the mean of the 7 interference items. Based on the BPI-SF scoring manual, the following items are not used in scoring pain severity or pain interference domains: items #1, #2, #7 and #8. Item #7 (a free text field) describing pain medication use is captured separately in more detail using the Analgesic Log.

Subjects will complete the BPI-SF daily on the ePRO device for the 7 days prior to day 1 randomization visit and every 4 weeks as outlined in the study schedule (see Table 3, Table 4 and Table 5). The “7 consecutive days prior to randomization” does not have to be the immediately

preceding 7 days prior to randomization. These 7 consecutive days can be anywhere within the 28 days screening window. Average worst pain, composite pain severity and pain interference will be computed when a subject completes the diary for at least 4 of the 7 days. The 4 days do not have to be consecutive but should be within the 7 consecutive days timeframe.

5.3.1.2 FACT-P

The FACT-P (Appendix G) is a disease-specific 39-item questionnaire included for the purpose of assessing health-related quality of life (HRQoL) and prostate cancer-specific symptoms. It is a well-established measure of HRQoL/health status commonly used in prostate cancer clinical studies. The FACT-P was developed specifically for patients with advanced prostate cancer and has been found to be reliable and valid in this population (Esper et al 1997). The FACT-P consists of 5 subscales: Physical Well-Being (PWB; 7 items), Functional Well-Being (FWB; 7 items), Emotional Well-Being (EWB; 6 items), Social Well-Being (SWB; 7 items), and Additional Concerns or Prostate Cancer Subscale (PCS) specific to prostate cancer (12 items). The PCS relate to prostate-specific questions, which include sexuality, bowel/bladder function, and pain (Esper et al 1997). All FACT-P questions are scored on a 5-point Likert scale from 0 to 4 (0 being not at all and 4 being very much). Negatively stated items are reversed by subtracting the response from 4. After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all subscales, symptoms index, and individual item scores, the higher the score, the better the HRQoL/symptom. Thus, a score of 0 is a severely symptomatic patient, and the highest possible score is an asymptomatic patient. In addition to the Total and Subscale scores, the FACT-P also supports the calculation of a Trial Outcome Index (TOI) score (the sum of the PWB, FWB and PCS scores), and the FACT Advanced Prostate Symptom Index 6 (FAPSI-6), a symptom score made up of 6 items from within the FACT-P (pain – 3 items, fatigue – 1 item, weight loss – 1 item, and concerns about the condition getting worse – 1 item). Changes from baseline in all of these scores will be assessed, in addition to time to deterioration in the scores. The FACT-P will be measured at the times outlined in the study schedules (see Table 3, Table 4 and Table 5).

Scoring of the FACT-P will be based on the user manual. Higher scores equate to better quality of life. 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

5.3.1.3 PRO-CTCAE

The PRO-CTCAE is included to address tolerability from the patients' perspective. It was developed by the National Cancer Institute (NCI). The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Basch et al 2009 and Litwin et al 1998). These symptoms have been converted to patient terms (e.g., CTCAE term "myalgia" converted to "aching muscles"). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. These items have been extensively evaluated in patients with cancer to be clear, comprehensible, and measuring the symptom of interest. In this study, 8 items or symptomatic AEs

constituting 15 questions that are considered relevant for the study treatment arms are selected (see Appendix G).

Subjects will complete the PRO-CTCAE every 2 weeks (starting on Day 1) for the first 8 weeks, then every 4 weeks thereafter, until 6 months after discontinuation of study treatment (see Table 3, Table 4 and Table 5).

5.3.1.4 Patient Global Impression of Change (PGIC)

The PGIC item is included to assess how a subject perceives their overall change in health status since the start of study treatment. Subjects will choose from response options ranging from "Very Much Improved" to "Very Much Worse." This item is useful in characterizing the overall impact of the treatment (see Appendix G). The PGIC assessments will be performed at the times outlined in the study schedule (Table 3).

5.3.1.5 Analgesic Log

The analgesic log will be implemented using the ERT Medication Module™, a component of the ERT eCOA System that serves for accurately tracking subject consumption of concomitant and/or rescue medications. The Medication Module allows medication data capture via the ERT eCOA Universal App, followed by the review and management of that data by sites and sponsors. The Medication Module provides a consistent, easier-to-use and more efficient tool as compared to paper-based reporting. Using the module, subjects will record all analgesic medication dosages & dosage times to track pain medications use. The Medication Module includes the following components:

(a) Global Master Medication List –This list will be developed collaboratively by ERT and AstraZeneca and will contain all approved analgesic drug names including generic names and formulations. The list will be updated over the course of the study via an approval workflow process, when necessary.

(b) eCOA Universal App Medication Diary – The medication diary will allow subjects to record analgesic medications between visits and identify when any new medications not previously approved have been taken.

(c) Medication Report – This interactive report allows sites to see when their subjects have taken new medications, resolve those medications through an approval workflow, and remotely update the tailored list of medications available on a subjects' eCOA Universal App.

The Analgesic Log is study specific (not generic) and screenshots will be available and submitted along with the CSP to IRB/Ethics Committees.

5.3.1.6 Analgesic Use Scoring

Although information on all analgesics used by patients in pain control will be collected using the Analgesic Log, only changes in opiate are considered in pain progression evaluation in line with FDA recommendation. Opiates consumed by patients will be converted into oral morphine equivalents as defined in Chung et al 2014. The Analgesic Quantification Algorithm (AQA) developed by Chung et

al 2014 will be used to quantify and score analgesic use in the study. The AQA is an eight-point scale that assigns a score as follows:

- 0=No analgesic
- 1=Non-opioid analgesics
- 2=Weak opioids (e.g., codeine, tramadol)
- 3=Strong opioids ≤75 mg oral morphine equivalence (OME) per day
- 4=Strong opioids >75–150 mg OME per day
- 5=Strong opioids >150–300 mg OME per day
- 6=Strong opioids >300–600 mg OME per day
- 7=Strong opioids >600 mg OME per day

Average daily opiate use (based on OME) will be computed using the sum of all opiates used over the 7 days per the assessment schedule (see Table 3, Table 4 and Table 5). The average daily OME will require at least 4 days of data and will be used to assign the AQA score. An increase of 1 point or more in the AQA score from a starting value of 1 or higher OR ≥ 2 points in AQA score from a starting value of 0 is considered a clinically meaningful increase in opiate use. Similarly, a decrease of 1 point or more in the AQA score from a starting value of 2 or higher is considered a clinically meaningful decrease in opiate use.

5.3.1.7 EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the European Quality of Life (EuroQoL) Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990), see Appendix G. 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 as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQol Group 2013). Since 2009, the EuroQoL group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L), which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5 level (5L) version improves upon the properties of the 3 level (3L) measure in terms of reduced ceiling effect, increased reliability, and an improved ability to differentiate between different levels of health (Pickard et al 2007, Janssen et al 2008a and Janssen et al 2008b). The subject will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale (VAS), where the subject will be asked to rate current health status on a scale of 0 to 100, with zero being the worst imaginable health state. The EQ-5D-5L will be measured at the times outlined in the study schedule (see Table 3, Table 4 and Table 5).

5.3.2 Administration of PRO questionnaires

The PRO instruments will be self-administered by the subjects as ePROs using handheld devices. The analgesic use log using the Medication Module will also be administered electronically alongside the ePROs.

All assessments should be completed according to the following parameters:

- Without assistance from site staff or relatives/friends according to the assessment schedules (see Table 3, Table 4 and Table 5).
- Before any other study procedures are conducted at a given visit.
- Before being seen by a study nurse or physician.

Each center must allocate the responsibility for the administration of the ePROs to a specific individual (e.g., a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent. Approximately 15 to 30 minutes is required for subjects to complete the questionnaires. Subjects may complete some of the ePROs at study sites if the assessment time point coincides with a scheduled site visit; otherwise, subjects may complete the ePROs at home. Similarly, during the post-progression period, subjects should complete ePROs at home or at the study site if a scheduled visit coincides with the time point. If subjects have had scans or other tests at an outside facility or missed a scheduled data collection site visit, ePROs should still be completed by the subject at home for that scheduled visit within the window period.

Subjects should be instructed to complete the BPI-SF (Pain Diary) and the Analgesic Log daily for 7 consecutive days every 4 weeks (from date of randomization), independent of when site visits are scheduled. Baseline BPI-SF (Pain Diary) and Analgesic Log must be completed daily for 7 consecutive days during the 28 day screening period prior to randomization

The investigator will arrange for relevant training in the set-up of the electronic device and training subjects in how to self-administer the questionnaires and analgesic use log using the electronic device. Subjects should complete the questionnaires in accordance with the study schedules (see Table 3, Table 4 and Table 5). Subjects must complete the BPI-SF and Analgesic Log, the FACT-P, and the PGIC, EQ-5D-5L, prior to completing the PRO-CTCAE.

The significance and relevance of the data should be explained carefully to participating subjects so that they are motivated to comply with data collection. Reminders should be sent to subjects at home as needed to ensure compliance with the assessment schedules.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- PRO questionnaires must be completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid bias in subject's responses to the questions.
- When each instrument is due to be completed, the following order should be observed: BPI-SF, Analgesic Log, FACT-P, PGIC, EQ-5D-5L, and then PRO-CTCAE.

- PRO questionnaires must be completed by the subject in private.
- The research nurse or appointed site staff must explain to subject the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the subjects have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the subject on how to use the ePRO device, using the materials and training provided by the ePRO vendor, and provide guidance on whom to call if there are problems with the device if the subject is completing the ePRO at home.
- The research nurse or appointed site staff should remind subjects that there are no right or wrong answers.
- The research nurse or appointed staff must avoid clarifying items in order to avoid bias.
- The subject must not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a subject uses visual aids (e.g., spectacles or contact lenses) for reading and does not have them when he attends the clinic, the subject will be exempted from completing the PROs at the clinic.
- Site staff must not read or complete the PRO questionnaires on behalf of the subject. If the subject is unable to read the questionnaire (e.g., is blind or illiterate), that subject is exempted from completing PRO questionnaires and may still participate in the study. Subjects exempted in this regard should be flagged appropriately by the site staff.
- The subject should be given sufficient time to complete the PRO questionnaires at his or her own speed.

The research nurse or appointed site staff must monitor compliance to ensure all data is captured. Compliance must be checked at each study visit to identify problems early. If a subject's compliance drops below 85%, they will be flagged in the routine compliance report generated by the ePRO system and a check-in call from the site to ask the subject if he or she has any difficulties is highly recommended.

5.3.3 Healthcare Resource Use

To explore the impact of treatment and disease on healthcare resource use. Healthcare resource use will be captured including inpatient admissions, ICU and length of stay in hospital. Appropriate analyses of resource use will be undertaken to examine the impact of disease and treatment on resource use to primarily support the health economic evaluation of AstraZeneca therapies.

5.3.3.1 Assessment of Healthcare Resource Use

The study site staff should complete the "Hospital Admission (HOSPAD)" eCRF at the site at every scheduled clinic visit up to and including the study treatment discontinuation follow up visit. If the subject discontinues study treatment for reasons other than RECIST progression, the "HOSPAD" eCRF should continue to be administered until progression has been determined by BICR or by investigator after primary rPFS analysis (see assessment schedule in Table 3, Table 4 and Table 5).

5.4 Pharmacokinetics

5.4.1 Collection of samples

PK sampling will be performed in a subset of at least 35 subjects in Cohort A and 15 subjects in Cohort B dosed with olaparib and in at least 50 subjects dosed with olaparib in both cohorts at select sites. [redacted]

PK samples are to be taken as a blood sample (2 mL) for determination of olaparib concentrations in plasma. At the Week 4 visit, PK samples will be collected at the following times: Pre-dose (- 30 min ± 15 min), and post dose at 30 min ± 15 min, 2 ± 0.5 h, 5 ± 0.5 h and 8 ± 1h. The actual date and time of dosing on the PK study day and the actual date and time of dosing 3 days prior to the pre-dose sample must be recorded.

Samples will be collected, labeled, stored and shipped as detailed in the Laboratory manual.

5.4.2 Determination of drug concentration

Samples for determination of olaparib concentrations in plasma will be analyzed by Covance on behalf of AstraZeneca R&D, using a validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Full instructions for collection, labeling, storage and shipment of samples are provided in the Laboratory manual. Results will only be reported for samples shipped within a timeframe for which the stability of olaparib in the samples has been validated and shown to be acceptable.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier) unless requested for future analyses, where consented to by the subject.

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

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 Clinical Study Report but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to an AstraZeneca designated biobank; see details in the Laboratory Manual).

5.5 Pharmacodynamics

Pharmacodynamics samples will not be taken during the study

5.6 Pharmacogenetics

5.6.1 Collection of pharmacogenetics samples

The subject's consent to participate in the pharmacogenetic research (PGx) components of the study is optional. The background, rationale, objectives, and inclusion/exclusion criteria for the pharmacogenetics analysis are detailed in Appendix C: Pharmacogenetics Research. Please refer to Appendix C and the Laboratory manual for further information surrounding timing of blood sample collection, blood sample storage, and destruction. [redacted]

5.7 Biomarker analysis

Biological samples (e.g., archived tumor samples or blood) will be collected as detailed in the Laboratory manual in order to carry out prospective and retrospective biomarker screening.

5.7.1 HRR gene panel testing of tumor biopsy sample

All subjects must provide a tumor sample that meets the tissue specifications outlined in the Laboratory manual, for tissue based HRR gene panel mutation testing using the Lynparza HRR Assay. The tumor sample will be used to test 15 biomarkers simultaneously: *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*. Subjects who meet all eligibility criteria will be assigned to treatment in the IVRS/IWRS as follows:

Table 8 Treatment assignment by Tumor Sample Mutation Result

Tumor Sample Mutation Result	Treatment Assignment
BRCA1, BRCA2, *ATM*	Cohort A
BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51C, RAD51B, RAD51D, RAD54L	Cohort B

5.7.2 Collection, Analysis and Reporting of Tumor Samples

Tumor samples will be collected as detailed in the pathology and genomics testing manual. Subjects must consent to provide either an archival tumour block, or a de novo tumour biopsy sample for analysis. Consideration should be given to the potential benefit to the subject (should he be eligible for study) in the context of the risk posed by the biopsy procedure. Tissue biopsy sampling should be conducted in accordance with expert guidelines, only by investigators experienced in performing these sampling methods in appropriate clinical settings. Samples that meet the minimum tumor content and tissue volume as specified in the pathology and genomics testing manual will be shipped at Screening Part 1 (post confirmation of other (*) marked eligibility criteria, see Section 3.1 and 3.2) to FMI (Cambridge MA, USA) to determine HRR status. [redacted]

If the first biopsy submitted for testing is inconclusive due to technical test failure, a further biopsy sample may be submitted for testing. Submission and testing of new samples can only be performed if the original testing failed due to technical failure. Please refer to the pathology and genomics testing manual for further details regarding retesting procedures.

For each subject that passes tissue sample and sequencing quality control, FMI will generate a report specifying presence or absence of qualifying HRR gene mutations. A subject has a qualifying mutation if any deleterious or suspected deleterious mutation is found in the HRR genes. A mutation is regarded as deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site mutations), or select missense mutations well-known to be deleterious in ClinVar/BIC databases in certain genes (*BRCA1, BRCA2*, and *ATM*). Furthermore, larger scale alterations such as genomic truncating rearrangements or homozygous deletions will also be classified as qualifying. Subjects without qualifying HRR gene mutations as determined by the Lynparza HRR Assay will not be eligible for the study.

[redacted] **if a subject has a previously confirmed deleterious or suspected deleterious mutation in one of the 15 HRR study genes using the FoundationOne® assay:** the subject may meet biomarker testing requirements provided all of the following conditions are met:

(a) The results are from a prior screening of a prostate cancer tissue specimen by the commercially available FoundationOne® assay as performed by FMI (Cambridge, MA, USA). No other local testing results or other commercially offered NGS analyses are permitted.

(b) Subject to patient consent, residual DNA (stored at FMI) from the original FoundationOne® test will be used to confirm presence of a qualifying gene mutation using the Lynparza HRR Assay. Subjects who do not have sufficient residual DNA from their original test will be analysed in-silico for qualifying HRR gene mutations using data from their previous FoundationOne® test. Upon documented confirmation that FMI has re-evaluated the subject's mutation and confirms the presence of a qualifying HRR gene mutation, the subject may be randomized provided all other eligibility criteria are met.

(c) Subjects who do not have sufficient residual DNA from their original FoundationOne® test must confirm availability of sufficient formalin fixed, paraffin embedded (FFPE) tumor sample to carry out central confirmation using the Lynparza HRR Assay. The subject is not required to wait for the results of the Lynparza HRR Assay to proceed with Screening Part 2 and randomization, assuming all other eligibility criteria are met. [redacted] the tumor sample for central confirmation should be shipped to Foundation Medicine upon enrollment.

5.7.3 Blood Sample for Germline HRR Testing

5.7.3.1 Screening Part 1: Optional Blood Sample for Germline Testing

Subjects who consent to provide an optional sample for germline testing will provide a blood sample at Screening Part 1. The sample will be stored for future testing to explore diagnostic test development and thus results will not be available to subjects, or their treating physician. [redacted]

5.7.3.2 Screening Part 2: Mandatory Blood Sample for Germline Testing

A significant proportion of tumor mutations are reflective of pre-existing germline mutations. Subjects confirmed to have a qualifying HRR gene mutation, will be required to submit a blood sample at screening Part 2 for central germline analysis. The cancer gene profiling test analyzes the coding sequence and select introns of hereditary cancer-related genes, including a subset of the 15 clinical study genes, for variants and/or rearrangements. The results of retrospective germline testing may be made available to the treating physician in accordance with local procedures for research use only.

5.7.4 Exploratory blood samples for biomarker analysis (e.g., ctDNA analysis)

There are two main approaches for the retrieval of tumor material: to obtain contemporary tissue biopsies upon disease progression, or to utilize archival specimens from previous stages of the disease. The former approach requires invasive biopsies, where tissue may be limited in quantity and quality and archival specimens predate progression to mCRPC, and hence, may not reflect tumor evolution and alteration of mutational profile that may have occurred in the intervening time span. In order to overcome these risks and limitations in the future, exploratory biomarker research will be conducted. Testing will include (but is not limited to):

- if there is sufficient ctDNA in plasma for mutation testing,
- if ctDNA in plasma can be used to determine HRR mutation status and
- the correlation between tumor and plasma mutation status

Subjects must provide a blood sample at screening Part 1 (see Table 2). The sample is requested prior to treatment in order to maximize the probability of detecting ctDNA where the tumor burden is relatively high. A second sample will be taken at disease progression (see Table 3 and Table 4).

Please refer to Laboratory manual for further details of biomarker blood sample collection, shipping, and storage. [redacted]

5.7.5 Circulating tumor cells (CTCs)

Whole blood samples will be taken for analysis of CTC conversion rate using the CellSearch® CTC assay at a central lab and the EPIC CTC assay (EPIC, San Diego, CA, USA) for CTC biomarker measurement at the times shown in the study schedule (see Table 3 and Table 4). [redacted]

Samples will be shipped under ambient conditions on the day of acquisition to be received by the AstraZeneca approved laboratory within 48 hours of blood sampling. Please refer to the separate Laboratory manual for further details of sample collection, shipping, and storage.

5.7.6 Exploratory use of residual biomarker samples and data generated from tumor testing (Optional)

The investigational Lynparza HRR Assay used in this study is being developed for approval as a companion diagnostic for olaparib. The Lynparza HRR Assay analyses 15 HRR genes for the presence of deleterious or suspected deleterious mutations to determine eligibility for this study. The underlying gene panel used in this investigational test is based on the clinical-grade FoundationOne® cancer gene profiling test which analyzes the coding sequence of 310 cancer-related genes plus introns from select genes for variants and/or rearrangements. A full list of all genes is available in the laboratory manual. Subjects will be asked to consent to the use of this additional gene data by AstraZeneca for exploratory research, biomarker analysis in relation to olaparib, and development of future diagnostic tests.

Any residual tumour samples may be used for exploratory research by AstraZeneca (in this case, residual samples will be shipped to an AstraZeneca designated Biobank; see details in Laboratory manual). [redacted]

5.7.7 Storage, re-use and destruction of biological samples

Biological samples for future research will be retained at AstraZeneca or its designee for a maximum of 15 years following the finalization of the Clinical Study Report or as per local regulation, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.8 Labelling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled 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 B '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 subject unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

5.7.9 Chain of custody of biological samples

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

The Principal Investigator at each center keeps full traceability of collected biological samples from the subjects while in storage at the center 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.

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

Samples retained for further use are registered in the AstraZeneca Biobank system during the entire life cycle. [redacted]

5.7.10 Withdrawal of Informed Consent for donated biological samples

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

The Principal Investigator:

- Ensures Subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that Subject, 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 of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the Subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central 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.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this Section.

6.1 Definition of adverse events

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

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

6.1.1 Olaparib adverse events of special interest

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

6.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- 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 jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events, including Serious Adverse Events, will be collected from the time of signature of informed consent throughout the treatment period up to and including the 30-day follow-up period*. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow-up period after the last dose of study medication, must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

*Exception: In screening part 1, only SAEs related to study procedures must be reported (AEs do not require reporting). From screening part 2 onwards - all AEs/SAEs must be reported.

6.3.1.1 Adverse events after the 30 day follow up period

For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the subject has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a subject has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, 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.

If subjects who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e., 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 subjects. This includes new AEs/SAEs in subjects still being followed up for survival but who have completed the post treatment follow up period (30 days).

6.3.2 Follow-up of unresolved adverse events

Any SAE or non-serious adverse event that is ongoing at the time of the 30-day follow up, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the subject is lost to follow up. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no), comparator drug (yes/no)
- Action taken with regard to investigational product/comparator drug
- Outcome.

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

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

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

Severity of AE

For each episode of an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade 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 6.2. 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 an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

The grading scales found in the National Cancer Institute (NCI) CTCAE 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation program website (http://ctep.cancer.gov).

6.3.4 Causality collection

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

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

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

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *‘Have you had any health problems since the previous visit/you were last asked?’*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms.

However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if one of the following is met:

- Any criterion for an SAE is fulfilled.
- Causes study treatment discontinuation.
- Causes study treatment interruption.
- Causes study treatment dose reduction.
- The investigator believes that the abnormality should be reported as an AE.

If the deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin 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.

6.3.7 Hy's Law

Cases where a subject 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 D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the signs and symptoms of the cancer. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.9 New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE (see Section 6.1.1 Olaparib Adverse Events of Special Interest). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the subject 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.

6.3.10 Lack of efficacy

When there is deterioration in the cancer, for which the study treatment(s) is being used, 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 study treatment 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.

6.3.11 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 study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.4 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 eCRF'.
- 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 within the usual timeframes.

6.4 Reporting of serious adverse events

All SAEs must be reported, whether or not considered causally related to the investigational product, or to the study procedure(s)*. All SAEs will be recorded in the CRF.

*Exception: In screening part 1, only SAEs related to study procedures must be reported.

If any SAE occurs in the course of the study, then Investigators or other site personnel must inform the appropriate AstraZeneca representatives within one day i.e., immediately but **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 1 calendar day** of

initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **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.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator product.

6.5 Overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established.

Study treatment must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg bid (tablet).

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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator 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 a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Paternal exposure

Subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

6.7 Management of toxicities related to olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Olaparib can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

For management of toxicities for subjects treated with abiraterone acetate or enzalutamide see Section 6.8.

Once dose is reduced, escalation is not permitted.

6.7.1 Management of hematological toxicity

6.7.1.1 Management of anemia

Table 9 Management of anemia

Hemoglobin	Action to be taken

Hb < 10 *but* **≥ 8 g/dl (CTCAE Grade 2)**	Give appropriate supportive treatment, continue to monitor and investigate causality.
	• For *first* incidence: investigator judgement to continue olaparib with or without supportive treatment (e.g., transfusion) or interrupt dose for a maximum of 4 weeks.
	• For *repeat* incidence (after recovery of first event)
	  • If Hb < **10** but ≥ 9 g/dl investigator judgement to continue olaparib with supportive treatment (e.g., transfusion) or dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).
	  • If Hb < **9** but ≥ **8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).

Table 9 Management of anemia

Hemoglobin	Action to be taken
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g., transfusion), continue to monitor and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce olaparib 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 (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. For cases where subjects develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence) , refer to Section 6.7.1.3 for the management of this.

6.7.1.2 Management of neutropenia, leukopenia and thrombocytopenia

Table 10 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAEa Grade 1-2	Investigator judgement to continue study treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg twice daily as a first step and 200 mg twice daily as a second step.

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a subject 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 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where subjects develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.7.1.3.

6.7.1.3 Management of prolonged hematological toxicities while on study treatment

If a subject develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the subject should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if subject's diagnosis of MDS and/or AML is confirmed.

6.7.2 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the subject should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

6.7.2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further 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 Study Physician.

6.7.2.2 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 subjects and 36% in the placebo treated subjects and vomiting was reported in 34% of the olaparib treated subjects and 14% in the placebo treated subjects. These events 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 for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, subjects 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. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e., 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer subjects (ESMO, NCCN), generally a single agent antiemetic should be considered e.g., dopamine receptor antagonist, antihistamines or dexamethasone.

6.7.2.3 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 subject 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.

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

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 needle biopsy procedure.

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

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, subjects should be advised to use caution while driving or using machinery if these symptoms occur.

Table 11 Dose reductions for olaparib

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily

6.8 Management of toxicities related to enzalutamide and abiraterone acetate

Detailed here, as guidance, are approved toxicity management guidelines for abiraterone acetate and enzalutamide (US Prescribing Information).

For toxicity management please adhere to these guidelines or, where appropriate, to local approved or clinical practice guidelines.

6.8.1 Dose adjustment recommendations for enzalutamide

If subject experiences a ≥ Grade 3 toxicity or an intolerable side effect, interrupt enzalutamide treatment for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), per investigator discretion.

6.8.2 Dose adjustment recommendations for abiraterone acetate

In subjects with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the dose of abiraterone acetate to 250 mg once daily. Permanently discontinue treatment with abiraterone acetate in subjects with baseline moderate hepatic impairment if ALT and/or AST > 5xULN or total bilirubin > 3xULN.

In subjects who develop hepatotoxicity during treatment, i.e., ALT and/or AST > 5xULN or total bilirubin > 3xULN, interrupt abiraterone acetate treatment until values return to subject's baseline value or to AST and ALT ≤2.5xULN and total bilirubin ≤ 1.5xULN. Treatment may be restarted at investigator discretion at a reduced dose of 750 mg as first step and 500 mg as second step. If hepatotoxicity recurs at the reduced dose of 500 mg once daily, treatment should be discontinued with no further dose reductions.

Permanently discontinue abiraterone acetate treatment for subjects with concurrent elevation of ALT > 3xULN and total bilirubin > 2xULN in the absence of biliary obstruction of other causes responsible for the concurrent elevation.

6.9 Medication error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but 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 completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 6.3.1) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix A.

6.10 Study governance and oversight

6.10.1 Steering Committee

A Steering Committee will be responsible for supervising the progress of the trial. This committee will include experts in prostate cancer and the Sponsor's representatives.

6.10.2 Data Monitoring Committee

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts and a statistician, who are not employed by AstraZeneca, and do not have any major conflict of interest. Following the review, the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product and comparators

The AstraZeneca Pharmaceutical Technology and Development R&D Supply Chain will supply olaparib. Abiraterone acetate and enzalutamide will be sourced locally or centrally and should be administered according to local prescribing information, including any treatment restrictions.

Abiraterone acetate must be dosed with prednisone in accordance with the approved label (prednisolone is permitted for use instead of prednisone if necessary).

Table 12 Identity of investigational product and comparators

Investigational product	Dosage form and strength
Olaparib	100 and 150 mg tablets
Abiraterone acetate[b]	250 mg and/or 500 mg tablets
Enzalutamide	40 mg capsules/tablets

[a] Descriptive information for olaparib can be found in the olaparib IB. Manufacturer will be included in the quality section of the IMPD.
[b] With prednisone

For all centers, olaparib tablets 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 will be required for dispensing in order to make up the desired dose.

7.2 Dose and treatment regimens

Subjects will be randomized to receive either olaparib or investigator choice of abiraterone acetate or enzalutamide in a 2:1 ratio, respectively. Subjects will continue to receive study treatment until BICR-assessed radiographic progression, or after the date of DCO for the primary analysis until investigator-assessed radiographic progression, as long as they do not meet any of the criteria for treatment discontinuation.

Olaparib is available as film-coated tablet containing 150 mg or 100 mg of olaparib.

Subjects will be administered olaparib orally twice daily at 300 mg bid continually. Two x 150 mg olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. If required, dose reductions to 250 mg bid and a further dose reduction to 200 mg bid are permitted, however once dose reduced, no return to the higher dose will be allowed.

The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food. On PK sampling days, subjects should fast from 1 hour before olaparib dosing to 2 hours after.

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 subject enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the subject 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 subject should take their allotted dose at the next scheduled time.

Enzalutamide will be administered orally at 160 mg once daily. Four x 40 mg capsules/tablets should be taken a similar time each day. Capsules/tablets should be swallowed whole and can be taken with or without food, in full accordance with local prescribing information.

Abiraterone acetate will be administered orally at 1,000 mg once daily. Four x 250 mg or two x 500 mg tablets should be taken at a similar time each day in combination with prednisone 5 mg administered orally twice daily (each prednisone dose approximately 12 hours apart). Subjects should take abiraterone acetate doses at a similar time each day. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate and one hour after the dose of abiraterone acetate. The tablets should be swallowed whole with water and not crushed or chewed, in full accordance with local prescribing information.

Dose Reductions

For guidance on dose reductions for management of AEs refer to Section 6.7 (for olaparib) and Section 6.8 (for enzalutamide and abiraterone acetate).

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors and strong CYP2C8 inhibitors (for enzalutamide) cannot be avoided see Section 7.7.

Renal Impairment

If subsequent to study entry and while still on study therapy, a subject's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for subjects who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg bid.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in subjects with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if subjects develop severe impairment or end stage disease it is recommended that olaparib be discontinued.

7.3 Labelling

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

Each bottle/pack of IMP will have an investigational product label permanently affixed to the outside stating that the material is for clinical study/investigational use only and should be kept out of reach and sight of children. The label will include a space for the enrollment code (E-code) to be completed at the time of dispensing.

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

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

7.4 Storage

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

7.5 Compliance

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

Subjects should be given clear instructions on how and when to take their study treatment. Subjects will self-administer study treatment. 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 staff will make tablet/capsule counts at regular intervals during treatment. Compliance will be assessed by the tablet /capsule count and the information will be recorded in the appropriate Section of the eCRF. After the tablet/capsule count has been performed, the remaining tablets/capsules will not be returned to the subject but will be retained by the Investigative site until reconciliation is completed by the study monitor. All subjects should return their bottles/packs of study medication at the appropriate scheduled visit, when new bottles/packs will be dispensed. Subjects will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF.

*Exception: Tablet/capsule counts do not have to be recorded on eCRF for locally supplied drug, but all study drug usage, including any missed doses, still needs to be recorded on appropriate section of eCRF.

Subjects must return all containers and any remaining tablets at the end of the study.

7.6 Accountability

The study drug 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 subjects in accordance with the protocol.

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

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.

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

Study site personnel, if applicable, or the AZ monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, and destruction should be signed.

7.7 Concomitant and other treatments

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 case report form (CRF).

Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (except LHRH agonist/antagonist which is required during treatment phase), biological therapy or other novel agent, incl. corticosteroids if given for anti-cancer indication) is to be permitted while the subject is receiving study medication.

Live virus and live bacterial vaccines should not be administered whilst the subject is receiving study medication 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.

Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg bid for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg bid for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Strong or Moderate CYP3A inducers

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

If the use of any strong or moderate CYP3A inducers are considered necessary for the subject's safety and welfare this could diminish the clinical efficacy of olaparib.

If a subject requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of olaparib.

Refer to local prescribing information for guidance on dose modification for abiraterone acetate and enzalutamide in situations where co-administration with strong CYP3A4 inducers cannot be avoided.

Strong CYP2C8 inhibitors

Co-administration of enzalutamide with strong CYP2C8 inhibitors may increase exposure to enzalutamide and thus should be avoided if possible. If subjects must be co-administered a strong CYP2C8 inhibitor, reduce the enzalutamide dose to 80 mg once daily (or per local prescribing information if different). If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (e.g., amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

Effect of olaparib on other drugs

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, 2B6, 2C9, 2C19 and P-gp.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

Anticoagulant Therapy

Subjects who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrheals

From screening part 2 onwards, should a subject develop nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs (see Section 6.3) and appropriate treatment of the event given.

Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Olaparib should be discontinued for a minimum of 3 days before a subject undergoes therapeutic palliative radiation treatment. Olaparib should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Administration of other anti-cancer agents

Continuous androgen deprivation therapy (ADT) with an LHRH agonist/antagonist (unless bilateral orchiectomy) must be continued during the trial. Since LHRH is standard of care, it will not be provided nor reimbursed.

Subjects must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Subjects may continue the use of bisphosphonates or denosumab for bone disease provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate Sections of the eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded at aggregate level until database lock and protocol violations identified. Prior to the database lock, any analysis tasks being performed will use a dummy random scheme.
- Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

The sample size of 240 subjects randomized in a 2:1 ratio to olaparib tablets (300 mg orally bid) versus predeclared investigator choice of either enzalutamide (160 mg orally od) or abiraterone acetate (1,000 mg orally od with 5 mg bid prednisone) in Cohort A of this study was selected to be consistent with the research hypothesis as described in Section 1.1.2. The primary endpoint of the study is rPFS.

It is expected that the targeted sample size of 240 subjects in Cohort A with approximately 143 rPFS events (60% maturity) will provide 95% power to demonstrate a statistical significant difference in

rPFS at a 2-sided alpha level of 5% assuming true treatment effect was a HR=0.53. This translates to an approximately 4.5-month improvement in median rPFS over an assumed 5-month median rPFS on enzalutamide or abiraterone acetate assuming rPFS is exponentially distributed. The smallest treatment difference that would be statistically significant at the final analysis is a HR of 0.71. It is anticipated that the study accrual period will be approximately 28 months and that 143 progression and death events will occur approximately 35 months after the first subject is randomized in the study.

Cohort B of the study will consist of approximately 100 subjects with qualifying HRR mutations other than *BRCA1*, *BRCA2* and *ATM*. These subjects will be randomized in a 2:1 ratio to olaparib tablets versus predeclared investigator choice of either enzalutamide or abiraterone acetate.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

Cohort A Full Analysis Set (FAS):

The primary statistical analysis of the efficacy of olaparib in comparison to investigator choice of either enzalutamide or abiraterone acetate in Cohort A will include all subjects who randomized in Cohort A as part of the global enrollment regardless of the treatment actually received. The global recruitment to the study closed when approximately 340 subjects were randomized. Subjects who were randomized in Cohort A as part of the global enrollment but did not subsequently go on to receive study treatment are included in the full analysis set (FAS) on Cohort A. All efficacy and health- related quality of life (HRQoL) data will be analyzed using the Full Analysis Set.

[redacted]

Cohort B Full Analysis Set (FAS):

The analysis of the efficacy of olaparib in Cohort B will include all subjects randomized to olaparib or investigator choice of either enzalutamide or abiraterone acetate in Cohort B as part of the global enrollment regardless of the treatment actually received. Subjects who were randomized in Cohort B but did not subsequently go on to receive study treatment are included in the FAS of Cohort B. All efficacy and HRQoL data will be analyzed using the Full Analysis Set.

Cohort A+B Full Analysis Set (FAS):

The analysis based on Cohort A+B will include subjects from both Cohort A Full Analysis Set and Cohort B Full Analysis Set.

8.3.2 Safety analysis set

All subjects who are randomized as part of the global enrollment and received at least one dose of randomized study treatment in Cohort A or in Cohort B, will be included in the safety analysis set in the respective cohorts. If a subject receives at least one dose of olaparib study treatment they will be summarized in the olaparib arm for safety summaries (e.g., olaparib arm will include subjects

randomized to olaparib who receive at least one dose of olaparib or those subjects who receive at least one dose of olaparib study treatment in error at any time). If a subject randomized to olaparib receives only investigator choice of either enzalutamide or abiraterone acetate then they will be summarized as part of the investigator choice arm. Safety data captured on subjects receiving investigator choice who have subsequently switched to olaparib upon progression will be summarized per the treatment at the time of the onset of safety condition or lab result and reported in a separate section.

[redacted]

8.3.3 PK analysis set

All subjects who have received at least one dose of study medication and provided at least one post-dose analyzable plasma sample for PK analysis will be included in the PK analysis set. Subjects with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK may be excluded from the PK analysis set.

8.3.4 PRO analysis set

The analysis of Patient Reported Outcomes will be based on the Full Analysis Set as defined in Section 8.3.1 for the respective Cohorts A and B.

Table 13 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data - rPFS - Time to pain progression - Overall survival (OS) - Time from randomization to the date of opiate use for cancer-related pain. - PFS2	FAS
Efficacy Data - ORR - DoR	 Subjects with measurable disease (FAS) Subjects with measurable disease at baseline that have a confirmed response (FAS)
Demography	FAS
Disposition	FAS
Plasma concentration	PK Analysis Set
HRQoL data	FAS
Safety Data - Compliance and Exposure	Safety Analysis Set

Table 13 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
- Adverse Events - Lab measurements - Vital Signs - Concomitant Medications	

8.4 Outcome measures for analyses

8.4.1 Primary Endpoints

8.4.1.1 Radiological Progression Free Survival (rPFS)

Progression-free survival is defined as the time from randomization until the date of objective disease progression (see Section 5.1.1.1 and Table 6) or death (by any cause in the absence of progression) regardless of whether the subject withdraws from randomized therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed (defined as CR, PR or SD by RECIST 1.1 for soft tissue disease, or non-PD for bone disease, see Section 5.1.2 and Appendix E) at the time of analysis will be censored at the time of the latest date of their last evaluable RECIST assessment or bone scan. However, if the subject progresses or dies after 2 or more missed radiologic assessments, the subject will be censored at the time of the latest evaluable RECIST 1.1 or bone scan assessment prior to the two missed visits. If the subject 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 subject at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

CT/MRI and bone scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- For BICR (RECIST 1.1 and PCWG3) assessments, the date of progression will be determined based on the **earliest** of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of the reviewer who read baseline first if there is no adjudication for ICR data.
- For investigator assessments, the date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- For BICR and investigator assessments, when censoring a subject for rPFS, the subject will be censored at the latest of the dates contributing to a particular overall visit assessment.

The primary analysis will be based on the blinded independent central review (BICR) of the radiological scans. There is no plan for BICR to read any scans dated after the date of DCO for the primary analysis. There will be no need to request confirmation of BICR PD after this time point, and the investigator-assessed radiographic progression will prevail. [redacted] A charter for the BICR will be developed in advance of the start of study. A sensitivity analysis based on the programmatically derived rPFS based on investigator recorded assessments will be performed.

8.4.2 Secondary Endpoints

8.4.2.1 Confirmed Overall Objective Response Rate (ORR)

For the secondary endpoint ORR assessed by BICR (RECIST 1.1 and PCWG3), only subjects with measurable disease (target lesions) at entry will be included in the analysis. A responder will be any subject with a confirmed best overall response of PR or CR in their soft tissue disease assessed by RECIST 1.1, in the absence of progression on bone scan assessed by PCWG3. A subject will be classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied (as well as the absence of confirmed progression on bone scan assessed by PCWG3) at any time up to and including the defined analysis cut-off point. For each treatment group, the objective response rate (ORR) is the number of subjects with a CR and PR divided by the number of subjects in the treatment group in the FAS with measurable disease at baseline.

ORR will also be defined on the basis of RECIST only (soft tissue disease only). Additionally, analyses will also be performed on ORR assessed by investigator.

8.4.2.2 Time to Pain Progression

Time to pain progression is defined as time from randomization to time point at which worsening in pain is observed for asymptomatic subjects and symptomatic subjects (at baseline) as follows:

Asymptomatic subjects at baseline (average BPI-SF Item 3 score of 0 and not taking opioids)

- Increase of 2 or more points in the average (i.e., average of 7-day assessments) “worst pain in 24 hours” (BPI-SF item 3) from baseline observed at 2 consecutive follow-up assessments/visits (separated by 3-4 weeks)

Or

- Initiation of opioid use for pain

Symptomatic subjects at baseline (average BPI-SF Item 3 score >0 and/or currently taking opioids)

- Increase of 2 or more points in the average (i.e., average of 7-day assessments) “worst pain in 24 hours” (BPI-SF item 3) from baseline observed at 2 consecutive follow-up assessments/visits (separated by 3-4 weeks) and an average worst pain score ≥4, and no decrease in average (i.e., average of 7-day assessments) opioid use measured as 1 or more points decrease in AQA score from a starting value of 2 or higher

Or

- Increase in the average (i.e., average of 7-day assessments) opioid use measured as 1 or more points increase (or at least 2 points increase if the starting value is 0) in the AQA score from baseline observed at 2 consecutive follow-up assessments/visits (separated by 3-4 weeks)

Subjects satisfying one or more of the criteria above will be considered to have pain progression. Subjects who do not satisfy any of the criteria above will be censored at the time of the last known assessment that showed an absence of pain progression.

Details on the BPI-SF and Analgesic score are provided in Sections 5.3.1.1 and 5.3.1.5, respectively.

8.4.2.3 Overall Survival

Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the subject withdraws from randomized therapy or receives another anti-cancer therapy. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive. Note: Survival calls will be made in the week following the date of DCO for the analysis, and if subjects are confirmed to be alive or if the death date is post the DCO date these subjects will be censored at the date of DCO. See Section 3.10.2 for methods that can be used to determine status of subjects who withdraw consent or are lost to follow up.

8.4.2.4 Time to first Symptomatic Skeletal –Related Event (SSRE)

Time from randomization to first symptomatic skeletal–related event as defined by any of the following or a combination:

- Use of radiation therapy to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation is required.
- Occurrence of spinal cord compression. Radiologic documentation required.
- Orthopedic surgical intervention for bone metastasis.

Subjects who have not experienced any of the above conditions will be censored at time of death, or time of analysis if the subject is living.

8.4.2.5 Duration of Response

Duration of response (DOR) will be defined as the time from the date of first documented confirmed response (by BICR using RECIST 1.1 and PCWG3) until date of documented progression (by BICR) 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 PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a subject does not progress following a response, then their duration of response will use the PFS censoring date as the date at which that subject is censored for DOR. The time to response is the time from randomization to the first onset of an objective tumor response.

8.4.2.6 Time to Opiate Use for Cancer Pain

Time to Opiate use is defined as the time from randomization to the date of opiate use for cancer-related pain on subjects who have not received any opiates at baseline. Subjects who have not received opiates during the study or died prior to receiving opiates will be considered censored at the last known on study date of no opiate use.

8.4.2.7 Prostate Specific Antigen (PSA) Response

PSA response is defined as the proportion of subjects achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later

- A subject 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 subject 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 3 weeks later (i.e., decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

8.4.2.8 Circulating Tumor Cell (CTC) Conversion rate

Defined as the proportion of subjects achieving a decline in the number of CTCs from ≥5 cells/7.5 mL at baseline to <5 cells/7.5 mL post baseline.

8.4.2.9 Time from randomization to second progression or death (PFS2)

Defined as the time from the date of randomization to the earliest of the investigator assessed progression event (subsequent to that used for the primary variable PFS) or death.

8.4.2.10 Pain Severity

The BPI-SF pain severity domain/subscale consists of 4 items (#3, #4, #5, and #6) that assess pain at its "worst," "least," "average," and "now" (current pain) respectively on an 11-point numeric rating scale (NRS). A pain severity subscale or composite score from all the 4 items (a mean score) will be evaluated as time to 'pain severity' progression and assessed from the time of randomization as follows for asymptomatic and symptomatic subjects:

Asymptomatic subjects at baseline (average "pain severity" subscale score of 0 and not taking opioids)

- Increase of ≥ 2 points in the average "pain severity" subscale score from baseline observed at 2 consecutive follow-up assessments/visits (separated by 3-4 weeks)

Or

- Initiation of opioid use for pain.

Symptomatic subjects at baseline (average "pain severity" subscale score >0 and/or currently taking opioids)

- Increase of ≥ 2 points in the average "pain severity" subscale score from baseline observed at 2 consecutive follow-up assessments/visits (separated by 3-4 weeks) and an average "pain severity" subscale score ≥4, and no decrease in average opioid use measured as 1 or more points decrease in AQA score from a starting value of 2 or higher

Or

- Increase in the average (i.e., average of 7-day assessments) opioid use measured as 1 or more points increase (or at least 2 points increase if the starting value is 0) in the AQA score from baseline observed at 2 consecutive follow-up assessments/visits (separated by 3-4 weeks).

8.4.2.11 Pain Interference

The BPI-SF pain interference domain includes 7 items: general activity (item #9A), mood (item #9B), walking ability (item #9C), normal work (item #9D), relations with other people (item #9E), sleep (item #9F), and enjoyment of life (item #9G). The pain interference domain is scored as the mean of the 7 interference items. The mean can be used if more than 50% of the total items, or 4 of 7, have been completed on a given administration (Cleeland 2009). Absolute and change from baseline scores of pain interference will be evaluated.

8.4.2.12 FACT-P

For the FACT-P total score, TOI, FAPSI-6, PCS, PWB, and FWB sub-scales, absolute and change from baseline scores for each time point will be calculated for each treatment group.

A best response of 'Improved', 'No Change' and 'Worsened', defined according to Table 14 and Table 15, will be calculated for each subject for scales assessing prostate cancer symptoms, impact on functional well-being etc: FACT-P Total, TOI, FAPSI-6, PCS, PWB, and FWB subscales.

Table 14 details how responders will be defined for the FACT-P total, TOI, FAPSI-6, PCS, PWB, and FWB scores (Cella et al 2009).