

**A Multicenter, Open-label, Single-arm, Study of
Enzalutamide Re-Treatment in Metastatic Castration-
Resistant Prostate Cancer, As First Treatment Post-
Chemotherapy in Patients who Have Previously Received
Enzalutamide in the Pre-Chemotherapy Setting**

ISN/Protocol 9785-MA-1008

Final Version 3.0, dated 22-July-2016

ClinicalTrials.gov Identifier: NCT02441517

Sponsor: Astellas Scientific and Medical Affairs (ASMA)

1 Astellas Way

Northbrook, IL 60062

**A Multicenter, Open-label, Single-arm, Study of Enzalutamide
Re-Treatment in Metastatic Castration-Resistant Prostate Cancer,
As First Treatment Post-Chemotherapy in Patients who Have
Previously Received Enzalutamide in the Pre-Chemotherapy
Setting**

ISN/Protocol 9785-MA-1008

Version 3.0/22 July 2016

IND 74,563

Sponsor:

APGD Medical Affairs, Americas

1 Astellas Way

Northbrook, IL 60062

This confidential document is the property of the Sponsor. No unpublished information contained in this document may be disclosed without prior written approval of the Sponsor.

Table of Contents

| | | |
|-------------|--|-----------|
| I. | SIGNATURES | 7 |
| II. | CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL | 9 |
| III. | LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS | 10 |
| IV. | SYNOPSIS | 13 |
| V. | SCHEDULE OF ASSESSMENTS | 20 |
| 1 | INTRODUCTION | 22 |
| 1.1 | Background | 22 |
| 1.2 | Non-clinical and Clinical Data | 22 |
| 1.3 | Summary of Key Safety Information for Study Drugs | 26 |
| 1.4 | Risk-Benefit Assessment | 27 |
| 2 | STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS | 27 |
| 2.1 | Study Objectives | 27 |
| 2.2 | Study Design and Dose Rationale | 27 |
| 2.2.1 | Study Design | 27 |
| 2.2.2 | Dose Rationale | 28 |
| 2.3 | Endpoints | 28 |
| 2.3.1 | Primary Endpoint | 28 |
| 2.3.2 | Secondary Endpoints | 29 |
| 2.3.3 | Exploratory Endpoints | 29 |
| 3 | STUDY POPULATION | 29 |
| 3.1 | Selection of Study Population | 29 |
| 3.2 | Inclusion Criteria | 29 |
| 3.3 | Exclusion Criteria | 30 |
| 4 | TREATMENT(S) | 32 |
| 4.1 | Identification of Investigational Product(s) | 32 |
| 4.1.1 | Test Drug(s) | 32 |
| 4.1.2 | Comparative Drug(s) | 32 |
| 4.2 | Packaging and Labeling | 32 |
| 4.3 | Study Drug Handling | 32 |
| 4.4 | Blinding | 33 |
| 4.5 | Assignment and Allocation | 33 |

| | | |
|----------|--|-----------|
| 5 | TREATMENTS AND EVALUATION | 33 |
| 5.1 | Dosing and Administration of Study Drug(s) and Other Medication(s) | 33 |
| 5.1.1 | Dose/Dose Regimen and Administration Period | 33 |
| 5.1.2 | Increase or Reduction in Dose of the Study Drug(s) | 33 |
| 5.1.3 | Previous and Concomitant Treatment (Medication and Non-Medication Therapy) | 34 |
| 5.1.3.1 | Previous Treatment (Medication and Non-Medication Therapy) | 34 |
| 5.1.3.2 | Concomitant Treatment (Medication and Non-Medication Therapy) | 34 |
| 5.1.4 | Treatment Compliance | 35 |
| 5.1.5 | Criteria for Continuation of Treatment | 35 |
| 5.2 | Demographics and Baseline Characteristics | 36 |
| 5.2.1 | Demographics | 36 |
| 5.2.2 | Medical History | 36 |
| 5.2.3 | Diagnosis of the Target Disease, Severity, and Duration of Disease | 36 |
| 5.2.4 | Performance Status | 36 |
| 5.2.5 | Chest X-Ray and/or Chest CT | 36 |
| 5.3 | Efficacy Assessment | 37 |
| 5.3.1 | CT/MRI and Bone Scan | 37 |
| 5.3.2 | PSA | 37 |
| 5.3.3 | Correlative Samples | 38 |
| 5.3.4 | Survival Follow-up | 38 |
| 5.4 | Safety Assessment | 38 |
| 5.4.1 | Vital Signs | 38 |
| 5.4.2 | Adverse Events | 38 |
| 5.4.2.1 | Adverse Events of Possible Hepatic Origin | 38 |
| 5.4.3 | Laboratory Assessments | 39 |
| 5.4.4 | Physical Examination | 40 |
| 5.4.5 | Electrocardiogram (ECG) | 40 |
| 5.4.6 | Imaging | 40 |
| 5.5 | Adverse Events and Other Safety Aspects | 40 |
| 5.5.1 | Definition of Adverse Events (AEs) | 40 |
| 5.5.2 | Disease Progression | 41 |
| 5.5.3 | Definition of Serious Adverse Events (SAEs) | 41 |
| 5.5.4 | Special Situations | 41 |
| 5.5.5 | Criteria for Causal Relationship to the Study Drug | 42 |

| | | |
|----------|--|-----------|
| 5.5.6 | Criteria for Defining the Severity of an Adverse Event | 43 |
| 5.5.7 | Reporting of Serious Adverse Events (SAEs) | 43 |
| 5.5.8 | Follow-up of Adverse Events | 44 |
| 5.5.9 | Monitoring of Common Serious Adverse Events | 44 |
| 5.5.10 | Procedure in Case of Pregnancy | 45 |
| 5.5.11 | Emergency Procedures and Management of Overdose | 45 |
| 5.5.12 | Supply of New Information Affecting the Conduct of the Study | 45 |
| 5.6 | Test Drug Concentration | 45 |
| 5.7 | Other Measurements, Assessments or Methods | 45 |
| 5.7.1 | Blood Sample for Molecular Profiling of CTCs | 45 |
| 5.7.2 | Serum Sample for Biomarker Analysis | 46 |
| 5.8 | Total Amount of Blood | 46 |
| 6 | DISCONTINUATION | 46 |
| 6.1 | Discontinuation of Individual Subject(s) | 46 |
| 6.2 | Discontinuation of the Site | 47 |
| 6.3 | Discontinuation of the Study | 48 |
| 7 | STATISTICAL METHODOLOGY | 48 |
| 7.1 | Sample Size | 48 |
| 7.2 | Analysis Set | 48 |
| 7.2.1 | Full Analysis Set (FAS) | 49 |
| 7.2.2 | Per Protocol Set (PPS) | 49 |
| 7.2.3 | Safety Analysis Set (SAF) | 49 |
| 7.2.4 | Biomarker Analysis Set (BAS) | 49 |
| 7.3 | Demographics and Other Baseline Characteristics | 49 |
| 7.4 | Analysis of Efficacy | 49 |
| 7.4.1 | Analysis of Primary Endpoint | 49 |
| 7.4.1.1 | Primary Analysis | 49 |
| 7.4.1.2 | Secondary Analysis | 49 |
| 7.4.1.3 | Subgroup Analysis | 49 |
| 7.4.2 | Analysis of Secondary Endpoints | 50 |
| 7.4.3 | Analysis of Exploratory Endpoints | 50 |
| 7.5 | Analysis of Safety | 51 |
| 7.5.1 | Adverse Events | 51 |
| 7.5.2 | Laboratory Assessments | 51 |

| | | |
|-----------|--|-----------|
| 7.5.3 | Vital Signs | 51 |
| 7.5.4 | Physical Examination | 51 |
| 7.5.5 | ECGs | 51 |
| 7.6 | Analysis of Pharmacogenomics | 51 |
| 7.7 | Protocol Deviations | 51 |
| 7.8 | Interim Analysis (and Early Discontinuation of the Clinical Study) | 51 |
| 7.9 | Handling of Missing Data, Outliers, Visit Windows, and Other Information | 52 |
| 8 | OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS | 52 |
| 8.1 | Procedure for Clinical Study Quality Control | 52 |
| 8.1.1 | Data Collection | 52 |
| 8.1.2 | Specification of Source Documents | 52 |
| 8.1.3 | Clinical Study Monitoring | 53 |
| 8.1.4 | Direct Access to Source Data/Documents | 53 |
| 8.1.5 | Data Management | 53 |
| 8.1.6 | Protocol Deviations | 53 |
| 8.1.7 | End of Trial in All Participating Countries | 54 |
| 8.2 | Ethics and Protection of Subject Confidentiality | 54 |
| 8.2.1 | Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA) | 54 |
| 8.2.2 | Ethical Conduct of the Study | 55 |
| 8.2.3 | Informed Consent of Subjects | 55 |
| 8.2.3.1 | Subject Information and Consent | 55 |
| 8.2.3.2 | Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information | 55 |
| 8.2.4 | Subject Confidentiality | 56 |
| 8.3 | Administrative Matters | 56 |
| 8.3.1 | Arrangement for Use of Information and Publication of the Clinical Study | 56 |
| 8.3.2 | Documents and Records Related to the Clinical Study | 56 |
| 8.3.3 | Protocol Amendment and/or Revision | 57 |
| 8.3.4 | Signatory Investigator for Clinical Study Report | 57 |
| 9 | QUALITY ASSURANCE | 57 |
| 10 | STUDY ORGANIZATION | 58 |
| 10.1 | Independent Data-Monitoring Committee (IDMC) Data and Safety Monitoring Board (DSMB) Monitoring Committee Other Evaluation Committee(s) | 58 |

| | | |
|-----------|--|-----------|
| 11 | REFERENCES | 59 |
| 12 | APPENDICES | 62 |
| 12.1 | List of Prohibited and Restricted Concomitant Medications..... | 62 |
| 12.2 | Liver Safety Monitoring and Assessment | 64 |
| 12.3 | Common Serious Adverse Events..... | 67 |
| 13 | SIGNATURES | 68 |

I. SIGNATURES

1. SPONSOR'S SIGNATURE

A Multicenter, Open-label, Single-arm, Study of Enzalutamide Re-Treatment in Metastatic Castration-Resistant Prostate Cancer, As First Treatment Post-Chemotherapy in Patients who Have Previously Received Enzalutamide in the Pre-Chemotherapy Setting

ISN/Protocol 9785-MA-1008 /Version 3.0 dated 22 July 2016

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors, etc.) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

A Multicenter, Open-label, Single-arm, Study of Enzalutamide Re-Treatment in Metastatic Castration-Resistant Prostate Cancer, As First Treatment Post-Chemotherapy in Patients who Have Previously Received Enzalutamide in the Pre-Chemotherapy Setting

ISN/Protocol 9785-MA-1008 /Version 3.0 dated 22 July 2016

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature:

Date (DD Mmm YYYY)

Printed Name:

Address:

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

| | |
|---|--|
| 24h-Contact for Serious Adverse Events (SAEs) See Section 5.5 | <p>[REDACTED], MD MS [REDACTED] APGD, Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 USA Office: [REDACTED] Mobile: [REDACTED] Email: [REDACTED]</p> <p>Please fax or email the SAE Worksheet to: Astellas Pharma Global Development, Inc. Global Pharmacovigilance North America telefax numbers: [REDACTED] [REDACTED] International telefax number: [REDACTED] Email: [REDACTED]</p> |
| Clinical Research Contact: | <p>[REDACTED] [REDACTED] APGD, Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 Phone: [REDACTED] Email: [REDACTED]</p> |
| Study Physician: | <p>[REDACTED], MD MS [REDACTED] APGD, Medical Affairs, Americas 1 Astellas Way Northbrook, IL 60062 USA Office: [REDACTED] Mobile: [REDACTED] Email: [REDACTED]</p> |

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

| Abbreviations | Description of abbreviations |
|-----------------|---|
| AA | Abiraterone Acetate |
| ADR | Adverse Drug Reaction |
| ADT | Androgen Deprivation Therapy |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase (GPT) |
| AR | Androgen Receptor |
| AR-V7 | Androgen Receptor Splice Variant 7 |
| AR-V12/v567es | Androgen Receptor Splice Variant 12/ Variant with Exons 5, 6 and 7 Skipped |
| APGD | Astellas Pharma Global Development, Inc. |
| AST | Aspartate Aminotransferase (GOT) |
| AUC | Area Under the Curve |
| AUST | Astellas US Technologies, Inc. |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CI | Confidence Interval |
| CLCR | Creatinine Clearance |
| CO ₂ | Carbon Dioxide |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTC | Circulating Tumor Cells |
| DHEA | Dehydroepiandrosterone |
| DILI | Drug-induced Liver Injury |
| dL | Deciliter |
| ECG | Electrocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EGFR | Epidermal Growth Factor Receptor |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| g/dL | Grams per DeciLiter |
| GGT | Gamma-Glutamyl Transferase |
| GMP | Good Manufacturing Practices |
| GnRH | Gonadotropin-Releasing Hormone |
| GR | Glucocorticoid Receptor |
| HCT | Hematocrit |
| HgB | Hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IGF | Insulin-like Growth Factor 1 |

| Abbreviations | Description of abbreviations |
|---------------|--|
| IL6 | Interleukin 6 |
| IL8 | Interleukin 8 |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISN | International Study Number |
| JAK/STAT | Janus Kinase / Signal Transducer and Activator of Transcription |
| LA-CRF | Liver Abnormality Case Report Form |
| LBD | Ligand Binding Domain |
| LDH | Lactate Dehydrogenase |
| LFT | Liver Function Tests |
| LVEF | Left Ventricular Ejection Fraction |
| mCRPC | Metastatic Castration - Resistant Prostate Cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg/dL | Milligram/Deciliter |
| mmHg | Millimeters of Mercury |
| mmol/L | Millimoles/Liter |
| MOA | Mechanism of Action |
| MRI | Magnetic Resonance Imaging |
| mTOR | Mammalian Target of Rapamycin |
| MUGA | Multiple Gated Acquisition |
| NASH | Non-alcoholic Steatohepatitis |
| NCI-CTCAE | National Cancer Institute - Common Terminology Criteria for Adverse Events |
| Ng | Nanogram |
| nmol/L | Nanomole/Liter |
| NYHA | New York Heart Association |
| OS | Overall Survival |
| PCWG2 | Prostate Cancer Clinical Trials Working Group |
| PGAS | Pharmacogenomic Analysis Set |
| PHI | Protected Health Information |
| PK | Pharmacokinetics |
| PSA | Prostate-Specific Antigen |
| RBC | Red Blood Cell |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| rPFS | Radiographic Progression-Free Survival |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SOP | Standard Operating Procedure |
| TBL | Total Bilirubin |
| TLF | Tables, Listings and Figures |
| sTNF1 | Soluble Tumor Necrosis Factor Receptor – 1 |
| TNF-alpha | Tumor Necrosis Factor - Alpha |
| TMF | Trial Master File |
| μL | Microliter |
| ULN | Upper Limit of Normal |
| US | United States |
| WBC | White Blood Cell |

Definition of Key Study Terms

| Terms | Definition of terms |
|-----------------------------|--|
| Baseline | Observed values/findings which are regarded observed starting point for comparison. |
| Enroll | To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject. |
| Intervention | The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics). |
| Investigational period | Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug. |
| Post investigational period | Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period. |
| Screening period | Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject. |
| Randomization | The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. |
| Screening | A process of active consideration of potential subjects for enrollment in a trial. |
| Screen failure | Potential subject who did not meet one or more criteria required for participation in a trial. |
| Study period | Period of time from the first site initiation date to the last site completing the study. |
| Variable | Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values. |

IV. SYNOPSIS

| | |
|---|--------------------------------------|
| Sponsor: APGD, Medical Affairs, Americas | Protocol Number: 9785-MA-1008 |
| Name of Study Drug: Enzalutamide | Phase of Development: N/A |
| Title of Study: A Multicenter, Open-label, Single-arm, Study of Enzalutamide Re-Treatment in Metastatic Castration-Resistant Prostate Cancer, As First Treatment Post-Chemotherapy in Patients who Have Previously Received Enzalutamide in the Pre-Chemotherapy Setting | |
| Planned Study Period: From Q3 2015 - Q3 2018 | |
| Study Objective(s): <u>Primary:</u> <ul style="list-style-type: none"> To determine radiographic progression-free survival (rPFS) of re-treatment with enzalutamide + GnRH analogue <u>Secondary:</u> <ul style="list-style-type: none"> Assess additional measures of efficacy: <ul style="list-style-type: none"> Overall survival rate at 1 year Time to PSA progression PSA response rate [maximum decline of $\geq 30\%$, $\geq 50\%$, and $\geq 90\%$ from baseline, (PSA30, PSA50, and PSA90), respectively] Objective response rate Time to first use of a subsequent antineoplastic therapy Assess safety of enzalutamide re-treatment in the post-chemo setting Assess correlative science in the post-chemo setting | |
| Planned Total Number of Study Centers and Location(s): 5-10 centers in the US | |
| Study Population: Patients previously treated with enzalutamide for a minimum of 8 months, followed by docetaxel and/or cabazitaxel chemotherapy for a minimum of 4 cycles. Exposure to intervening systemic anti-cancer therapies such as abiraterone prior to chemotherapy is allowed. | |
| Number of Patients to be Enrolled / Randomized: 40 | |
| Study Design Overview: <p>This is a US-based, multicenter, open-label, single-arm, study evaluating the efficacy, safety, and tolerability of open-label enzalutamide in the re-treatment setting. A total of 40 patients will be enrolled. Patients must have been previously treated with enzalutamide in the pre-chemotherapy setting for a minimum of 8 months, followed by docetaxel and/or cabazitaxel for a minimum of 4 cycles. Exposure to intervening systemic anti-cancer therapies such as abiraterone prior to chemotherapy is allowed. Subjects will receive treatment with open-label enzalutamide (160 mg daily), administered as four 40 mg capsules, by mouth, once daily, until radiographic or clinical progression (such as pathological fracture, cord compression, worsened pain requiring radiation therapy, or opioid analgesic dose increase or initiation), or unacceptable toxicity. Per the Investigator's clinical judgment and with sponsor approval, patients may be allowed to continue enzalutamide until the next treatment is initiated. If another non-cytotoxic, non-investigational, antineoplastic agent is initiated after protocol-defined progression has been determined, enzalutamide may be continued per the Investigator's clinical judgment and with sponsor approval as long as the patient is tolerating enzalutamide and continues androgen deprivation therapy.</p> <p>The consensus guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and the</p> | |

Prostate Cancer Clinical Trials Working Group 2 (PCWG2) will be utilized to determine radiographic disease progression. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease. Bone disease progression is considered when a minimum of two new lesions are observed. Progression on bone scan at time points prior to or at Week 9 requires a confirmatory scan performed six or more weeks later. This confirmatory scan should demonstrate at least 2 additional new lesions compared to the Week 9 scan (PCWG2).

The following assessments of prostate cancer status will be collected during the course of the trial: soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, and PSA.

Study films (CT/MRI and bone scan) should be read on site. Each site should ideally designate the same reader who will evaluate the images for any one subject for the duration of the trial.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs, physical examinations, and safety laboratory evaluations.

Subjects will have a Safety Follow-Up visit approximately 30 days following the last dose of study drug or prior to the initiation of a subsequent anti-cancer drug or investigational agent, whichever occurs first. Survival will be followed every 12 weeks for a maximum of 3 years from first dose. The study will end when the last subject has been followed for 1 year from date of first dose.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without signet ring cell features.
2. Presence of metastatic disease (M1) as assessed by CT/MRI and/or whole-body radionuclide bone scan.
3. Subject has been previously treated with enzalutamide for at least 8 months, and stopped enzalutamide due to progressive disease (not due to adverse events), followed by at least 4 cycles of docetaxel and/or cabazitaxel chemotherapy, with or without other intervening anti-cancer therapies (including but not limited to aminoglutethimide, ketoconazole, abiraterone acetate, Rad-223, or sipuleucel-T) prior to receiving chemotherapy. Note: for patients who receive sequential taxanes, there must not have been progressive disease upon ending the first taxane or use of any anti-cancer agents between the two taxanes.
4. Ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue or prior bilateral orchiectomy (medical or surgical castration). For patients who have not had bilateral orchiectomy, there must be a plan to maintain effective GnRH-analogue for the duration of the trial.
5. Testosterone ≤ 1.73 nmol/L (≤ 50 ng/dL) at screening.
6. Age 18 years or older.
7. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
8. ECOG performance status of 0-2 at screening.
9. Estimated life expectancy of ≥ 6 months at screening.
10. Ability to swallow study drug and to comply with study requirements throughout the study.
11. Throughout study, male subject and a female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom barrier method

of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration. Two acceptable methods of birth control thus include the following:

- a. Condom (barrier method of contraception)
AND
 - b. One of the following is required:
 - i. Established use of oral, injected, or implanted hormonal method of contraception by the female partner;
 - ii. Placement of an intrauterine device or intrauterine system by the female partner;
 - iii. Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner;
 - iv. Tubal ligation in the female partner performed at least 6 months before screening;
 - v. Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), performed at least 6 months before screening
12. Must not donate sperm from screening through 3 months after final study drug administration.

Exclusion Criteria:

Patients will be excluded from participation if any of the following apply:

1. Known or suspected neuroendocrine/small cell feature.
2. Use of any antineoplastic treatment post-chemotherapy, including but not limited to aminoglutethimide, ketoconazole, abiraterone acetate, Rad-223, sipuleucel-T, or enzalutamide. Continuing steroids is permitted.
3. Palliative radiation therapy within 2 weeks of Day 1, or within 4 weeks of Day 1 if a radionuclide was utilized.
4. Use of an investigational agent within 4 weeks of Day 1 visit.
5. Major surgery within 4 weeks prior to Day 1 visit.
6. History of seizure or any condition that may predispose to seizures (e.g., prior cortical stroke or significant brain trauma) at any time in the past. History of loss of consciousness or transient ischemic attack within 12 months of screening.
7. History of clinically significant cardiovascular disease including:
 - a. Myocardial infarction or uncontrolled angina within 3 months;
 - b. History of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within three months results in a left ventricular ejection fraction that is $\geq 45\%$;
 - c. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes);
 - d. History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
8. Clinically significant cardiovascular disease at screening including:
 - a. Hypotension as indicated by systolic blood pressure < 86 millimeters of mercury (mm Hg) at screening;
 - b. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG) and on physical examination;
 - c. Uncontrolled hypertension as indicated by at least 2 consecutive measurements of a

| |
|---|
| <p>resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the screening visit.</p> <ol style="list-style-type: none"> 9. Subject has a known or suspected hypersensitivity to enzalutamide or any components of the formulation used. 10. Severe concurrent disease, infection, or co-morbidity that, in the judgment of the investigator, would make the patient inappropriate for enrollment. 11. Known or suspected brain metastasis or leptomeningeal disease. 12. Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last 3 months); 13. Absolute neutrophil count < 1,500/μL, platelet count < 75,000/μL, or hemoglobin < 5.6 mmol/L (9 g/dL) at screening. 14. Total bilirubin or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) \geq 2.5 times upper limit of normal (ULN) at screening. 15. Creatinine > 177 μmol/L (> 2 mg/dL) at screening. 16. Albumin < 30 g/L (3.0 g/dL) at screening. 17. Treatment with abiraterone acetate prior to enzalutamide for mCRPC in the pre-chemotherapy setting. (<i>Note:</i> Patients who have received concomitant enzalutamide and abiraterone acetate therapies are not excluded). |
| <p>Investigational Product(s): Enzalutamide 40 mg soft gelatin capsules</p> <p>Dose(s): Enzalutamide 160 mg/day.</p> <p>Mode of Administration: Enzalutamide capsules are administered orally with or without food.</p> |
| <p>Comparative Drug(s): None.</p> |
| <p>Background Therapy: The study sites will provide GnRH agonist or antagonist from pharmacy stock.</p> |
| <p>Concomitant Medication Restrictions or Requirements: The following medications are prohibited while patients are on enzalutamide treatment and have not had disease progression:</p> <ul style="list-style-type: none"> • Chemotherapy with anti-tumor activity against prostate cancer such as cabazitaxel, mitoxantrone, etc. • Sipuleucel-T • Rad-223 • Androgen-receptor antagonists (bicalutamide, flutamide, nilutamide) • 5α-reductase inhibitors (finasteride, dutasteride) • Estrogens • Cyproterone acetate • Androgens (testosterone, dehydroepiandrosterone [DHEA], etc.) • Ketoconazole |

- Abiraterone acetate
- Any other investigational agent

The dosage and regimen of the following medications and any chronic permitted medications should be stabilized during the screening period (> 4 weeks prior to randomization) and held constant through the study:

- Denosumab and bisphosphonate
- GnRH agonist/antagonist therapy

There is a potential for enzalutamide to affect exposures to other medicinal products, or for other medicinal products to affect exposure to enzalutamide:

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) or CYP2C8 inducers (e.g. rifampicin) are to be avoided. If subject must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If a 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.
- Strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) or moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort) should be avoided if possible as they may reduce enzalutamide plasma concentration if co-administered. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4 (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g. phenytoin, warfarin), CYP2C19 (e.g. S-mephenytoin), or UGT1A1 should be avoided, as enzalutamide may decrease their exposure. If enzalutamide is co-administration with warfarin cannot be avoided, additional INR monitoring should be conducted.
- Enzalutamide is an inhibitor of human P-glycoprotein (p-gp) and may increase exposure to medicines that are P-gp substrates. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) should be used with caution when administered concomitantly with enzalutamide.

No other new systemic therapy or new radiotherapy for treatment (exception for spinal cord compression, pain management, etc.) for prostate cancer is permitted while subject is on the study. Subjects with pre-existing non-target lesions (e.g., bone metastases) receiving palliative radiography for pain treatment before participation in the study are allowed to continue receiving radiotherapy during the study.

Duration of Treatment:

Treatment on study will be continued until disease progression including radiographic or clinical progression (such as pathological fracture, cord compression, worsened pain requiring radiation therapy, or opioid analgesic dose increase or initiation), or unacceptable toxicity.

Endpoints for Evaluation:

Primary:

- Radiographic progression-free survival (rPFS)

Secondary:

- Overall survival rate at 1 year
- Time to PSA progression

PSA response rate [maximum decline of $\geq 30\%$, $\geq 50\%$, and $\geq 90\%$ from baseline, (PSA30, PSA50, and PSA90), respectively]

- Objective response rate
- Time to first use of a subsequent antineoplastic therapy
- Safety (e.g., SAEs, AEs)

Exploratory:

- Biomarker Assessment and correlation with efficacy endpoints

Statistical Methods:

All endpoints will be descriptively summarized and their correlation with biomarkers and efficacy endpoints explored via regression models as appropriate. One interim efficacy analysis is planned 13 weeks after the 40th subject is enrolled. Final analysis will be conducted 12 months after last subject is enrolled.

Sample Size Justification:

Prior clinical trials data in the post-chemo setting have shown the following median rPFS for subject randomized to initial placebo, placebo+prednisone, or mitoxantrone+prednisone therapy:

- AFFIRM: Placebo = 2.9 months
- COU-301: Placebo + Prednisone = 3.6 months
- TROPIC: Mitoxantrone + Prednisone = 1.4 months

With a sample size of 40 subjects and an assumed median rPFS of 4 months for the therapy defined in this single-arm study, approximately 34 events are expected over a 12-month accrual and 12-month minimum follow-up. Further assuming uniform accrual, 10% loss to follow-up, and an exponential distribution for the rPFS event times the expected lower bound of the 90% confidence interval for the median is approximately 2.5 months based upon simulations.

Safety:

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0 and all adverse events will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and maximum CTCAE grade. Descriptive statistics will be used rather than inferential statistics.

Laboratory values will be classified by toxicity grade based on the NCI-CTCAE, version 4.0. Tables of laboratory CTCAE grade shift from baseline to maximum CTCAE grade across subsequent visits will be provided.

Correlative Studies:

Objectives:

- Explore the prevalence and dynamics of resistance biomarkers
- Explore potential correlation of the resistance biomarkers with rPFS, PSA response, and PSA progression

- Explore potential correlation of the sensitivity biomarkers with rPFS, PSA response, and PSA progression
- Explore potential correlation of inflammatory proteins with rPFS, PSA response, and PSA progression
- Explore potential correlation of AR and glucocorticoid receptor levels and mutations/polymorphism with rPFS, PSA response, and PSA progression

Blood samples will be collected to capture CTCs at Week 1, Week 13, and at the time of PSA progression and/or at the time of radiographic progression, for (but not limited to) assessment of the following:

- Expression levels of androgen receptor variants (AR-V's): AR-V7 and AR-V12/ARv567es
- Expression levels of AR full length (AR-FL) and glucocorticoid receptor full length (GR-FL)
- AR mutations - e.g. L702H, W741C, F876L and T877A.

Serum samples will be collected at Week 1, Week 13, and at the time of PSA progression and/or at the time of radiographic progression for (but not limited to) inflammatory biomarkers, such as IL6, IL8, Tumor necrotic factor alpha (TNF- α), and soluble TNF receptor-1 (sTNF1), and neuroendocrine (NE) markers such as chromogranin A (CgA), neuron specific enolase (NSE), and synaptophysin.

V. SCHEDULE OF ASSESSMENTS

Table 1 Study Schedule of Activities

| Study Day | Screening Visit | 1 | 29 | 57 | 85 | 113 | 141 | 169 | Safety F/U | Unscheduled Visit ^a | Long-term F/U |
|---|--------------------|----------------|-----|-----|-----|-----|-----|----------------------------------|--------------------------------------|--------------------------------|----------------|
| Week | -4 to -1 (28 days) | 1 | 5 | 9 | 13 | 17 | 21 | 25 and every subsequent 12 weeks | 30 days after last dose ^b | n/a | Every 12 weeks |
| Window (days) | | | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 7 | n/a | ± 7 |
| Informed Consent | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | |
| Physical Examination ^c , Weight ^d | X ^d | X | X | X | X | X | X | X | X | X | |
| 12-Lead ECG | X | | | | | | | | | | |
| MUGA/Echocardiogram ^e | X | | | | | | | | | | |
| Clinical Labs ^f | X | X ^g | | | X | | | X | X | X | |
| PSA ^h | X | X | | X | X | X | X | X | X | | |
| CT/MRI and Bone Scan ⁱ | X | | | X | | X | | X | | | |
| CXR or Chest CT | X | | | | | | | | | | |
| ECOG PS | X | X | | | X | | | X | X | X | |
| Adverse Events ^j | X | X | X | X | X | X | X | X | X | X | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | |
| Study Drug Dispensing | | X | X | X | X | X | X | X | | | |
| Long-Term F/U Assessments ^k | | | | | | | | | | | X |
| Study Drug Treatment ^l | | X | X | X | X | X | X | X | | | |
| Blood Samples for CTCs and molecular profiling ^m | | X | | | X | | | | | | |
| Serum Samples ^m | | X | | | X | | | | | | |

^a Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow up on adverse events, at the patient's request or if deemed necessary by the investigator.

^b Or before the initiation of another systemic antineoplastic therapy, whichever comes first. AE and clinical lab assessments will be performed during the Safety Follow-Up visit, regardless of initiation of another antineoplastic therapy prior to last dose of enzalutamide.

^c A brief physical examination is required at each study visit, with the exception of the Screening visit during which a complete physical examination will be completed.

Footnotes continued on next page

^d Weight is required at screening visit only.

^e A MUGA scan or echocardiogram is required if the patient has a history of anthracycline treatment, or if the subject has congestive heart failure New York Heart Association (NYHA) class 3 or 4.

^f Laboratory assessments include serum chemistries and hematology.

^g Collect a blood sample for additional safety testing if indicated.

^h PSA progression, defined as a $\geq 25\%$ increase and an absolute increase of ≥ 2 $\mu\text{g/L}$ (2 ng/mL) above the nadir, needs to be confirmed by a second consecutive value obtained 3 or more weeks later.

ⁱ The window for all radiological assessments is ± 7 days. At Weeks 9, 17, 25 and subsequent assessments prior to treatment discontinuation, all other procedures must be completed within the ± 3 day window. Bone progression at the first reassessment at Week 9 requires a confirmatory scan 6 or more weeks later.

^j Adverse events, serious or non-serious, will be collected from the time the patient signs the consent form until the Safety Follow-Up visit, regardless of initiation of another anti-neoplastic therapy prior to last dose of enzalutamide.

^k Long-term follow-up for radiographic progressions (until progression or initiation of new anti-neoplastic therapy), survival, and subsequent anticancer therapies should be performed every 12 weeks for a maximum of 3 years from first dose. The study will end when the last subject has been followed for 1 year from date of first dose.

^l Enzalutamide will be administered until disease progression, including radiographic progression or unequivocal clinical progression. Per the Investigator's clinical judgment and with sponsor approval, patients may be allowed to continue enzalutamide until the next treatment is initiated. If another non-cytotoxic, non-investigational, antineoplastic agent is initiated after protocol-defined progression has been determined, enzalutamide may be continued per the Investigator's clinical judgment and with sponsor approval as long as the patient is tolerating enzalutamide and continues androgen deprivation therapy

^m Blood samples for CTC molecular profiling and serum samples will be collected at Week 1, Week 13, and at the **time of PSA progression** and/or at the **time of radiographic progression**.

1 INTRODUCTION

1.1 Background

Other than skin cancer, prostate cancer is the most commonly diagnosed cancer among men. The American Cancer Society estimates that 180,890 new cases will be diagnosed and approximately 26,120 men will die of prostate cancer in the US during 2016. Prostate cancer is the second leading cause of cancer death in America, behind only lung cancer [American Cancer Society 2016]. The androgen receptor (AR) signaling pathway is critical for prostate cancer cell growth and survival. Androgen deprivation therapy (ADT) comprising Gonadotropin-releasing hormone (GnRH) analogue or bilateral orchiectomy provides effective suppression of serum testosterone and downstream AR transcriptional activity, resulting in symptomatic relief and reduction in serum levels of prostate-specific antigen (PSA). Disease progression often occurs despite ADT, as tumors resort to upregulation of AR, androgen biosynthesis in adrenal glands, or intratumoral androgen biosynthesis via conversion of adrenal precursors into testosterone and dihydrotestosterone [Montgomery et al, 2008]. Therefore, in the setting of metastatic castration-resistant prostate cancer (mCRPC), continued AR signaling inhibition remains a therapeutic goal.

Among therapies that were shown to improve survival, namely enzalutamide [Scher et al, 2012; Beer et al, 2014], abiraterone acetate (AA) [De Bono et al, 2011; Ryan et al, 2013], docetaxel [Tannock et al, 2004], cabazitaxel [De Bono et al, 2010], sipuleucel-T [Kantoff et al, 2010], and Radium-223 [Parker et al, 2013], act or partially act on the AR axis. Enzalutamide and AA targets AR signaling directly. The taxanes inhibit AR nuclear translocation through inhibiting microtubule polymerization [Thadani-Mulero et al, 2014].

Despite the advance, systemic treatment option is limited after disease progression from docetaxel. Recent data suggest cross-resistance between AA and enzalutamide. Lorig et al. reported a shorter duration of effect and less serum PSA kinetic change in 8 patients given abiraterone and prednisone after docetaxel and enzalutamide [Lorig et al, 2013]. Cabazitaxel is associated with significant toxicity: 82% grade 3-4 ($\text{Gr} \geq 3$) neutropenia (7% febrile), 98% anemia (11% $\text{Gr} \geq 3$), 48% thrombocytopenia (4% $\text{Gr} \geq 3$), 47% diarrhea (6% $\text{Gr} \geq 3$), 37% fatigue (5% $\text{Gr} \geq 3$), 34% nausea, 22% vomiting, 20% asthenia (5% $\text{Gr} \geq 3$), 13% peripheral neuropathy (motor/sensory), etc. [Cabazitaxel US Package Insert, 2014].

1.2 Non-clinical and Clinical Data

Enzalutamide (formerly known as MDV3100) competitively binds to the ligand binding domain (LBD) of AR and inhibits AR translocation to the cell nucleus, recruitment of cofactors, and binding to DNA [Tran et al, 2009]. One of the mechanisms of resistance to enzalutamide is over-expression of constitutively active AR splice variants lacking LBD Androgen [Li et al, 2013]. It has been shown in prostate cancer cells and CRPC xenografts treated with enzalutamide or abiraterone that increased expression of two constitutively active AR-Vs, AR-V7 and ARv567es activate a distinct expression signature enriched for cell-cycle genes without requiring the presence of AR-FL [Hu et al, 2012]. Other resistance mechanisms include mutations of the LBD that result in AR activation by anti-androgens or

glucocorticoids/steroids [Duff et al 2005, Balbas et al 2013, Carreira et al. 2014], and cross-talk between AR and AR independent growth factor and oncogenic kinase pathways including IGF signaling, JAK/STAT signaling and modulation of mTOR [Szmulewitz et al, 2014].

Pro-inflammatory proteins have been associated with aggressive and/or drug resistant tumors. Proteins associated with inflammation (e.g. IL6, IL8, TNF-alpha, TNF receptors) have been reported to be associated with aggressive prostate tumors and drug resistance (Chadha et al, 2014; Eiro et al, 2014; Liu et al, 2014; Feng et al, 2009; Codony-Servat et al, 2013). Preclinical studies have demonstrated that the inflammatory cytokine IL6 is a driver of tumor cell aggressiveness and can confer resistance to androgen receptor inhibitors (Feng et al, 2009; Liu et al, 2014). Targeting IL6 was observed to reverse the resistance to an androgen receptor inhibitor (Liu et al, 2014), thereby supporting the molecular and biomarker link between the inflammatory cytokines such as IL6 with drug resistance to androgen receptor inhibitors (Feng et al, 2009; Liu et al, 2014).

Pharmacokinetics

The pharmacokinetics and metabolism of enzalutamide have been evaluated in patients with CRPC, hormone-naïve prostate cancer patients, healthy male volunteers, and subjects with mild or moderate hepatic impairment. Individual doses have ranged from 30 to 600 mg. Pharmacokinetic studies of enzalutamide in women have not been completed.

After oral administration to patients with CRPC, the median time to reach maximum enzalutamide plasma concentrations was 1 hour, and the mean terminal half-life was 5.8 days. Enzalutamide steady state was achieved by day 28, and the accumulation ratio was 8.3-fold. At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the range of 30 to 360 mg/day.

Enzalutamide is primarily eliminated by hepatic metabolism. Food does not have a clinically relevant effect on the AUC of enzalutamide and its active metabolite so it can be taken with or without food. Composite AUC of enzalutamide plus its active metabolite after single-dose enzalutamide was similar in subjects with impaired baseline hepatic function (i.e. Child-Pugh Class A, B, or C) relative to subjects with normal hepatic function, and no starting dose adjustment is needed.

Based on population pharmacokinetics modeling, age, weight and renal function (creatinine clearance [CLCR] ≥ 30 mL/min) do not have clinically meaningful effects on enzalutamide exposures; therefore, no dose adjustments are indicated for these covariates. Clinical data are insufficient to assess the potential effect of severe renal impairment ($\text{CLCR} < 30$ mL/min) and end-stage renal disease on enzalutamide pharmacokinetics.

DDI studies in prostate cancer patients showed that enzalutamide can affect exposures to other co-medications. At steady state, enzalutamide is a strong CYP3A4 inducer and moderate CYP2C9 and CYP2C19 inhibitor, and was shown to have reduced the AUC of oral midazolam (CYP3A4 substrate), S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Substrates of CYP3A4, CYP2C9 and

CYP2C19 with a narrow therapeutic index are to be avoided, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring is to be conducted. Enzalutamide (160 mg/day) did not have a clinically relevant effect on exposure to intravenous docetaxel (CYP3A4 substrate) or oral pioglitazone (CYP2C8 substrate).

Human CYP2C8 and CYP3A4 are responsible for metabolism of enzalutamide; CYP2C8 is the primary enzyme responsible for the metabolism of enzalutamide and the subsequent formation of the active metabolite (N-desmethyl enzalutamide).

DDI studies in healthy subjects showed that concomitant medications can affect exposure to enzalutamide. Coadministration of gemfibrozil (a strong CYP2C8 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold; therefore, strong CYP2C8 inhibitors are to be avoided. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide is to be reduced to 80 mg once daily. Coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold; as this small change is not clinically meaningful; no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors.

Coadministration of rifampin (moderate CYP2C8 inducer and strong CYP3A4 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%.

In vitro data indicate that enzalutamide and its major metabolites are not substrate for human P-glycoprotein (P-gp); enzalutamide and N-desmethyl enzalutamide are inhibitors for P-gp.

In vitro data also show that enzalutamide and N-desmethyl enzalutamide do not appear to be substrate for human breast cancer resistance protein (BCRP), however, enzalutamide and N-desmethyl enzalutamide are inhibitors of BCRP at clinically relevant concentrations.

Two phase III randomized trials have demonstrated significant activity of enzalutamide in men with mCRPC. In the phase III AFFIRM trial [Scher et al, 2012], 1199 men with prior chemotherapy exposure who were randomly assigned to receive enzalutamide versus placebo, a statistically significant improvement in OS of 18.4 versus 13.6 months was detected with enzalutamide (HR, 0.63; 95% CI, 0.53 to 0.75; $P < .001$). Radiographic PFS (rPFS) was 8.3 versus 2.9 months (HR, 0.40; $P < .001$), PSA response was 54% versus 2% ($P < .001$), time to PSA progression was 8.3 versus 3.0 months (HR, 0.25; $P < .001$), and time to first skeletal-related event was 16.7 versus 13.3 months (HR, 0.69; $P < .001$), all in favor of enzalutamide. Overall QOL benefit was observed in 43% versus 18% ($P < .001$) of patients receiving enzalutamide compared with placebo, whereas fatigue, diarrhea, and hot flushes were more common with enzalutamide. Five patients (0.6%) experienced seizures in the enzalutamide group.

In the Phase III PREVAIL trial [Beer et al, 2014], 1717 men without prior chemotherapy exposure were randomized to receive enzalutamide or placebo. Compared to placebo, enzalutamide improved rPFS (rPFS rate at 12-month: 65% vs 12%; HR= 0.19; 95% CI, 0.15 to 0.23; $P < 0.001$) and overall survival (HR=0.71; 95% CI, 0.60 to 0.84; $P < 0.001$). The

benefit of enzalutamide was shown with respect to all secondary endpoints, including the time until the initiation of cytotoxic chemotherapy (HR= 0.35), the time until the first skeletal-related event (HR= 0.72), a complete or partial soft-tissue response (59% vs. 5%), the time until PSA progression (HR, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) (P<0.001 for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment.

No clinical data are available on activity of enzalutamide after sequential treatment with enzalutamide and chemotherapy. Modest activity of enzalutamide after therapy with abiraterone acetate and docetaxel were reported. The reported rate of $\geq 50\%$ PSA decline range between 13% to 46% [Bianchini et al, 2014; Azad et al, 2014; Schrader et al, 2014].

Clinical prevalence of biomarkers implicated in resistance has been reported. Approximately 30-40% patients have circulating tumor cells positive for ARv7 after enzalutamide or AA therapy [Antonarakis et al, 2014]. No PSA response was observed on either enzalutamide or abiraterone among these patients. ARv567es was reported to be expressed in at least 1 metastatic lesion among 71% of 13 subjects who underwent biopsy [Sun et al, 2010].

Rationale for Enzalutamide re-treatment

Benefit of re-treatment with a molecularly targeted agent after intervening therapies that are not cross-resistant with the initial therapies have been observed in other tumor types such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and in EGFR- mutant non-small cell lung cancer [Riely et al, 2007; Song et al, 2013].

To date, a study of enzalutamide re-treatment following enzalutamide and intervening chemotherapy has not been performed. Limited data are available on re-treatment with an AR-targeting agent. A retrospective review of a small cohort of patients that received AA re-treatment (n=12), no biochemical response was observed among patients who did not initially respond to AA; among the 7 patients who initially responded to AA, upon re-treatment, the rate of PSA reduction by 30% and 50% was 86% and 46%, respectively. Given the similarity in MOA, evaluation of enzalutamide re-treatment in men with limited other therapeutic options is warranted [Leibowitz-Amit et al, 2014].

Rationale for chemotherapy prior to Enzalutamide re-treatment

Docetaxel may overcome resistance to enzalutamide in a manner that is both AR-dependent and AR-independent. Recent work suggests that the microtubule network of prostate cells is critical for androgen receptor nuclear translocation and activity. Unlike AR-V7, ARv567es/AR-V12 has hinge domain. This allows ARv567es/AR-V12 to co-sediment with microtubules or co-precipitate with dynein motor protein in the same way as AR-FL. Docetaxel was shown to suppress ARv567es/AR-V12 nuclear translocation and transcription activation [Thadani-Mulero et al, 2014]. In addition, being a cytotoxic agent, docetaxel has been shown to induce mitotic catastrophe subsequent to G2/M arrest, and activation of bcl-2 and bcl-xL gene dependent and independent apoptotic pathways [Fabbri et al, 2008]. This provides the AR-independent mechanism of overcoming the resistance. The study will enroll patients who have received at least 4 cycles of docetaxel and/or cabazitaxel to allow a

selection of a subset of patients for whom chemotherapy can overcome resistance. AR-V7 and AR-V12, as well as AR mutations will be studied to help assess response to enzalutamide re-treatment.

Cabazitaxel may overcome resistance to enzalutamide in a similar manner as docetaxel. Cases of reversions from AR-V7 positive to negative status following cabazitaxel treatment have been reported [Nakazawa et al, 2015].

1.3 Summary of Key Safety Information for Study Drugs

The safety profile of enzalutamide in patients with metastatic CRPC is primarily derived from two randomized, placebo-controlled phase 3 studies AFFIRM and PREVAIL. Several other studies in patients with prostate cancer and healthy volunteers provide additional safety data.

Enzalutamide treatment was generally well tolerated across all studies, and the safety profile in enzalutamide was generally consistent with that observed in CRPC. As expected for this patient population with advanced prostate cancer, nearly all enzalutamide-treated and placebo-treated patients experienced at least 1 adverse event (AE) during each study. In PREVAIL, a higher proportion of enzalutamide-treated patients experienced grade 3 or higher AEs compared with placebo-treated patients (42.9% vs 37.1%); the median time to first grade 3 or higher AE in PREVAIL was 22.3 months in the enzalutamide group versus 13.3 months in the placebo group. A similar pattern was observed in time to first grade 3 or higher event in the combined population.

Adverse events or laboratory abnormalities occurring in at least 5% of the patients and more frequently in the enzalutamide treatment group with at least a 2% higher absolute incidence over placebo are the following: constipation (23.9% vs. 20.7%), diarrhea (19.2% vs. 15.4%), fatigue (35.1% vs. 27.0%), asthenia (15.8% vs 10.9%), edema peripheral (12.8% vs. 9.3%), fall (8.8% vs. 4.0%), weight decreased (12.3% vs. 9.2%), decreased appetite (23.8% vs 20.8%), back pain (27.5% vs. 23.0%), arthralgia (20.9% vs. 16.5%), musculoskeletal pain (12.7% vs. 9.6%), muscular weakness (6.9% vs. 4.4%), headache (11.5% vs. 6.5%), dysgeusia (6.1% vs. 3.6%), spinal cord compression (5.9% vs. 3.9%), insomnia (8.4% vs. 5.8%), anxiety (5.2% vs. 3.1%), mental impairment (including amnesia, memory impairment, cognitive disorder, disturbance in attention, 5.1% vs. 1.6%), haematuria (7.9% vs. 5.4%), hot flush (19.1% vs. 8.6%), hypertension (10.5% vs. 3.7%), neutropenia (15% vs. 6%).

In PREVAIL, a higher incidence of serious adverse events (SAEs) was observed for enzalutamide compared with placebo (32.0% vs 26.8%), but with a longer median time to first SAE (not yet reached vs 23.3 months). A similar pattern was observed for the incidence of SAEs and time to first SAE in the combined population.

Seizure occurred in 0.9% of patients receiving enzalutamide who previously received docetaxel, and in 0.1% of patients who were chemotherapy-naïve. There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide

For additional safety information, please refer to the Enzalutamide Full Prescribing Information and the Enzalutamide Investigator Brochure.

1.4 Risk-Benefit Assessment

In previous clinical studies, over 5500 patients with prostate cancer, over 400 women with breast cancer, and over 300 male subjects with no known cancer (including healthy men and subjects with liver impairment) have received at least 1 dose of enzalutamide in completed and ongoing clinical studies as of February 2016. The safety and tolerability of enzalutamide continues to be evaluated on an ongoing basis for all enzalutamide program studies. No study has been terminated early for safety reasons.

The benefit of re-treatment with enzalutamide has not been established. Considering the limited number of treatment options after chemotherapy, a well-tolerated safety profile for enzalutamide, and that chemotherapy may address resistance to enzalutamide via a non-cross resistant mechanism, this study of re-treatment with enzalutamide in mCRPC is warranted. The biomarker correlative component of the trial will provide additional data to inform strategies to overcome resistance to mCRPC treatment.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

The primary objective is:

- To determine radiographic progression-free survival (rPFS) of re-treatment with enzalutamide + GnRH analogue

The secondary objectives are:

- To assess additional measures of efficacy:
 - Overall survival rate at 1 year
 - Time to PSA progression
 - PSA response rate [maximum decline of $\geq 30\%$, $\geq 50\%$, and $\geq 90\%$ from baseline, (PSA30, PSA50, and PSA90), respectively]
 - Objective response rate
- Time to first use of a subsequent antineoplastic therapy
- To assess safety of enzalutamide re-treatment in the post-chemo setting.
- To assess correlative science in the post-chemo setting.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a US-based, multicenter, open-label, single-arm, study evaluating the efficacy, safety, and tolerability of open-label enzalutamide in the re-treatment setting. A total of 40 patients will be enrolled. Patients must have been previously treated with enzalutamide in the pre-chemotherapy setting for a minimum of 8 months, followed by docetaxel and/or cabazitaxel for a minimum of 4 cycles. Exposure to intervening systemic anti-cancer therapies such as abiraterone prior to chemotherapy is allowed. Subjects will receive treatment with open-label enzalutamide (160 mg daily), administered as four 40 mg capsules, by mouth, once daily, until radiographic or clinical progression (such as pathological

fracture, cord compression, worsened pain requiring radiation therapy, or opioid analgesic dose increase or initiation), or unacceptable toxicity. Per the Investigator's clinical judgment and with sponsor approval, patients may be allowed to continue enzalutamide until the next treatment is initiated. If another non-cytotoxic, non-investigational, antineoplastic agent is initiated after protocol-defined progression has been determined, enzalutamide may be continued per the Investigator's clinical judgment and with sponsor approval as long as the patient is tolerating enzalutamide and continues androgen deprivation therapy.

The consensus guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) will be utilized to determine radiographic disease progression. Radiographic disease progression is defined by RECIST 1.1 for soft tissue disease. Bone disease progression is considered when a minimum of two new lesions are observed. Progression on bone scan at time points prior to or at Week 9 requires a confirmatory scan performed six or more weeks later. This confirmatory scan should demonstrate at least 2 additional new lesions compared to the Week 9 scan (PCWG2).

The following assessments of prostate cancer status will be collected during the course of the trial: soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, and PSA.

Study films (CT/MRI and bone scan) should be read on site. Each site should ideally designate the same reader who will evaluate the images for any one subject for the duration of the trial.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs, physical examinations, and safety laboratory evaluations.

Subjects will have a Safety Follow-up visit approximately 30 days following the last dose of study drug or prior to the initiation of a subsequent anti-cancer drug or investigational agent, whichever occurs first. Survival will be followed every 12 weeks for a maximum of 3 years from first dose. The study will end when the last subject has been followed for 1 year from date of first dose.

2.2.2 Dose Rationale

A dose of 160 mg enzalutamide (four 40 mg capsules) once daily administered orally is the FDA approved daily dose.

2.3 Endpoints

2.3.1 Primary Endpoint

The primary efficacy endpoint is:

- Radiographic progression-free survival (rPFS).

2.3.2 Secondary Endpoints

Secondary endpoints are:

- Overall survival rate at 1 year
- Time to PSA progression
- PSA response rate [maximum decline of $\geq 30\%$, $\geq 50\%$, and $\geq 90\%$ from baseline, (PSA30, PSA50, and PSA90), respectively]
- Objective response rate
- Time to first use of a subsequent antineoplastic therapy
- Safety (e.g., SAEs, AEs)

2.3.3 Exploratory Endpoints

The exploratory endpoint is:

- Biomarker Assessment and correlation with efficacy endpoints

3 STUDY POPULATION

3.1 Selection of Study Population

This study will enroll 40 patients previously treated with enzalutamide for a minimum of 8 months, followed by docetaxel and/or cabazitaxel for a minimum of 4 cycles. Exposure to intervening systemic anti-cancer therapies such as abiraterone prior to chemotherapy is allowed.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without signet ring cell features.
2. Presence of metastatic disease (M1) as assessed by CT/MRI and/or whole-body radionuclide bone scan.
3. Subject has been previously treated with enzalutamide for at least 8 months, and stopped enzalutamide due to progressive disease (not due to adverse events), followed by at least 4 cycles of docetaxel and/or cabazitaxel chemotherapy, with or without other intervening anti-cancer therapies (including but not limited to aminoglutethimide, ketoconazole, abiraterone acetate, Rad-223, or sipuleucel-T), prior to receiving chemotherapy. Note: for patients who receive sequential taxanes, there must not have been progressive disease upon ending the first taxane, or use of any anti-cancer agents between the two taxanes.
4. Ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue or prior bilateral orchiectomy (medical or surgical castration). For patients who have not had bilateral orchiectomy, there must be a plan to maintain effective GnRH-analogue for the duration of the trial.
5. Testosterone ≤ 1.73 nmol/L (≤ 50 ng/dL) at screening.
6. Age 18 years or older.

7. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
8. ECOG performance status of 0-2 at screening.
9. Estimated life expectancy of ≥ 6 months at screening.
10. Ability to swallow study drugs and to comply with study requirements throughout the study.
11. Throughout study, male subject and a female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration. Two acceptable methods of birth control thus include the following:
 - a. Condom (barrier method of contraception)

AND

 - b. One of the following is required:
 - i. Established use of oral, injected, or implanted hormonal method of contraception by the female partner performed at least 6 months before screening;
 - ii. Placement of an intrauterine device or intrauterine system by the female partner;
 - iii. Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner;
 - iv. Tubal ligation in the female partner.
 - v. Vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy), performed at least 6 months before screening
12. Must not donate sperm from screening through 3 months after final study drug administration.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply (waivers to the exclusion criteria will **NOT** be allowed):

1. Known or suspected neuroendocrine/small cell feature.
2. Use of any antineoplastic treatment post-chemotherapy, including but not limited to aminoglutethimide, ketoconazole, abiraterone acetate, Rad-223, sipuleucel-T, or enzalutamide. Continuing steroids is permitted.

3. Palliative radiation therapy within 2 weeks of Day 1, or within 4 weeks of Day 1 if a radionuclide was utilized.
4. Use of an investigational agent within 4 weeks of Day 1 visit.
5. Major surgery within 4 weeks prior to Day 1 visit.
6. History of seizure or any condition that may predispose to seizures (e.g., prior cortical stroke or significant brain trauma) at any time in the past. History of loss of consciousness or transient ischemic attack within 12 months of screening.
7. History of clinically significant cardiovascular disease including:
 - a. Myocardial infarction or uncontrolled angina within 3 months;
 - b. History of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within three months results in a left ventricular ejection fraction that is $\geq 45\%$;
 - c. History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes);
 - d. History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
8. Clinically significant cardiovascular disease at screening including:
 - a. Hypotension as indicated by systolic blood pressure < 86 millimeters of mercury (mm Hg) at screening;
 - b. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG) and on physical examination;
 - c. Uncontrolled hypertension as indicated by at least 2 consecutive measurements of a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at the screening visit.
9. Subject has a known or suspected hypersensitivity to enzalutamide or any components of the formulation used.
10. Severe concurrent disease, infection, or co-morbidity that, in the judgment of the investigator, would make the patient inappropriate for enrollment.
11. Known or suspected brain metastasis or leptomeningeal disease.
12. Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last 3 months);
13. Absolute neutrophil count $< 1,500/\mu\text{L}$, platelet count $< 75,000/\mu\text{L}$, or hemoglobin < 5.6 mmol/L (9 g/dL) at screening.
14. Total bilirubin or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times ULN at screening.
15. Creatinine $> 177 \mu\text{mol/L}$ (> 2 mg/dL) at screening.
16. Albumin < 30 g/L (3.0 g/dL) at screening.

17. Treatment with abiraterone acetate prior to enzalutamide for mCRPC in the pre-chemotherapy setting. (*Note:* Patients who have received concomitant enzalutamide and abiraterone acetate therapies are not excluded).

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

Enzalutamide is an opaque white to off-white oblong liquid filled soft gelatin capsule for oral administration. Each capsule contains 40 mg enzalutamide.

4.1.2 Comparative Drug(s)

Not applicable.

4.2 Packaging and Labeling

Enzalutamide is supplied by APGD, Medical Affairs, Americas. Enzalutamide will be packaged in high-density polyethylene bottles with child-resistant induction seal closure.

Enzalutamide will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas US Technologies, Inc. (AUST) in accordance with APGD, Medical Affairs, Americas-AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

4.3 Study Drug Handling

Enzalutamide will be stored in a secure location with limited access at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Subjects will be instructed to store study drug at room temperature and out of the reach of children.

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator/or designee and

- that such deliveries are recorded,
- that enzalutamide is handled and stored according to labeled storage conditions,
- that enzalutamide with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- that enzalutamide is returned to the Sponsor.

Drug inventory and accountability records for enzalutamide will be kept by the Investigator/or designee. Enzalutamide accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply enzalutamide to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the enzalutamide in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense enzalutamide.

- An enzalutamide inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return enzalutamide to the Sponsor or designee at the end of the study or upon expiration.

The study sites will provide GnRH agonist or antagonist from pharmacy stock.

4.4 Blinding

This section is not applicable as this is an open-label study.

4.5 Assignment and Allocation

This is an open-label study, so subjects who meet all inclusion criteria and no exclusion criteria will be assigned to begin study treatment. Registration must occur following informed consent process and prior to initiation of investigational therapy. Each site will receive a unique Site ID and each subject at each site will be assigned a subject ID in sequential order as he enrolls in the study. Discontinued subjects will not be replaced.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

Subjects will receive treatment with enzalutamide (160 mg daily), administered as four 40 mg capsules, by mouth, once daily, until radiographic or clinical progression, or unacceptable toxicity.

Study drug should be taken as close to the same time each day as possible. Study drug can be taken with or without food.

Subjects must also be receiving ongoing androgen deprivation therapy with a GnRH agonist, antagonist, or have had a previous bilateral orchiectomy. The study sites will provide GnRH agonist or antagonist from pharmacy stock.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

Subjects who experience a Grade 3 or greater toxicity considered to be related to enzalutamide that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity.

Subjects may subsequently be re-started on study drug at a reduced dose following a discussion between the Investigator and the sponsor.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

5.1.3.1 Previous Treatment (Medication and Non-Medication Therapy)

Medication taken within four weeks prior to Baseline (Day 1) and any medications prescribed chronically or intermittently during the study or dose adjustments of these medications must be captured on the case report form.

5.1.3.2 Concomitant Treatment (Medication and Non-Medication Therapy)

Concomitant medications will be captured from the Screening Visit through 30 days after last dose.

Prohibited Medications

The following medications are prohibited while patients are on enzalutamide treatment and have not had disease progression:

- Chemotherapy with anti-tumor activity against prostate cancer such as cabazitaxel, mitoxantrone, etc.
- Sipuleucel-T
- Rad-223
- Androgen-receptor antagonists (bicalutamide, flutamide, nilutamide)
- 5 α -reductase inhibitors (finasteride, dutasteride)
- Estrogens
- Cyproterone acetate
- Androgens (testosterone, dehydroepiandrosterone [DHEA], etc.)
- Ketoconazole
- Abiraterone acetate
- Any other investigational agent

Restricted Medications

The dosage and regimen of the following medications and any chronic permitted medications should be stabilized during the screening period (> 4 weeks prior to randomization) and held constant throughout the study:

- Denosumab and bisphosphonates
- GnRH agonist/antagonist therapy

There is a potential for enzalutamide to affect exposures to other medicinal products, or for other medicinal products to affect exposure to enzalutamide:

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) or CYP2C8 inducers (e.g., rifampicin) are to be avoided. If subject must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If a 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.

- Strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampin) or moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort) should be avoided if possible as they may reduce enzalutamide plasma concentration if co-administered. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.
- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4 (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g. phenytoin, warfarin), CYP2C19 (e.g. S-mephenytoin), or UGT1A1 should be avoided if possible, as enzalutamide may decrease their exposure.
- If enzalutamide co-administration with warfarin cannot be avoided, additional INR monitoring should be conducted.
- Enzalutamide is an inhibitor of human P-glycoprotein (P-gp) and may increase exposure to medicines that are P-gp substrates. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) should be used with caution when administered concomitantly with enzalutamide.

No other new systemic therapy or new radiotherapy for treatment (exception for spinal cord compression, pain management, etc.) for prostate cancer is permitted while subject is on the study. Subjects with pre-existing non-target lesions (e.g., bone metastases) receiving palliative radiography for pain treatment before participation in the study are allowed to continue receiving radiotherapy during the study.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug at each study visit after Baseline. Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

If compliance is less than 80% or more than 120%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects who are less than 80% or more than 120% compliant with the dosage regimen for any two consecutive visit periods during the study should be withdrawn from the study.

5.1.5 Criteria for Continuation of Treatment

Subjects will receive treatment until the time of disease progression, including radiographic or unequivocal clinical progression, or unacceptable toxicity. Per the Investigator's clinical judgment and with sponsor approval, patients are allowed to continue study drug until next treatment is initiated. If another non-cytotoxic, non-investigational, antineoplastic agent is

initiated after protocol-defined progression has been determined, study drug therapy may be continued per the Investigator's clinical judgment and with sponsor approval as long as the patient is tolerating the study drug and continues androgen deprivation therapy.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The subject's date of birth, sex, race, ethnicity, and weight will be recorded at the Screening Visit.

5.2.2 Medical History

Medical history (other than for prostate cancer) will be obtained at the Screening Visit from each subject. All relevant past and present conditions, as well as prior surgical procedures will be recorded.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

A detailed prostate cancer history for each subject will be obtained at the Screening Visit. This will include documenting the subject's initial diagnosis of prostate cancer, Gleason score at time of diagnosis, dates and type of primary therapy and other disease specific information as designated in the eCRF.

5.2.4 Performance Status

The ECOG PS [Oken et al, 1982] will be used to assess performance status.

Table 2 ECOG Performance Status

| Grade | Description |
|--------------|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

ECOG PS score will be collected at the Screening Visit, Week 1 (Baseline), Week 13, Week 25, at subsequent 12 week intervals, at any unscheduled visits, and at the Safety Follow-Up visit 30 days after last dose.

5.2.5 Chest X-Ray and/or Chest CT

At the Screening Visit, a chest x-ray will be performed. A chest CT is required for efficacy assessment (see below) if the screening chest x-ray reveals suspected metastatic chest disease.

5.3 Efficacy Assessment

5.3.1 CT/MRI and Bone Scan

Imaging including abdominopelvic CT/MRI, chest CT (if screening chest x-ray leads to diagnosis of thoracic metastasis), and Technicium-99m (Tc-99m) bone scintigraphy will be performed at the Screening Visit and assessed at Week 9, Week 17, Week 25 and at subsequent 12 week intervals. For subjects that discontinue for reasons other than radiographic progression or initiation of a new anti-neoplastic therapy, the imaging will be conducted every 12 weeks until progression, initiation of new anti-neoplastic therapy, loss to follow-up or death. Imaging performed prior to informed consent may be used as baseline so long as it is performed within the Screening period (days -28 to -1).

Scans should be scheduled in such a way that the scan results are available at the regularly scheduled visit.

The imaging method utilized for baseline scans must be utilized throughout the entire study.

Imaging may be performed at any time to confirm suspected progression of disease.

Radiographic evaluation of metastatic disease is determined separately for soft tissue and bone disease. Radiographic disease assessment for soft tissue disease is based on CT or MRI scan and is defined by RECIST 1.1. Radiographic disease assessment for bone lesions is based on bone scan and progression is considered when a minimum of two new lesions compared to baseline are observed.

Progression on bone scan at time points prior to or at Week 9 require a confirmatory scan performed six or more weeks later. This confirmatory scan should demonstrate at least 2 additional new lesions compared to the Week 9 scan (PCWG2).

Assessment will include tumor measurements for target lesions, non-target lesions, and assessment for any new lesions. An overall assessment will be characterized for that time point evaluation. At the end of study for that subject, the overall best response to the study regimen will be characterized.

Images (abdominopelvic [lung when applicable] CT/MRI and bone scan) should be read on site. Each site should ideally designate the same reader who will evaluate the images for any one subject for the duration of the study.

The same imaging method used for an individual patient at baseline should be used throughout the entire study for that patient.

PET scans should not be used to determine disease progression.

5.3.2 PSA

Samples for PSA will be collected and analyzed at the site's local laboratory. PSA testing will be performed at the Screening Visit, Week 1 (Baseline), Week 9, Week 13, Week 17, Week 21, Week 25, at subsequent 12 week intervals, and at the Safety Follow-up visit 30 days after last dose.

The PSA test performed at the Screening Visit does not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of the Screening Visit.

5.3.3 Correlative Samples

Whole blood and serum samples will be collected at Week 1 (baseline), Week 13, and at the time of PSA progression and/or at the time of radiographic progression. See Sections [5.7.1](#) and [5.7.2](#) for details.

5.3.4 Survival Follow-up

For all subjects, survival status and subsequent anti-cancer therapies will be followed every 12 weeks for a maximum of 3 years from first dose. The study will end when the last subject has been followed for 1 year from date of first dose.

5.4 Safety Assessment

The safety evaluations including vital signs, adverse event recording, clinical laboratory assessments and physical examination will be performed according to [Table 1](#) Study Schedule of Activities.

Please review the requirements related to the evaluation, reporting and analysis of Drug-Induced Liver Injury (DILI) information found in Appendix [12.2](#) (Liver Safety Monitoring and Assessment). In the event of a confirmed, marked hepatic abnormality as defined in Appendix [12.2](#) it is the Investigator's responsibility to ensure contact with the Sponsor/ delegated CRO by telephone or fax immediately (i.e., within 24 hours of awareness).

5.4.1 Vital Signs

Vital signs including blood pressure, heart rate, and temperature will be assessed at the Screening Visit, at every clinic visit while on study drug and at the 30-day Safety Follow-Up visit (see [Table 1](#) Study Schedule of Activities).

For each blood pressure measurement, the patient should be seated comfortably for at least 5 minutes with the back supported, feet on the floor, arm supported in a horizontal position, and the blood pressure cuff at heart level. The Investigator will use the same device model and cuff size throughout the study. The same arm should be used throughout the study.

5.4.2 Adverse Events

AE collection will begin from the time of informed consent and continue through 30 days after last dose. See Section [5.5](#) **Adverse Events and Other Safety Aspects** for information regarding adverse event collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See Appendix [12.2](#) **Liver Safety Monitoring and Assessment** for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g.: AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AE's of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Routine laboratory assessments for hematology and chemistry will be collected and analyzed at the site's local laboratory. Specifications regarding sample collection (including date and time) must be recorded in the source documentation. The site will provide all lab certification documents and reference ranges to Astellas. The same information will need to be stored in the Regulatory Binder.

Laboratory assessments will be assessed at the Screening Visit, Week 1 (Baseline), Week 13, Week 25, at subsequent 12 week intervals, at any unscheduled visits, and at the Safety Follow-Up visit 30 days after last dose.

The laboratory assessments performed at the screening visit do not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of the Screening Visit.

Laboratory assessments must be obtained prior to study drug administration.

Below is a table of the laboratory tests that will be performed during the conduct of the study. See [Table 1](#) Study Schedule of Activities for study visit collection dates.

| | | |
|---|--------------|---|
| Screening, Week 1, Week 13, Week 25, at subsequent 12 week intervals, at any unscheduled visits, and at the Safety Follow-Up visit 30 days after last dose. | Hematology | CBC RBC Hgb HCT WBC Platelets WBC Differential |
| Screening, Week 1, Week 13, Week 25, at subsequent 12 week intervals, at any unscheduled visits, and at the Safety Follow-Up visit 30 days after last dose. | Biochemistry | Sodium Potassium Calcium Chloride Magnesium Phosphorus Glucose Creatinine Alkaline phosphatase bALP LDH ALT AST GGT Total bilirubin Total protein Albumin CO2 BUN |

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

5.4.4 Physical Examination

A complete physical exam, including weight, will be performed at the Screening Visit. A brief physical exam is required at all subsequent office visits. The physical examination performed at the Screening Visit does not need to be repeated on Day 1, if the Day 1 visit occurs within 72 hours of the Screening Visit. Any clinically relevant adverse changes will be recorded as AEs in the eCRF (see Section 5.5.6).

5.4.5 Electrocardiogram (ECG)

A 12-lead ECG will be recorded at the Screening Visit. The ECG will be taken with the subject in the sitting position.

All tracings will be read locally by the Investigator to ensure patient safety and care management. Any abnormalities must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the Investigator must determine if it is clinically significant.

5.4.6 Imaging

A MUGA scan or echocardiogram showing LVEF $\geq 45\%$ is required at the Screening Visit only for subjects with a history of anthracycline or anthracenedione (mitoxantrone) treatment, or if the subject has congestive heart failure New York Heart Association (NYHA) class 3 or 4.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

5.5.2 Disease Progression

It is anticipated that a proportion of subjects will experience disease progression. Disease progression should not be reported as an adverse event. Clinical signs and symptoms due to disease progression will be collected as AEs. Individual signs and symptoms will be listed rather than the term “disease progression” with the following exception: if disease progression is the cause of death, this event may be recorded as an AE with “metastatic prostate cancer disease progression” as the reported term.

5.5.3 Definition of Serious Adverse Events (SAEs)

An adverse event is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an adverse event is considered “life-threatening” if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

5.5.4 Special Situations

The following special situations, although not necessarily considered to be AEs or ADRs must be reported in the same way as ADRs, as described in Section [5.5.7](#) Reporting of Serious Adverse Events (SAEs):

- Off-label use: situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
- Overdose: administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.

- Misuse of a medicinal product: situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse of a medicinal product: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Medication errors: are broadly defined as any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not.
- Occupational exposure: this refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation.

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and the SAE worksheet.

5.5.5 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out".

| Causal relationship to the study drug | Criteria for causal relationship |
|---------------------------------------|--|
| Not Related | A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations. |
| Possible | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. |
| Probable | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge). |

5.5.6 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

| Grade | Assessment Standard |
|--------------------|---|
| 1-Mild | Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated. |
| 2-Moderate | Local or noninvasive intervention indicated. |
| 3-Severe | Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization. |
| 4-Life Threatening | Life threatening consequences, urgent intervention indicated |
| 5-Death | Death related to AE |

5.5.7 Reporting of Serious Adverse Events (SAEs)

For patients known to be taking enzalutamide, all Serious Adverse Events, Special Situations (as outlined in Section 5.5.4) and non-serious AE's considered related to this (and any) Astellas product must be reported by the investigator to Astellas Global Pharmacovigilance via email or fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to Astellas Global Pharmacovigilance by email or fax immediately (within 24 hours of awareness).

All completed SAE forms should be sent to:

| | |
|--|--|
| Astellas Global Pharmacovigilance | Email: [REDACTED] North America telefax numbers: [REDACTED] (alternate [REDACTED]) International telefax number: [REDACTED] |
|--|--|

If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel.

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and on the (e)CRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e. IND Safety Reports) to the regulatory agencies (i.e. FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e. EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor or Sponsor's designee will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements IRB/IEC/head of the study site.

The heads of the study sites/Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

5.5.8 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the adverse event progresses to an "SAE", or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to **Appendix 12.2 Liver Safety Monitoring and Assessment** for detailed instructions on Drug Induced Liver Injury (DILI).

5.5.9 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in **Appendix 12.3 Common Serious Adverse Events** for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events" as specified in **Appendix 12.3 Common Serious Adverse Events**. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in **Section 5.5.7 Reporting of Serious Adverse Events (SAEs)**.

5.5.10 Procedure in Case of Pregnancy

If a partner of a male subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator should report the information to the Sponsor as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

5.5.11 Emergency Procedures and Management of Overdose

There is no antidote for enzalutamide. In the event of an overdose, stop treatment with enzalutamide and initiate general supportive measures based on the clinical presentation of the patient. Subjects may be at increased risk of seizures following an overdose.

5.5.12 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

Not applicable for this study.

5.7 Other Measurements, Assessments or Methods

5.7.1 Blood Sample for Molecular Profiling of CTCs

Whole blood samples will be collected at Week 1, Week 13 and at the time of PSA progression and/or at the time of radiographic progression. Seventeen milliliters (17 mL) of

whole blood in two 8.5 mL ACD Sol A tubes are needed at each time point to ensure at least 5 mL for AR and GR analysis. Samples will be collected on Monday-Thursday and shipped overnight to [REDACTED] for testing per vendor instructions. Remaining samples may be stored for future biomarker analysis. Methods as described by Antonarakis et al., 2014 will be used to capture CTC and quantification of messenger RNA (mRNA) of AR-FL, AR variants and GR-FL via Quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays. AR DNA was polymerase chain reaction-amplified and the product will be analyzed.

5.7.2 Serum Sample for Biomarker Analysis

Serum samples collected at Week 1, Week 13, and at the time of PSA progression and/or at the time of radiographic progression, will be shipped to a central lab for testing for, but not limited to, the analysis of inflammatory proteins such as IL6, IL8, TNF- α , soluble TNF1, etc. and neuroendocrine markers such as chromogranin A (CgA), neuron specific enolase (NSE), and synaptophysin. Five milliliters of blood will be collected to yield approximately 2 mL of serum. Remaining samples may be stored for future biomarker analysis.

5.8 Total Amount of Blood

The total amount of blood collected for routine laboratory tests and correlative biomarker analysis for each subject will vary depending on how long they stay on treatment. The maximum amount of blood collected for a subject within 24 hours during the treatment period is approximately 37 mL, including 15 mL for routine lab (i.e., CBC with differential, PSA, and comprehensive metabolic panel), and 22 mL for correlative biomarker analysis (Section 5.7). Furthermore, if any laboratory abnormalities are found for a subject, additional blood may be drawn for monitoring.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

The following events will result in the removal of subjects from enzalutamide therapy:

- Subject develops an adverse event, intercurrent illness, or toxicity, where continued administration of study drug is deemed not in the subject's best interest by the investigator and/or the sponsor. For example,
 - Seizure;
 - Posterior Reversible Encephalopathy Syndrome;
 - Laboratory abnormality defined by protocol as follows:
Creatinine > 354 µmol/L (> 4.0 mg/dL);
 - AST, ALT, or total bilirubin > 5 times ULN;
 - Absolute neutrophil count < 750/µL;
 - Platelet count < 50,000/mL.
- Decision by the investigator and subject to initiate a new anti-neoplastic therapy;
- Gross noncompliance with protocol: The medical monitor or investigator may request permanent treatment discontinuation in the event of a major protocol deviation such as administration of prohibited concomitant medication, lack of cooperation, or noncompliance.

Unless the subject withdraws consent, all subjects discontinuing study drug for any reason will have a Safety Follow-up visit 30 days after their last dose of study drug or prior to initiation of subsequent anti-neoplastic therapy for prostate cancer, whichever occurs first.

Subjects that discontinue study drug for a reason other than radiographic progression or initiation of a new anti-neoplastic therapy will have a PSA test performed 30 days from date of last dose and undergo long-term follow-up every 12 weeks from date of last dose. Long term follow-up will assess for survival, subsequent anti-neoplastic therapy for prostate cancer and radiographic progression. Subjects will be followed for a maximum of 3 years from first dose. The study will end when the last subject has been followed for 1 year from date of first dose. Radiographic imaging will end when the patient has developed a radiographic progression, or initiated subsequent anti-neoplastic therapy. Reasonable effort should be made to contact any subject lost to follow-up during the course of the study in order to complete study related assessments and retrieve any outstanding data and study drug. Following unsuccessful telephone contact, an effort to contact the subject by mail using a method that provides proof of receipt should be attempted. Such efforts should be documented in the source documents.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of Astellas. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be documented in the Clinical Study Report (CSR).

Prior to Database Lock, a Final Review of Data and TLFs Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints. Kaplan-Meier estimates will be used to estimate medians and provide figures for time-to-event data (e.g., rPFS, time to PSA progression, and time to first use of a subsequent antineoplastic therapy).

7.1 Sample Size

Prior clinical trials data in the post-chemo setting have shown the following median rPFS for subject randomized to initial placebo, placebo+prednisone, or mitoxantrone+prednisone therapy:

- AFFIRM: Placebo = 2.9 months
- COU-301: Placebo + Prednisone = 3.6 months
- TROPIC: Mitoxantrone + Prednisone = 1.4 months

With a sample size of 40 subjects and an assumed median rPFS of 4 months for the therapy defined in this single-arm study, approximately 34 events are expected over a 12-month accrual and 12-month minimum follow-up. Further assuming uniform accrual, 10% loss to follow-up, and an exponential distribution for the rPFS event times, the expected lower bound of the 90% confidence interval for the median is approximately 2.5 months based upon simulations.

7.2 Analysis Set

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who are enrolled, receive at least one dose of study drug, and have at least one post baseline evaluation. This will be the primary analysis set for efficacy analyses.

7.2.2 Per Protocol Set (PPS)

Not applicable.

7.2.3 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who took at least one dose of study medication, and will be used for safety analyses.

7.2.4 Biomarker Analysis Set (BAS)

The Biomarker analysis set (BAS) consists of the subset of the FAS population for which biomarker data are available to facilitate derivation of at least one of the correlative biomarkers.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the SAF. Other baseline characteristics will include baseline disease severity measures and prior prostate cancer therapies. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

7.4 Analysis of Efficacy

The primary efficacy analysis will be conducted on the FAS.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint, rPFS, will be analyzed using Kaplan-Meier methodology to account for censored outcomes (i.e. no observation of rPFS event within the study follow-up period).

Ninety percent (90%) confidence interval will be provided for the median rPFS.

7.4.1.2 Secondary Analysis

Not applicable.

7.4.1.3 Subgroup Analysis

The analysis described in Section [7.4.1.1](#) may be repeated in subsets defined by baseline characteristics such as prior treatment, prior response to enzalutamide, biomarkers, etc. In addition, multivariable analyses may be conducted using multivariable analyses. This analysis will be conducted using the FAS.

7.4.2 Analysis of Secondary Endpoints

The overall survival rate at 1 year will be estimated via Kaplan-Meier methodology with censoring defined by the time of last contact with the subject for those subjects who do not have a reported death. This analysis will be repeated in each subset defined by prior treatment with exposure.

For patients with PSA declines, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of $\geq 2 \mu\text{g/L}$ (2 ng/mL) above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. For patients with no PSA declines, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of $\geq 2 \mu\text{g/L}$ (2 ng/mL) above the baseline is documented, which is confirmed by a second consecutive value 3 or more weeks later. The time to PSA progression will then be estimated via Kaplan-Meier methodology with censoring defined by the time of the last available PSA measure. This analysis will be repeated in each subset defined by prior treatment with exposure.

The proportion of subjects achieving a maximum PSA decline from baseline of at least 30% (PSA30), 50% (PSA50), and 90% (PSA90), respectively, and having an objective response will be provided along with 90% confidence intervals. Analyses for PSA response rates will include all subjects with at least one post-baseline PSA measure. Analysis for objective response will include all subjects with measurable disease at baseline. These analyses will be repeated in each subset defined by prior treatment with exposure.

The time to first use of a subsequent antineoplastic therapy will be estimated via Kaplan-Meier methodology with censoring defined by the time of last contact with the subject for those subjects who do not have a reported use of antineoplastic therapy. This analysis will be repeated in each subset defined by prior treatment with exposure.

The analysis described in Section 7.4.1.3 will be repeated for secondary endpoints as appropriate.

7.4.3 Analysis of Exploratory Endpoints

Descriptive statistics (e.g., N, mean, standard deviation, minimum, median, maximum, frequency, and percentage) will be provided for baseline blood and plasma samples and by each post-baseline scheduled timepoint.

Baseline biomarker measurements will be included in regression models to assess correlation with the following endpoints: rPFS, time to OS, PSA30, PSA50, PSA90, and objective response. Time-to-event data endpoints will be modelled via Cox proportional hazards model. Binary endpoints will be modeled via logistic regression. Univariate models will be used to assess significance of individual biomarker measures. Multivariable models may also be considered to control for baseline demographic, disease, and treatment characteristics.

7.5 Analysis of Safety

7.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class and preferred term. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by time point. Laboratory values will be classified by toxicity grade based on the NCI-CTCAE, version 4.0. Tables of laboratory CTCAE grade shift from baseline to maximum CTCAE grade across subsequent visits will be provided. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by time. Vital signs data will be displayed in listings.

7.5.4 Physical Examination

Physical examination will be listed.

7.5.5 ECGs

The 12-lead ECG results will be summarized by time point.

7.6 Analysis of Pharmacogenomics

See Section [7.4.3](#)

7.7 Protocol Deviations

Protocol deviations as defined in Section [8.1.6](#) Protocol Deviations will be summarized for all enrolled subjects overall as well as by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

An interim efficacy analysis will be conducted 13 weeks after enrollment of the 40th subject to report on PSA response rates.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to determine whether a medication was given concomitantly and whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

See the SAP for details of the definitions for windows to be used for analyses by visit.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within the timeframe defined for the study.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

Routine laboratory tests will be performed locally and entered into the eCRF. The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Correlative samples will be collected and analyzed at a central laboratory designated by the Sponsor. Laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

For Screen failures, the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and Adverse Events will be collected in the eCRF.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates

- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section [8.1.2](#) "Specification of Source Documents") when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science of the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. (e)CRF completion will be described in the (e)CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the

IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding one year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD, Medical Affairs, Americas-sponsored studies.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the

subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be

kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The Sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the CRFs supplied for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments/substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator(s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Other Evaluation Committee(s)

Not applicable.

11 REFERENCES

- American Cancer Society . Prostate Cancer Key Statistics 2016. Atlanta: American Cancer Society:2016. Available from:
<http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics>.
- Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*. 2014 Sep;371:1028-1038.
- Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer patients. *Eur Urol*. 2014 Jul. <http://dx.doi.org/10.1016/j.eururo.2014.06.045>.
- Balbas MD, Evans MJ, Hosfield DJ, Wongvipat J, et al. Overcoming mutation-based resistance to antiandrogens with rational drug design. *Elife*. 2013 Apr 9;2:e00499.
- Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CS, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014 Jul;371(5):424-433.
- Bianchini D, Lorente D, Rodriguez-Vida A, Omlin A, Pezaro C, Ferraldeschi R, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. *European Journal of Cancer*. 2014 Jan; 50(1):78-84.
- Carreira S, Romanel A, Goodall J, Grist E, et al. Tumor clone dynamics in lethal prostate cancer. *Sci Transl Med* 6, 254ra125 (2014)
- Cabazitaxel [package insert]. Bridgewater (NJ): Sanofi-Aventis US LLC; 2014.
- Chadha KC, Miller A, Nair BB, Schwartz AS, Trump DL, Underwood W. New serum biomarkers for prostate cancer diagnosis. *Clin Cancer Investig J*. 2014;3:72-79.
- Codony-Servat J, Marin-Aguilera M, Visa L, Garcia-Albeniz X, Pineda E, Fernandez PL, et al. Nuclear factor-kappa B and interleukin-6 related docetaxel resistance in castration-resistant prostate cancer. *The Prostate*. 2013;73:512-521.
- De Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011 May;364(21):1995-2005.
- De Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010 Oct;376(9747):1147-1154.
- Duff J and McEwan IJ. Mutation of histidine 874 in the androgen receptor ligand-binding domain leads to promiscuous ligand activation and altered p160 coactivator interactions. *Mol Endocrinol*. 2005 Dec;19(12):2943-54.
- Eiro N, Bermudez-Fernandez S, Fernandez-Garcia B, Atienza S, Beridze N, Escaf S. Analysis of the expression of interleukins, interferon b, and nuclear factor-k B in prostate cancer and their relationship with biochemical recurrence. *J Immunother*. 2014;37:366-373.

- Fabbri F, Amadori D, Carloni S, Briigliadori G, Tesei A, Ulivi P, et al. Mitotic catastrophe and apoptosis induced by docetaxel in hormone-refractory prostate cancer cells. *J. Cell. Physiol.* 2008;217:494–501.
- Feng S, Tang Q, Sun M, Chun JY, Evans CP, Gao AC. Interleukin-6 increases prostate cancer cells resistance to bicalutamide via TIF2. *Mol Cancer Ther.* 2009 March;8(3):665-671.
- Hu R, Lu C, Mostaghel EA, Yegnasubramanian S, Gurel M, Tannahill C, et al. Distinct transcriptional programs mediated by the ligand-dependent full-length androgen receptor and its splice variants in castration-resistant prostate cancer. *Cancer Res.* 2012; 72(14); 3457–3462
- Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363:411-422.
- Leibowitz-Amit R, Alimohamed N, Vera-Badillo FE, Seah JA, Templeton AJ, Knox JJ, et al. Retreatment of men with metastatic castrate-resistant prostate cancer with abiraterone. *Prostate.* 2014 Oct;74(14):1462-1464.
- Li Y, Chan SC, Brand LJ, Hwang TH, Silverstein KA, Dehm SM. Androgen receptor splice variants mediate enzalutamide resistance in castration-resistant prostate cancer cell lines. *Cancer Res.* 2013 Jan;73(2):483-489.
- Liu C, Zhu Y, Lou W, Cui Y, Evans CP, Gao AC. Inhibition of constitutively active stat3 reverses enzalutamide resistance in LNCaP derivative prostate cancer cells. *The Prostate.* 2014;74:201-209.
- Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol.* 2013;24(7):1807-1812.
- Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res.* 2008;68:4447-4454.
- Nakazawa M, Lu C, Chen Y, Paller CJ, Carducci MA, Eisenberger MA et al. Serial blood-based analysis of ar-v7 in men with advanced prostate cancer. *Ann Onc.* 2015 Jun: <http://dx.doi.org/10.1093/annonc/mdv282>.
- Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982 Dec;5(6):649-655.
- Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213-223.
- Riely GJ, Kris MG, Zhao B, Akhurst T, Milton DT, Moore E, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res.* 2007;13(17):5150-5155.
- Ryan CJ, Smith MR, De Bono JS, Molina A, Logothetis CJ, De Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013 Jan;368(2):138-48.

- Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg C, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012 Sep. ;367(13):1187-1197.
- Schrader AJ, Boegemann M, Ohlmann CH, Schnoeller TJ, Krabbe LM, Jentzmik F, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *European Urology*. 2014 Jan;65(1):30-36.
- Song Z, Yu X, He C, Zhang B, Zhang Y. Re-administration after the failure of gefitinib or erlotinib in patients with advanced non-small cell lung cancer. *J Thorac Dis*. 2013;5(4):400-405.
- Sun S, Sprenger CC, Vessella RL, Haugk K, Soriano K, Mostaghel EA, et al. Castration resistance in human prostate cancer is conferred by a frequently occurring androgen receptor splice variant. *J Clin Invest*. 2010 Aug;120(8):2715-2730.
- Szmulewitz RZ, Kregel S, Isikbay M, Cai Y, Chen JL, Vander Griend DJ, et al. Androgen receptor independent acquired mechanisms of resistance to enzalutamide in castration-resistant prostate cancer. *J Clin Oncol*. 2014;32 (Supl 4; abstr 129).
- Tannock IF, De Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351:1502-12.
- Thadani-Mulero M, Portella L, Sun S, Sung M, Matov A, Vessella RL, et al. Androgen receptor splice variants determine taxane sensitivity in prostate cancer. *Cancer Res*. 2014;74(8):2270-2282.
- Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324(5928):787-790.

12 APPENDICES

12.1 List of Prohibited and Restricted Concomitant Medications

Part A – Prohibited Medications

The following medications are prohibited while patients are on enzalutamide treatment and have not had disease progression:

- Chemotherapy with anti-tumor activity against prostate cancer such as cabazitaxel, mitoxantrone, etc.
- Sipuleucel-T
- Rad-223
- Androgen-receptor antagonists (bicalutamide, flutamide, nilutamide)
- 5 α -reductase inhibitors (finasteride, dutasteride)
- Estrogens
- Cyproterone acetate
- Androgens (testosterone, dehydroepiandrosterone [DHEA], etc.)
- Ketoconazole
- Abiraterone acetate
- Any other investigational agent

Part B – Medications Permitted with Restrictions

The dosage and regimen of the following medications and any chronic permitted medications should be stabilized during the screening period (> 4 weeks prior to randomization) and held constant through the study:

- Denosumab and bisphosphonate
- GnRH agonist/antagonist therapy

There is a potential for enzalutamide to affect exposures to other medicinal products, or for other medicinal products to affect exposure to enzalutamide:

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) or CYP2C8 inducers (e.g. rifampicin) are to be avoided. If subject must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If a 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.
- Strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampin) or moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort) should be avoided if possible as they may reduce enzalutamide plasma concentration if co-administered. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.
- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4 (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g. phenytoin, warfarin),

CYP2C19 (e.g. S-mephenytoin), or UGT1A1 should be avoided if possible, as enzalutamide may decrease their exposure.

- If enzalutamide co-administration with warfarin cannot be avoided, additional INR monitoring should be conducted.
- Enzalutamide is an inhibitor of human P-glycoprotein (P-gp) and may increase exposure to medicines that are P-gp substrates. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) should be used with caution when administered concomitantly with enzalutamide.

No other new systemic therapy or new radiotherapy for treatment (exception for spinal cord compression, pain management, etc.) for prostate cancer is permitted while subject is on the study. Subjects with pre-existing non-target lesions (e.g., bone metastases) receiving palliative radiography for pain treatment before participation in the study are allowed to continue receiving radiotherapy during the study.

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to $> 3 \times \text{ULN}$ (to $> 5 \times \text{ULN}$ in subjects with liver metastases), or bilirubin $> 2 \times \text{ULN}$, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

| | ALT or AST | | Total Bilirubin |
|-----------------|---|-----|-------------------------|
| Moderate | $> 3 \times \text{ULN}$ (in patients without liver metastases), $> 5 \times \text{ULN}$ (in patients with liver metastases) | or | $> 2 \times \text{ULN}$ |
| Severe* | $> 3 \times \text{ULN}$ | and | $> 2 \times \text{ULN}$ |

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST $> 8 \times \text{ULN}$
- ALT or AST $> 5 \times \text{ULN}$ for more than 2 weeks (in the absence of liver metastases)
- ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST $> 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) or appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as a Serious Adverse Event (SAE). The Sponsor should be contacted and informed of all subjects for

whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as ‘adverse events’ on the AE page of (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject’s history, other testing may be appropriate including:
 - acute viral hepatitis (A,B, C, D, E or other infectious agents).
 - ultrasound or other imaging to assess biliary tract disease
 - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT’s, such as viral hepatitis, pre-existing or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject’s best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST $> 8 \times$ ULN
- ALT or AST $> 5 \times$ ULN for more than 2 weeks (in subjects without liver metastases)
- ALT or AST $> 3 \times$ ULN and TBL $> 2 \times$ ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST $> 5 \times$ ULN and (TBL $> 2 \times$ ULN in patients with liver metastases)
- ALT or AST $> 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant).” The two “requirements” for Hy’s Law are: 1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the ULN (“2 x ULN elevations are too common in treated and untreated patients to be discriminating”). 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert’s syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf.* 2006 Apr;15(4):241-3.]

Reference

Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA on July 2009.

12.3 Common Serious Adverse Events

The following is a list of serious adverse events that the Sponsor considers to be associated with the disease state being studied. **The list does NOT change your reporting obligations or prevent the need to report an adverse event meeting the definition of an SAE as detailed in Section 5.5.3 Definition of Serious Adverse Events (SAEs).** The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common serious adverse events”. You are required to follow the requirements detailed in **Section 5.5.7 Reporting of Serious Adverse Events (SAEs).**




For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

- Anemia
- Anorexia
- Asthenia / Fatigue
- Back pain
- Bone pain
- Catheter related infection
- Dyspnea
- Haematuria
- Hydronephrosis
- Metastases to bone
- Metastases to central nervous system
- Nausea
- Obstructive uropathy
- Pain
- Prostate cancer metastatic
- Renal failure
- Renal failure acute
- Spinal compression fracture
- Spinal cord compression
- Urinary retention
- Urinary tract infection
- Urinary tract obstruction
- Vomiting

13 SIGNATURES

1. SPONSOR'S SIGNATURE

1.1. PROTOCOL AUTHORS:

| | |
|---|--------------------|
| Signature: _____ | Date (DD Mmm YYYY) |
|  | |
| Major Contributors: | |
| Signature: _____ | Date (DD Mmm YYYY) |
|  | |
| Signature: _____ | Date (DD Mmm YYYY) |
|  | |

1.2. PROTOCOL APPROVED BY:

Protocol Approval Committee

| | |
|---------------------------------------|--------------------|
| Signature: _____ | Date (DD Mmm YYYY) |
| Chairman, Protocol Approval Committee | |

13 SIGNATURES

1. SPONSOR'S SIGNATURE

1.1. PROTOCOL AUTHORS:

| | | | |
|------------------------------|------------|--------------------|------------|
| Signature: | [Redacted] | Date (DD Mmm YYYY) | [Redacted] |
| Major Contributor Signature: | [Redacted] | Date (DD Mmm YYYY) | [Redacted] |
| Signature: | [Redacted] | Date (DD Mmm YYYY) | [Redacted] |

1.2. PROTOCOL APPROVED BY:

| | | | |
|--|------------|--------------------|------------|
| Protocol Approval Committee Signature: | [Redacted] | Date (DD Mmm YYYY) | [Redacted] |
| Chairman, Protocol Approval Committee | | | |