

**A Phase 2 Study Determining Safety and Tolerability of  
Enzalutamide (Formerly MDV3100) in Combination With  
Abiraterone Acetate in Bone Metastatic Castration-resistant  
Prostate Cancer Patients**

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**Sponsor: Astellas Pharma Global Development, Inc**

1 Astellas Way  
Northbrook, IL 60062

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Prostate Cancer Patients**

**Protocol for Phase 2 Study of Enzalutamide**

**ISN/Protocol 9785-CL-0011**

**Version 3.0**

**Incorporating Substantial Amendment 2 [See Attachment 1]**

**18 June 2014**

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Sponsor:

**Astellas Pharma Global Development, Inc. (APGD)**  
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## **I. SIGNATURES**

### **1. SPONSOR'S SIGNATURE**

#### **A Phase 2 Study Determining Safety and Tolerability of Enzalutamide (formerly MDV3100) in Combination with Abiraterone Acetate in Bone Metastatic Castration-Resistant Prostate Cancer Patients**

#### **ISN/Protocol 9785-CL-0011 / Version 3.0, Incorporating Substantial Amendment 2 18 June 2014**

Required signatures (e.g. protocol authors, sponsor's reviewers and contributors) are located in Section 14; e-signatures (when applicable) are located at the end of this document.

## 2. INVESTIGATOR'S SIGNATURE

### **A Phase 2 Study Determining Safety and Tolerability of Enzalutamide (formerly MDV3100) in Combination with Abiraterone Acetate in Bone Metastatic Castration-Resistant Prostate Cancer Patients**

**ISN/Protocol 9785-CL-0011 / Version 3.0, Incorporating Substantial Amendment 2  
18 June 2014**

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: \_\_\_\_\_

\_\_\_\_\_ MD

\_\_\_\_\_ Date

\_\_\_\_\_ MD Anderson Cancer Center

Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

## II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

<p><b>24h-Contact for Serious Adverse Events (SAEs)</b></p> <p>See Section 5.5.5</p>	<p>[REDACTED] MD, CCRP Astellas Pharma Global Development 1 Astellas Way Northbrook, IL 60062</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<p>Clinical Research Contact:</p>	<p>[REDACTED]</p> <p>Astellas Pharma Global Development</p> <p>[REDACTED]</p>
<p>Medical Monitor:</p>	<p>[REDACTED] MD</p> <p>Astellas Pharma Global Development</p> <p>[REDACTED]</p>

### III. LIST OF ABBREVIATIONS AND KEY TERMS

#### List of Abbreviations

Abbreviation	Definition of abbreviation
AE	Adverse event
ALT	Alanine Aminotransferase
APED/APEL	Astellas Pharma Europe Ltd
APGD	Astellas Pharma Global Development
AST	Aspartate Aminotransferase
AT	Aminotransferase
AR	Androgen Receptor
AUC	Area under the plasma concentration versus time curve
BID	Twice a Day
CAT (CT scan)	Computed Axial Tomography
CFR	Code of Federal Regulations
C <sub>max</sub>	Maximum concentration
C <sub>min</sub>	Minimum concentration
CR	Complete Response
CRPC	Castration-Resistant Prostate Cancer
CRO	Contract Research Organization
C <sub>trough</sub>	The point of minimum concentration of a drug
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CTEP	Cancer Therapy and Evaluation Program
CYP	Cytochrome P450
CXR	Chest x-ray
DES	Diethylstilbestrol
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
ESR	Expedited Safety Report
ET	End of Treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GnRH	gonadotropin releasing hormone
HIPAA	Health Insurance Portability and Accountability Act
IC <sub>50</sub>	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

<b>Abbreviation</b>	<b>Definition of abbreviation</b>
IHC	Immunohistochemistry
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
ISN	International Study Number
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LHRH	Luteinizing hormone-releasing hormone
LVEF	Left Ventricle Ejection Fraction
MDACC	MD Anderson Cancer Center
MedDRA	Medical Dictionary for Regulatory
mg	Milligram
mmHg	Millimeters of Mercury
MRI	Magnetic Resonance Imaging
MUGA	Multi-Gated Acquisition
NCI	National Cancer Institute
NDA	New Drug Application
NYHA	New York Heart Association
PB	Privacy Board
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive Disease
PFS	Progression Free Survival
PHI	Personal Health Information
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PO	By Mouth
PR	Partial Response
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
PTT	Partial thromboplastin time
QD	Once Daily
QRS	QRS Interval
QTcF	QTC Fridericia Calculator
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Stable Disease
SFL	Screening Failure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin Level
t <sub>max</sub>	time to maximum concentration
t <sub>½</sub>	Apparent Terminal Elimination Half-life
ULN	Upper Limit of Normal
WBC	White Blood Count

## List of Key Study Terms

<b>Terms</b>	<b>Definition of terms</b>
Adverse Event	An adverse event is as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment.
AFFIRM	A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy
Baseline	A period that begins at the Screening visit where all initial subject assessments and findings will be obtained prior to study drug administration on Day 1.
Discontinuation	A discontinuation is a subject who is enrolled in the study and for whom study drug is terminated for any reason.
Enroll	To register or enter into the study following the signing of informed consent.
Screening period	Period of time between Day -28 and Day -1.
Screening failure	Screened subject, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive open label study treatment, or decided not to participate anymore (withdrew consent) prior to completing pre-investigational period.
Study Drug	Agents given as part of a clinical trial. In this study, enzalutamide, abiraterone acetate and prednisone are the study drugs.
Subject	An individual who participates in this clinical trial, and will be a recipient of the study drug.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

#### IV. SYNOPSIS

<b>Title of Study</b>	A Phase 2 Study Determining Safety and Tolerability of Enzalutamide (formerly MDV3100) in Combination with Abiraterone Acetate in Bone Metastatic Castration-Resistant Prostate Cancer Patients
<b>Planned Study Period</b>	From 10 July 2012 to 17 June 2014
<b>Study Objective(s)</b>	<p>Primary</p> <ul style="list-style-type: none"> <li>To explore the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone.</li> </ul> <p>Secondary</p> <ul style="list-style-type: none"> <li>To explore the effect of enzalutamide in combination with abiraterone acetate plus prednisone on androgen receptor signaling and androgen levels.</li> <li>To explore the antitumor activity of enzalutamide in combination with abiraterone acetate plus prednisone as assessed by serum prostate-specific antigen (PSA), imaging of soft tissue and bone metastases and markers of bone metabolism.</li> </ul> <p>Exploratory</p> <ul style="list-style-type: none"> <li>To measure pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional).</li> </ul>
<b>Planned Total Number of Study Centers and Location</b>	One center in the United States
<b>Design and Methodology</b>	<p>This is an open label study to determine the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone in castration-resistant prostate cancer patients with bone metastases by clinical evaluations at protocol specified intervals.</p> <p>The study will also determine the modulation of androgen receptor (AR) signaling and androgen levels as measured by testosterone concentration in bone marrow aspirate and blood by Liquid Chromatography Mass spectrometry, expression of AR and its subcellular localization by immunohistochemistry (IHC), presence of known and assessable splice variants and CYP17 expression in epithelial and host compartment of the cancer by IHC. Tumor tissue will be collected to determine AR signaling and candidate pathways that may be part of a signaling network implicated in therapy resistance. The baseline determination and subsequent assessment of AR signaling will be correlated with progression-free survival (radiographic progression, PSA progression, clinical deterioration).</p> <p>Approximately 60 subjects will receive enzalutamide 160 mg daily, abiraterone acetate 1000 mg daily, prednisone 5 mg twice daily to be taken orally. Subjects will be unable to continue in the study if one of the above study drugs is discontinued.</p>

<p><b>Design and Methodology</b> continued</p>	<p>There will be a 28 day screening period to determine subject eligibility. For the study duration, all subjects will maintain androgen deprivation with a GnRH agonist or antagonist or orchiectomy.</p> <p>Study drug will be administered until disease progression. Disease progression is defined as a composite endpoint consisting of clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria.</p> <p>Optional PK blood samples for the determination of plasma concentrations of abiraterone will be collected pre-dose on Day 4 and Day 29. In addition, optional PK blood sample for the determination of plasma concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 will be collected on Day 29.</p> <p>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 (abdominopelvic CT/MRI [lung when applicable] and bone scan) should be read on site. Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examination, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs).</p> <p>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.</p>
<p><b>Number of Subjects Planned</b></p>	<p>Approximately 60 subjects</p>
<p><b>Selection Criteria</b></p>	<p><i>Inclusion Criteria:</i></p> <p>Subject is eligible for the study if all of the following apply:</p> <ol style="list-style-type: none"> <li>1. 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).</li> <li>2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.</li> <li>3. Presence of metastatic disease to the bone at the Screening visit.</li> <li>4. Ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue or orchiectomy (i.e., surgical or medical castration).</li> <li>5. Serum testosterone level <math>\leq</math> 50 ng/dL at the Screening visit.</li> <li>6. Subject receiving bisphosphonate or denosumab therapy must have been on stable doses for at least 4 weeks prior to Day 1.</li> </ol>

<p><b>Selection Criteria</b> Continued</p>	<p><i>Inclusion Criteria continued:</i></p> <ol style="list-style-type: none"><li>7. Progressive disease defined as one or more of the following three criteria (Note: subjects who received an antiandrogen must demonstrate disease progression following discontinuation of antiandrogen):<ul style="list-style-type: none"><li>• PSA progression defined by a minimum of two rising PSA levels with an interval of <math>\geq 1</math> week between each determination. The PSA value at the Screening visit should be <math>\geq 2</math> ng/mL.</li><li>• Soft tissue disease progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).</li><li>• Bone disease progression defined by PCWG2 criteria (two or more new lesions on bone scan compared with prior scan).</li></ul></li><li>8. Subject previously treated with chemotherapy must have no more than two prior chemotherapy regimens for the treatment of metastatic prostate cancer.</li><li>9. Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.</li><li>10. Estimated life expectancy of <math>\geq 6</math> months.</li><li>11. Able to swallow the study drug and comply with study requirements.</li><li>12. Agree to use a double-barrier method of contraception which involves the use of a condom in combination with one of the following: contraceptive sponge, diaphragm, or cervical ring with spermicidal gel or foam, if having sex with a woman of child-bearing potential during the length of the study and for one week after abiraterone is discontinued and for at least three months after enzalutamide is discontinued.</li><li>13. Subject agrees not to participate in another interventional study while on treatment.</li></ol> <p><i>Exclusion Criteria:</i></p> <p>Subject will be excluded from participation if any of the following apply:</p> <ol style="list-style-type: none"><li>1. Known allergy to the study drugs or any of its components.</li><li>2. Severe, concurrent disease, infection, or co-morbidity that, in the judgment of the investigator, would make the subjects inappropriate for enrollment.</li><li>3. Medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated.</li><li>4. Known or suspected metastases in the brain.</li><li>5. Absolute neutrophil count <math>&lt; 1,000/\mu\text{L}</math>, platelet count <math>&lt; 75,000/\mu\text{L}</math>, and hemoglobin <math>&lt; 9</math> g/dL at the Screening visit; (NOTE: subject may not have received any growth factors or blood transfusions within seven days of the hematologic laboratory values obtained at the Screening visit).</li><li>6. Total bilirubin (TBL), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <math>&gt; 2.5</math> times the upper limit of normal at the Screening visit.</li><li>7. Creatinine (Cr) <math>&gt; 2</math> mg/dL at the Screening visit.</li><li>8. History of another malignancy within the previous 2 years other than curatively treated non-melanomatous skin cancer.</li><li>9. Treatment with androgen receptor antagonists (bicalutamide, flutamide, nilutamide), 5-<math>\alpha</math> reductase inhibitors (finasteride, dutasteride), estrogens, chemotherapy, or biologic therapy within 4 weeks of Day 1 visit.</li></ol>
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<p><b>Selection Criteria</b> continued</p>	<ol style="list-style-type: none"><li>10. Radiation therapy within 3 weeks (if single fraction of radiotherapy within 2 weeks) of Day 1 visit or radionuclide therapy within 8 weeks of Day 1.</li><li>11. Planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery.</li><li>12. Structurally unstable bone lesions suggesting impending fracture.</li><li>13. History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumors, brain metastases, or alcoholism. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit).</li><li>14. Clinically significant cardiovascular disease including:<ul style="list-style-type: none"><li>• Myocardial infarction within 6 months of Screening visit.</li><li>• Uncontrolled angina within 3 months of Screening visit.</li><li>• Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, or history of anthracycline or anthracenedione (mitoxantrone) treatment, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) performed within three months of the Screening visit results in a left ventricular ejection fraction that is <math>\geq 45\%</math>.</li><li>• History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsade de pointes).</li><li>• Prolonged corrected QT interval by the Fridericia correction formula (QTcF) on the screening electrocardiogram (ECG) <math>&gt; 470</math> msec.</li><li>• History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.</li><li>• Hypotension (systolic blood pressure <math>&lt; 86</math> mmHg or bradycardia with a heart rate of <math>&lt; 50</math> beats per minute on the Screening ECG, unless pharmaceutically induced and thus reversible (i.e. beta blockers).</li><li>• Uncontrolled hypertension as indicated by a resting systolic blood pressure <math>&gt; 170</math> mmHg or diastolic blood pressure <math>&gt; 105</math> mmHg at the Screening visit.</li></ul></li><li>15. Prior use of ketoconazole, abiraterone or enzalutamide, or participation in a previous clinical trial of ketoconazole, abiraterone acetate or enzalutamide.</li><li>16. Use of an investigational agent within 4 weeks of Day 1.</li><li>17. Gastrointestinal disorder that may affect absorption (e.g., gastrectomy) of study drug.</li><li>18. Major surgery within 4 weeks prior to Day 1.</li><li>19. History of significant bleeding disorder unrelated to cancer, including:<ul style="list-style-type: none"><li>• Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease).</li><li>• Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies) of Screening visit.</li><li>• History of GI bleeding within 6 months of Screening visit.</li></ul></li><li>20. Active or symptomatic viral hepatitis or chronic liver disease.</li><li>21. Known history of pituitary or adrenal dysfunction.</li></ol>
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<p><b>Discontinuation Criteria</b></p>	<p>Subject will be discontinued from treatment if any of the following occur:</p> <ul style="list-style-type: none"> <li>• Subject develops disease progression defined as a composite endpoint, consisting of either clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria. Subjects with PSA progression alone will not be withdrawn from the study.</li> <li>• Subject develops an adverse event or toxicity, where continued administration of study drug is deemed not in the subject’s best interest by the investigator.</li> <li>• Abnormal lab values defined as: creatinine &gt; 305 μmol/L (4.0 mg/dL), absolute neutrophil count of ≤ 750 /μL and platelet count of &lt; 50,000/μL.</li> <li>• LFTs that meet one of the following:             <ul style="list-style-type: none"> <li>a. An ALT or AST value of &gt; 8x ULN</li> <li>b. An ALT or AST value of &gt; 5x ULN for more than 2 weeks</li> <li>c. An ALT or AST value of &gt; 3x ULN and TBL &gt; 2x ULN or INR &gt; 1.5</li> <li>d. If close monitoring for a subject with moderate (defined in Appendix 3 as ALT or AST &gt; 3x ULN or total bilirubin &gt; 2x ULN) hepatic laboratory tests is not possible, study drug should be discontinued.</li> <li>e. ALT or AST &gt; 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (&gt; 5%).</li> </ul> </li> <li>• Any seizure.</li> <li>• Investigator or study Medical Monitor decision that study drug continuation is not in the best interest of the subject.</li> <li>• Subject who is, in the opinion of the investigator or the Medical Monitor, grossly non-compliant with the protocol’s requirements.</li> <li>• Subject is unable to continue in the study, if one of the study drugs is discontinued.</li> <li>• Subject withdraws consent.</li> </ul>
<p><b>Test Drug Dose</b></p>	<p>Enzalutamide 160 mg QD and abiraterone acetate 1000 mg QD, prednisone 5 mg twice daily</p>
<p><b>Mode of Administration</b></p>	<p>Oral</p>
<p><b>Duration of Treatment</b></p>	<p>Subject will receive study drug treatment until disease progression or unacceptable toxicity.</p>
<p><b>Reference Therapy Dose</b></p>	<p>None</p>
<p><b>Concomitant Medication</b></p>	<p>The following medications are prohibited while the subject is continuing on study treatment:</p> <ul style="list-style-type: none"> <li>• Chemotherapeutic, biologic, or other agents with anti-tumor activity against prostate cancer other than the investigational agents in this study</li> <li>• Anti-androgens</li> <li>• 5-α reductase inhibitors</li> </ul>

<p><b>Concomitant Medication</b> continued</p>	<ul style="list-style-type: none"><li>• Estrogens, progestational agents</li><li>• Androgens</li><li>• Ketoconazole</li><li>• Herbal products that may decrease PSA levels (e.g., saw palmetto)</li></ul> <p>Please refer to Appendix 1 (List of Excluded Concomitant Medication).</p> <p>Subjects who had been receiving stable dose of bisphosphonates, denosumab or GnRH agonist or antagonist for 4 weeks prior to Day 1 may continue on therapy at the same dose.</p> <p><u>Caution is advised when considering the concomitant use of the following medications:</u></p> <ul style="list-style-type: none"><li>• Medications known to lower the seizure threshold. These include but are not limited to:<ul style="list-style-type: none"><li>○ Aminophylline/theophylline</li><li>○ Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)</li><li>○ Bupropion</li><li>○ Lithium</li><li>○ Pethidine</li><li>○ Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)</li><li>○ Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)</li></ul></li><li>• Sensitive P-gp substrates (e.g., digoxin, fexofenadine)</li><li>• Medications that inhibit platelet function or anticoagulants should be used with caution while receiving study treatment. Standard of care monitoring of anticoagulation should be implemented.</li><li>• Abiraterone is an inhibitor of CYP2D6 (based on drug-drug interaction trial) and a substrate of CYP3A4 (based on the vitro data). Avoid co-administration of abiraterone acetate with substrate of CYP2D6 with a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone treatment.</li><li>• Based on in vitro data, enzalutamide is an inhibitor of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 and may be an inducer of CYP3A4. Substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 that have a narrow therapeutic index (e.g., paclitaxel, phenytoin, warfarin) should be used with caution.</li><li>• Additionally, co-administration of enzalutamide with CYP3A4/5 substrates may affect oral bioavailability and/or elimination of the CYP3A4/5 substrate. Substrates of CYP3A4/5 that have a narrow therapeutic index should be used with caution. In vitro studies showed that enzalutamide is metabolized by CYP2C8 and CYP3A4/5. Use caution when co-</li></ul>
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	administering a strong CYP2C8 inhibitor (e.g., gemfibrozil) or strong CYP3A4/5 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, grapefruit juice) during enzalutamide treatment.
<b>Primary Variables</b>	<ul style="list-style-type: none"> <li>• Nature, frequency and severity of adverse events</li> <li>• Safety laboratory tests: chemistry and hematology</li> <li>• Vital signs (blood pressure, pulse rate and temperature)</li> <li>• 12 Lead ECG parameters</li> <li>• Physical examination results</li> </ul>
<b>Secondary Variables</b>	<ul style="list-style-type: none"> <li>• Androgen receptor signaling               <ul style="list-style-type: none"> <li>○ Expression and localization of AR</li> <li>○ CYP17 expression</li> <li>○ Splice variants</li> </ul> </li> <li>• Pathways linked with non-classical AR signaling &amp; Bone development               <ul style="list-style-type: none"> <li>Androgens                   <ul style="list-style-type: none"> <li>○ Testosterone concentration in bone marrow aspirate and blood</li> <li>○ DHT concentration in bone marrow aspirate and blood</li> </ul> </li> </ul> </li> <li>• Androgen pre-cursors and other associated metabolites. For example:               <ul style="list-style-type: none"> <li>○ Cortisol</li> <li>○ Androstenedione</li> <li>○ Pregnenolone</li> <li>○ Progesterone</li> </ul> </li> <li>• PSA levels</li> <li>• Progression-free Survival (PFS)</li> <li>• Objective response according to RECIST 1.1</li> <li>• Bone scan results</li> <li>• Markers of bone metabolism (bone specific alkaline phosphatase and urine N-telopeptides)</li> </ul>
<b>Exploratory Variables</b>	Pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional).
<b>Statistical Methods</b>	Unless otherwise specified, categorical variables will be summarized as counts and percentages, and continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum and maximum).

<p><b>Statistical Methods</b> continued</p>	<p><u>Sample size calculation</u></p> <p>A total of 60 subjects will provide sufficient data to assess the safety of the drug combination.</p> <p>The sample size and power calculation are based on the change of testosterone concentration or gene expressions (i.e. AR and CYP17) before and after therapy, which can be characterized based on effect size (i.e. mean difference of testosterone concentration or gene expression divided by standard deviation).</p> <p>Considering subjects with baseline and Week 9 laboratory results derived from bone marrow samples, a sample of 30 subjects provides 82% power to detect a change of testosterone concentration or gene expression with an effect size of at least 0.55, using a two sided paired t-test at a 0.05 significance level. A total of 60 subjects will be accrued to obtain at least 30 evaluable patients based on the prediction that the yield of evaluable bone marrow samples with prostate cancer cells is approximately 50%.</p> <p><u>Safety Analyses</u></p> <p>Safety will be assessed through summaries of adverse events, laboratory evaluations, vital signs, physical examinations, and ECGs. Safety analyses will be based on all enrolled subjects who receive any amount of study drug. Severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 and 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 severity. Descriptive statistics will be used rather than inferential statistics.</p> <p>Laboratory values will be classified by toxicity grade based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Laboratory shift tables of the baseline results to each of the subsequent visits will be produced.</p> <p><u>Efficacy Analyses</u></p> <ul style="list-style-type: none"><li>• Anti-tumor Activity</li></ul> <p>Efficacy analysis will be conducted on all enrolled subjects who received any amount of study drug. Progression-free survival (PFS) is defined as the time interval from the date of starting treatment until the date of documented progression or death in absence of progression. PFS will be reported using Kaplan-Meier methods, including the median and its 95% CI. PSA and PSA change from baseline over time will be descriptively summarized.</p> <p>Proportion of patients showing RECIST 1.1 objective response (partial or complete response) will be descriptively summarized. Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.</p> <ul style="list-style-type: none"><li>• Androgens, Androgen Receptor Signaling Androgen pre-cursors and other associated metabolites</li></ul> <p>Considering subjects with baseline and Week 9 laboratory results derived from bone marrow samples, androgens, androgen receptor signaling, androgen pre-</p>
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**Statistical Methods**  
continued

cursors and other associated metabolites will be summarized by descriptive statistics and, if appropriate, a paired t-test at a 0.05 level of significance will be performed on the change from baseline at Week 9.

Analysis of Pharmacokinetics

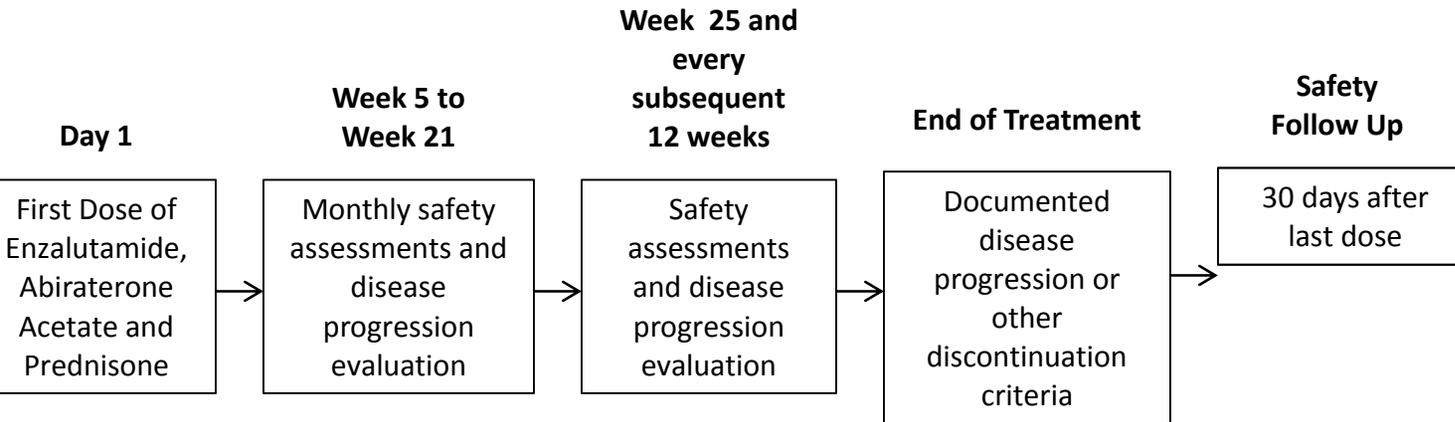
Summary statistics will be presented for each predose plasma concentration of abiraterone, enzalutamide and its metabolites MDPC0001 and MDPC0002, by scheduled visit. Summary statistics for the concentration data will include number of subjects, mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum.

Pre-dose concentrations of abiraterone obtained on Day 4 and on Day 29 will be compared to assess the potential effect of enzalutamide on the PK of abiraterone.

Drug Exposure

Drug exposure, including data on dose reduction will be summarized by descriptive statistics based on study drug accountability.

## T AND SCHEDULE OF ASSESSMENTS



**Table 1: Schedule of Assessments**

Study Day	Screening Visit	1	4	29	57	85	113	141	169	ET	Safety F/U
Week	-4 to -1 (28 days)	1	1	5	9	13	17	21	25 and every subsequent 12 weeks	End of Treatment	30 Days after last dose <sup>e</sup>
Window (days)				± 3	± 3	± 3	± 3	± 3	± 3	+ 3	± 7
Informed Consent	X										
Medical History	X										
Inclusion/Exclusion Criteria	X	X									
Vital Signs <sup>a</sup>	X	X		X	X	X	X	X	X	X	X
Physical Examination, Weight, Height <sup>j</sup>	X	X <sup>d</sup>		X <sup>n</sup>	X <sup>n</sup>	X <sup>n</sup>					
12-Lead ECG	X	X <sup>d</sup>		X <sup>r</sup>	X <sup>r</sup>	X <sup>r</sup>					
PT/PTT/INR <sup>b</sup>	X	X <sup>d</sup>		X	X	X	X	X	X	X	X
Clinical Labs <sup>b</sup> Including liver function test <sup>c</sup>	X	X <sup>d</sup>		X	X	X	X	X	X	X	X
PK of Abiraterone <sup>l</sup>			X	X							
PK of enzalutamide <sup>m</sup>				X							
PSA	X	X <sup>d</sup>		X	X	X	X	X	X	X	X
Urine N-telopeptide	X				X					X <sup>g</sup>	
Blood testosterone and DHT levels <sup>q</sup>	X				X					X <sup>g</sup>	
CT/MRI and Bone Scan	X <sup>i</sup>					X			X	X	
CXR or Chest CT	X <sup>k</sup>					X <sup>k</sup>				X <sup>k</sup>	
MUGA or ECHO <sup>f</sup>	X										
ECOG Performance Status	X	X		X	X	X	X	X	X	X	X
Bone Marrow Aspirate and Biopsy	X <sup>h</sup>				X					X <sup>g</sup>	
Archival Tumor Tissue <sup>o</sup>	X										
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Previous & Concomitant Medications	X	X		X	X	X	X	X	X	X	X
Study Drug Dispensing		X		X	X	X	X	X	X		
Study Drug Treatment		X		X	X	X	X	X	X		
Blood Sample for Genotyping <sup>p</sup>		X									

**Table 1 Footnotes:**

- a. Vital signs will be obtained prior to study drug administration and 1-2 hours after study drug administration.
- b. Clinical labs(hematology and chemistry) and, PT/PTT & INR, will be obtained prior to study drug administration. Day 1 chemistry and hematology do not need to be completed if the screening assessments were completed within 3 days prior to Day 1.
- c. Subjects will have liver function tests (including alkaline phosphatase, AST, ALT, direct and total bilirubin, and LDH) every 2 weeks for the first 12 weeks of treatment.
- d. If Day 1 visit occurs within 72 hours after screening, these assessments do not need to be repeated.
- e. 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.
- f. A MUGA scan or echocardiogram showing LVEF  $\geq 45\%$  is required for subjects with a history of anthracycline or anthracenedione (mitoxantrone) treatment, or if the subjects has congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past.
- g. Bone marrow biopsy and aspirate, blood sample for testosterone and DHT and urine sample for N-telopeptide will be collected at Screening, Week 9, and at the End of Treatment (ET) visits. If the End of Treatment visit falls between Week 9 and Week 13, and these samples were collected at Week 9 then an ET collection will not be required.
- h. Bone marrow aspirate and biopsy will be taken between screening and prior to first dose of study drug.
- i. Subjects must be assessed with CT/MRI and bone scan within 6 weeks prior to study drug administration (Day 1).
- j. Height will be recorded at the screening visit only.
- k. At screening, a chest X-ray or a chest CT will be performed. If the chest X-ray is performed and demonstrates metastatic chest disease, a chest CT is required. In the case of metastatic chest disease, additional chest CT's should be performed as follow-up at Week 13 (Day 85) and end of treatment (ET) visit.
- l. Optional PK blood sample for determination of plasma concentrations of abiraterone will be obtained predose on Day 4 and Day 29.
- m. Optional PK blood sampling for determination of plasma concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 will be obtained predose on week 5 (Day 29).
- n. A physical exam will be performed including weight.
- o. Archival tumor tissue will be obtained any time prior to Day 1.
- p. Sample for optional genotyping sub-study will be collected prior to Day 1 dosing.
- q. Blood sample testosterone and DHT should be collected within 2 hours of bone marrow biopsy and aspirate.
- r. ECG must be performed prior to dosing.

# 1 INTRODUCTION

## 1.1 Background

Cancer is a major health care problem in the US and worldwide. Prostate cancer is the most common cancer in males. It is anticipated that the incidence of prostate cancer, an age dependent neoplasm, will only increase with progressive aging of the population worldwide. Unlike other advanced cancer types, only modest advances have been made in therapy. The mainstay of therapy for patients with advanced cancer remains as androgen ablation. In further progression of disease, chemotherapy only achieves modest responses and is mostly palliative in nature. These observations stress the need to develop new therapeutic strategies based on the improved understanding of the biology driving prostate cancer progression.

Recently, a representative of a new drug class, androgen biosynthesis inhibitor, abiraterone acetate, has demonstrated improved survival in a post-chemotherapy CRPC patient population. Also, a novel androgen signaling inhibitor enzalutamide (formerly MDV3100) has demonstrated significant antitumor activity in a Phase 3 trial in this same patient population. However, this gain in survival might eventually be overcome by disease progression and death from the malignant disease. Thus, there is a need to explore the effect of novel combination of enzalutamide and abiraterone acetate.

### 1.1.1 Paracrine Androgen Signaling

There is increasing evidence that “intracrine” (autocrine/paracrine) androgen signaling is implicated in the castration resistant progression of prostate cancer. Enzalutamide is a novel small molecule designed to have increased affinity for the androgen receptor and more effective suppression of the downstream androgen signaling pathway. In pre-clinical models, enzalutamide has been shown to target the androgen signaling pathway at three distinct points: it blocks testosterone binding to the AR, impairs movement of the AR to the nucleus of prostate cancer cells (nuclear translocation), and inhibits binding to DNA. Enzalutamide has been shown to suppress cancer cell growth and induce cancer cells’ death (apoptosis).

### 1.1.2 Androgen Biosynthesis

CYP17 is an important enzyme in the synthetic pathway for the production of androgens in the testes and adrenal glands. It catalyzes the conversion of pregnenolone or progesterone into dehydroepiandrosterone (DHEA) or androstenedione, respectively, both are precursors of testosterone.

Abiraterone acetate is an FDA approved CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel [Centocor Ortho Biotech Inc., April 2011].

It inhibits the production of testosterone in adrenal glands and testes. Testosterone, a C19 androgen, is further converted to the more potent androgen, dihydrotestosterone (DHT), by

testosterone 5 $\alpha$ -reductase in the prostate; both testosterone and DHT are principal promoters of prostate cancer growth [Haidar, 2003; Ideyama, 1998; Duc, 2003].

The suppression of androgen signaling is effective in CRPC. Abiraterone acetate, a novel androgen biosynthesis inhibitor and enzalutamide, novel androgen signaling inhibitor, have shown efficacy in patient with CRPC with acceptable toxicity profiles [de Bono, 2011; Scher, 2010; Efstathiou, 2011]. Ligand-independent AR signaling has been implicated in abiraterone acetate resistance and increased testosterone in patients treated with enzalutamide [Efstathiou, 2010]. These observations are consistent with the hypothesis that persistent AR signaling is implicated in CRPC progression and provides rationale for the combination of enzalutamide with abiraterone acetate and prednisone.

## 1.2 Non-clinical and Clinical Data

### 1.2.1 Non-clinical Data

Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor (AR) signaling. Despite low or even undetectable levels of androgen, AR signaling continues to promote disease progression. Stimulation of tumor cell growth via the androgen receptor requires nuclear localization and DNA binding. Enzalutamide is a potent AR signaling inhibitor that blocks several steps in the androgen receptor signaling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors in the cytosol, inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor over expression and in prostate cancer cells resistant to anti-androgens. Enzalutamide decreases the growth of prostate cancer cells and can induce cancer cell death and tumor regression. Enzalutamide lacks androgen receptor agonist activity. In addition to the human androgen receptor, the targets for which significant interaction with enzalutamide was detected were only the human progesterone receptor ( $IC_{50} = 16.1 \mu M$ ) and the rat gamma amino butyric acid (GABA)-gated chloride channel ( $IC_{50} = 2.6 \mu M$ ). A major human metabolite, M2, also demonstrated significant binding to the progesterone receptor ( $IC_{50} = 6.2 \mu M$ ) and the GABA-gated chloride channel ( $IC_{50} = 7.1 \mu M$ ). A cell-based activity assay for the GABA-gated chloride channel ( $\alpha 1\beta 3$  GABA-A receptor subtype) demonstrated that both parent and metabolite M2 were functional inhibitors of this channel.

Available non-clinical and clinical data from abiraterone acetate and enzalutamide show that targeting androgen biosynthesis in the tumor micro-environment as well as androgen signaling is effective in CRPC. While non-clinical studies of the combination of enzalutamide and abiraterone acetate have not been conducted, available data suggests there is potential for additive effects if the two targeting approaches are used concomitantly.

Abiraterone is an inhibitor of CYP2D6 and a substrate of CYP3A4. Based on in vitro data, enzalutamide is an inhibitor of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 and may be an inducer of CYP3A4. Additionally, in vitro studies showed that enzalutamide is metabolized by CYP2C8 and CYP3A4/5.

### 1.2.2 Clinical Data

The tolerability, pharmacokinetics (PK), and antitumor activity of enzalutamide were studied in a multi-center, open-label, dose-escalation study of enzalutamide in 140 subjects with advanced prostate cancer. Subjects were treated with enzalutamide at doses of 30–600 mg/day until disease progression or intolerable side effects developed [Scher, 2010].

At the highest dose of 600 mg/day, two of three subjects had dose-limiting toxicities (seizure and rash, respectively). One witnessed seizure at 360 mg/day and a possible seizure at 480 mg/day were also reported. No deaths and no other drug-related serious adverse events were reported. Fatigue was the most frequently reported adverse event, with dose-dependent increases of Grade 3 fatigue (0% at 150, 9% at 240, 15% at 360, and 20% at 480 mg/day groups). Only one subject discontinued treatment due to fatigue. The dose of 240 mg/day was defined as the maximum tolerated dose.

Enzalutamide was absorbed rapidly after oral administration, with the median time to maximum plasma concentrations after a single dose occurring at 1 hour post dose (range 0.42 to 4 hours). No major deviations from dose proportionality were observed over the dose range 30 to 600 mg. Due to the long  $t_{1/2}$  (~ 5.8 days), it took approximately 1 month to reach steady state. With daily oral administration, enzalutamide accumulated approximately 8.3-fold relative to a single dose. The peak-to-trough ratio was approximately 1.25, indicating that the average difference between the peak ( $C_{max}$ ) and trough ( $C_{min}$ ) concentrations was  $\leq 25\%$ . As a result of the low daily fluctuations, plasma profiles at steady-state resembled a constant infusion. The  $C_{min}$  values in individual subjects remained constant beyond Day 28 of chronic therapy, suggesting time-linear pharmacokinetics once steady state was achieved.

A total of 1199 subjects were enrolled in a Phase 3 randomized, double-blind, placebo-controlled study in patients with progressive castration resistant prostate cancer previously treated with docetaxel-based chemotherapy (CRPC2/AFFIRM). The primary endpoint of this trial was overall survival. 800 study subjects were treated with enzalutamide at doses of 160 mg and 399 were treated with placebo.

An Independent Data Monitoring Committee (IDMC) has recommended unblinding of the AFFIRM study because the results met the requirements of a pre-specified interim analysis, and a positive median overall survival benefit to subjects treated with enzalutamide has been demonstrated compared to placebo. Results of the interim analysis demonstrated a statistically significant improvement ( $p < 0.0001$ ) in overall survival with a median improvement over placebo of 4.8 months [hazard ratio (HR) = 0.631]. The estimated median survival for men treated with enzalutamide was 18.4 months compared with 13.6 months for men treated with placebo. Enzalutamide provided a 37 percent reduction in risk of death compared to placebo (Hazard Ratio=0.631). Data with a data cut-off of 25 September 2011 show that 71.1% on the enzalutamide treatment arm and 95.2% on the placebo arm discontinued treatment. The median exposure in weeks was 36.3 weeks for enzalutamide and 13.0 weeks for placebo. In total 98.1% (enzalutamide) and 97.7% (placebo) presented with  $\geq 1$  treatment-emergent adverse event. There were 45.3% (enzalutamide) and 53.1% seen with  $\geq 1$  treatment-emergent adverse event. (Grade 3 or higher). The percentage of patients with treatment-emergent adverse event

(Grade 3 or higher) was 33.5% for enzalutamide and 38.6% for placebo. Enzalutamide was generally well-tolerated. Overall, the incidence of serious adverse events and deaths was higher among those treated with placebo compared to enzalutamide in the CRPC2 (AFFIRM) study. Five seizures, four witnessed and one unwitnessed, were reported in the study as of the data cut-off date, all occurred in patients randomized to enzalutamide representing an incidence of 0.6%.

Additionally, two separate trials have been performed to study the effect of enzalutamide or abiraterone on androgen signaling and bone marrow parameters.

Study CRPC-MDA-1 was a Phase 2 study designed to explore the effect of treatment with enzalutamide on androgen signaling and expression of survival/escape pathways in the bone marrow of patients with castration-resistant metastatic prostate cancer. Out of the 60 patients treated with 160 mg daily of enzalutamide, 75% had a decrease in PSA levels on therapy, 48.3% had a  $\geq 50\%$  decrease in PSA levels, and 25% had a  $\geq 90\%$  decrease in PSA levels. Results show elevated levels of testosterone in bone marrow prior to enzalutamide therapy, as well as tumor expression of androgen receptor and CYP17 which support the hypothesis that there is persistent androgen receptor signaling in castration-resistant prostate cancer. Further, it suggests that therapy with enzalutamide is associated with increases in blood and bone marrow testosterone indicative of a biologic response to effective androgen blockade.

There were no deaths due to adverse events in this study. There were two adverse events as the primary cause of study drug discontinuation, however neither event was assessed as related to enzalutamide therapy. The most commonly reported adverse events in this study were fatigue (reported in 71.7% of patients), anorexia (28.3%), constipation (28.3%), arthralgia (26.7%) and back pain (23.3%).

In another open label, observational study 57 patients with bone-metastatic CRPC received abiraterone acetate and prednisone. The results showed a strong correlation between pre-treatment circulating and microenvironment bone marrow aspirate testosterone levels and abiraterone acetate achieved sustained suppression of testosterone in both blood and bone marrow aspirate. In a limited number of patients an increase of AR copy numbers was observed.

Enzalutamide and abiraterone acetate plus prednisone have individually demonstrated suppression of androgen signaling and efficacy in subjects with CRPC. However, no formal trials has been conducted to further explore additive or synergistic activity.

## **1.3 Summary of Key Safety Information for Study Drugs**

### **1.3.1 Enzalutamide**

The safety and tolerability of enzalutamide have been evaluated in 13 studies, including 2 completed studies (Phase 1), 7 active studies (Phase 1 through 3), and 4 enrolling studies (Phase 2 through 3). It is estimated that a total of 124 healthy volunteers, 16 subjects with hepatic impairment, and approximately 1800 patients with prostate cancer have been exposed

to enzalutamide in completed, open-label, and ongoing blinded studies. In the completed interim analysis of the randomized, double-blind, placebo-controlled Phase 3 efficacy and safety study in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy (CRPC2), 800 patients received enzalutamide (160 mg daily). The duration of enzalutamide exposure in this study ranged from 1 day to 23.3 months (median 8.3 months). No study has been terminated early for safety reasons.

Safety data are presented from the formal interim analysis of data from the CRPC2 study, with a data cut-off date of 25 September 2011. Table 2 provides an overview of exposure to study drug, adverse events, and deaths.

**Table 2: Summary of Study Drug Exposure, Adverse Events, and Deaths (CRPC2)\***

<b>Treated (Safety Population)</b>	<b>enzalutamide (n = 800)</b>	<b>Placebo (n = 399)</b>
Discontinued Treatment	569 (71.1%)	380 (95.2%)
Treatment Duration (median months)	8.3	3.0
Patients with $\geq 1$ Treatment Emergent Adverse Event	785 (98.1%)	390 (97.7%)
Patients with $\geq 1$ Treatment Emergent Adverse Event (Grade 3 or Higher)	362 (45.3%)	212 (53.1%)
Patients with $\geq 1$ Serious Treatment Emergent Adverse Event	268 (33.5%)	154 (38.6%)
Patients with an Adverse Event Leading to Death	23 (2.9%)	14 (3.5%)
Patients with Adverse Events Leading to Study Drug Discontinuation	61 (7.6%)	39 (9.8%)
SUSARs (all in unique patients)	10	6
Deaths	308 (38.5%)	212 (53.1%)
*For up to date study information refer to the current edition of the Investigator's Brochure		

Enzalutamide (160 mg daily) was generally well-tolerated in the placebo-controlled CRPC2 study of 1199 patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy. Adverse events reported by those treated with enzalutamide (160 mg daily) with an incidence of at least 5% and by at least 2% greater than by those who received placebo included fatigue (33.6% v 29.1%), diarrhea (21.4% v 17.5%), hot flush (20.3% v 10.3%), musculoskeletal pain (13.6% v 10.0%), headache (11.6% v 5.5%), insomnia (8.6% v 6.0%), anxiety (6.4% vs. 4.0%), hypertension (6.1% v 2.8%), and nasopharyngitis (5.1% v 3.0%).

Other adverse events reported less commonly than 5% but that may be associated with enzalutamide treatment after careful assessment of the adverse events include: falls (4.0% vs. 1.3%), dry skin (3.6% vs. 1.3%), and pruritus (3.5% vs. 1.3%). A greater proportion of patients in the enzalutamide-treated group (4.1% vs. 1.8%) reporting the following adverse event terms: memory impairment, cognitive disorder, amnesia, disturbance of attention, and dementia. In

addition, event terms related to hallucination (visual hallucination, tactile hallucination, hallucination) were reported more frequently in the enzalutamide-treated group (1.6% vs. 0.3%).

Serious adverse events that occurred at a  $\geq 0.5\%$  absolute difference in event frequency and more frequently in the enzalutamide arm than the placebo arm included: spinal cord compression (6.0% vs. 3.8%), bone pain (1.5% vs. 1.0%), metastatic pain (1.5% vs. 0.8%), pathological fracture (1.5% vs. 0.5%), urinary tract infection (0.9% vs. 0.3%), and cauda equina syndrome (0.8% vs. 0.0%).

Seizure is a known potential toxicity of enzalutamide. In vitro studies have shown that enzalutamide and its metabolite M2 bind to the GABA-gated chloride channel with IC50 values of 1.2  $\mu\text{g/mL}$  and 3.3  $\mu\text{g/mL}$ , respectively and in a cell-based assay inhibit the channel's activity with IC50 values of 1.4  $\mu\text{g/mL}$  and 1.07  $\mu\text{g/mL}$ , respectively. Some compounds that inhibit the GABA-gated chloride channel are associated with seizures[Foster, 2011].

In the first clinical study of enzalutamide (S-3100-1-01), a dose-escalation study in men with castration-resistant prostate cancer with and without prior exposure to chemotherapy, the following doses were evaluated: 30, 60, 150, 240, 360, 480 (as 240 mg twice per day [BID]), and 600 (as 300 mg BID) mg/day. Three patients were reported to have dose-limiting toxicities of seizure, one each at doses of 360, 480, and 600 mg/day (Section 6.2.2.1). The results of this study led to the selection of the clinical dose of enzalutamide of 160 mg/day.

As of the database cut-off date for the respective unblinded or open-label studies reported in the Investigator's Brochure, 7 patients out of a total of 1100 patients (0.6%) exposed to enzalutamide at a dose of 160 mg/day have reported a seizure during the enzalutamide treatment emergent adverse event reporting period. These include one patient each in studies 9785-CL-0007 and 9785-CL-0321, and 5 patients in the CRPC2 study. Two additional patients have been identified by the Sponsor to have experienced adverse events that may have been seizures, including one case reported by the Investigator as syncope (CRPC2) and the other reported as a transient ischemic attack with an abnormal electroencephalogram (CRPC-MDA-1). As of the data cut-off date, treatment with enzalutamide at a daily dose of 160 mg is associated with a 0.6-0.8% risk of seizure in men with late-stage castration-resistant prostate cancer.

Taking into account information from ongoing blinded studies and events occurring after the database cut-off date, the range for seizure risk is unchanged. No seizures have been reported in the blinded placebo-controlled Phase 3 study enzalutamide-03 (PREVAIL) with over 1300 patients enrolled (randomized 1:1 to enzalutamide 160 mg/day or placebo). One additional patient in the CRPC2 study has been reported to have had a seizure after the safety data cut-off date, and one additional patient in an ongoing blinded study (9785-CL-0222) has also reported a seizure.

Please see the most current version of the Investigator Brochure for additional details.

### 1.3.2 Abiraterone Acetate

The most common adverse reactions ( $\geq 5\%$ ) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

In addition abiraterone acetate is known to cause the following conditions:

**Mineralocorticoid excess:** abiraterone acetate should be used with caution in subjects with a history of cardiovascular disease. The safety of abiraterone acetate in subjects with LVEF  $< 50\%$  or NYHA Class III or IV heart failure is not established. Hyper-tension should be controlled and hypokalemia should be corrected before treatment. Blood pressure, serum potassium and symptoms of fluid retention should be monitored at least monthly.

**Adrenocortical insufficiency:** symptoms and signs of adrenocortical insufficiency should be monitored. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

**Hepatotoxicity:** Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Liver function should be monitored and modify, interrupt, or discontinue abiraterone acetate dosing as recommended. Study subjects will have liver function tests (including alkaline phosphatase, AST, ALT, direct and total bilirubin, and LDH) every 2 weeks for the first 12 weeks of treatment.

Abiraterone acetate must be taken on an empty stomach. Exposure of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals.

Abiraterone acetate may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection (e.g., gloves). Subjects will also be informed that it is not known whether abiraterone acetate or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The subjects should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with abiraterone acetate.

Details and data in the package insert are to be referenced for more details [Centocor Ortho Biotech Inc., April 2011].

### 1.3.3 Prednisone

**Fluid and electrolyte disturbances:** sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

**Musculoskeletal:** muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, tendon rupture, particularly of the Achilles tendon, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones.

**Gastrointestinal:** peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis, increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following

corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome are reversible upon discontinuation.

Dermatologic: impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may suppress reactions to skin tests.

Neurological: convulsions, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, vertigo, headache.

Endocrine: menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

Metabolic: negative nitrogen balance due to protein catabolism.

Additional reactions: Urticaria, and other allergic, anaphylactic or hypersensitivity reactions.

For more details refer to package insert from [Actavis UK Ltd., July 2011].

## 1.4 Risk-Benefit Assessment

Enzalutamide (160 mg daily) was generally well-tolerated in the placebo-controlled CRPC2 study of 1199 patients with progressive CRPC previously treated with docetaxel-based chemotherapy. Adverse events reported by those treated with enzalutamide (160 mg daily) with an incidence of at least 5% and by at least 2% greater than by those who received placebo included:

- fatigue
- diarrhea
- hot flush
- musculoskeletal pain
- headache
- insomnia
- anxiety
- hypertension
- nasopharyngitis

Other adverse events reported less commonly than 5% but that may be associated with enzalutamide treatment after careful assessment of the adverse events include:

- falls
- dry skin
- pruritus

Additionally, a greater proportion of patients in the enzalutamide-treated group reporting the following combined adverse event terms: memory impairment, cognitive disorder, amnesia, disturbance of attention, and dementia. In addition, combined event terms related to hallucination (visual hallucination, tactile hallucination, hallucination) were reported more frequently in the enzalutamide-treated group.

Furthermore, enzalutamide has been demonstrated in nonclinical studies to induce seizures in a dose-dependent fashion. Inhibition of the GABA-gated chloride channel is a hypothesized-mechanism of action for this effect. Seizures have occurred in enzalutamide-treated patients and there appears to be a greater risk of seizure at higher doses. Confounding factors likely contributed to the occurrence of seizures in several of these cases; however, a role of enzalutamide in lowering the seizure threshold cannot be excluded. Caution should be used in administering enzalutamide to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumors or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medications that may lower the seizure threshold. Enzalutamide should be permanently discontinued in patients who have a seizure while on treatment.

The totality of the efficacy and safety data suggests a positive benefit/risk assessment of the use of enzalutamide in men with castration-resistant prostate cancer. The 4.8 month improvement in median survival observed in enzalutamide treated patients compared with placebo represents a major advantage for patients with castration-resistant prostate cancer that has progressed following chemotherapy. Moreover, enzalutamide was generally well-tolerated as described above, with seizures reported in less than 1% of patients. Taken together, the overall risk/benefit assessment is very favorable for enzalutamide.

Abiraterone acetate is an FDA approved CYP17 inhibitor indicated for use in combination with prednisone and the safety profile is described in the current package insert.

Enzalutamide and abiraterone acetate have not yet been given together, however, based on the safety and tolerability profile of both drugs, no severe toxicity with the proposed combinations is expected. Patient safety will be monitored through clinical vigilance. Subject safety is assured through clinical monitoring during the study. Any unusual clinical observations will be discussed immediately with the Principal Investigator, sponsor, or a sub-investigator if the PI is absent or not available. All subjects will be treated at M.D. Anderson Cancer Center and will be provided with their treating physicians and research nurse contact information.

In vitro studies showed that abiraterone acetate is a substrate of CYP3A4 and that enzalutamide may be an inducer of CYP3A4. Co-administration of enzalutamide with CYP3A4/5 substrates may affect oral bioavailability and/or elimination of the CYP3A4/5 substrate. There is a potential for drug interaction when administering both drugs at the same time in which enzalutamide may lower the circulating levels of abiraterone. An optional evaluation in this study will be performed to explore the effect of enzalutamide on the PK of abiraterone.

Abiraterone acetate may cause fetal harm when administered to a pregnant woman and is contraindicated in women who are or may become pregnant. Instructions will be given that women should not handle abiraterone acetate without protection (e.g., gloves).

The use of abiraterone is mandating the additional co-administration of prednisone for the treatment of its related adrenalcortical insufficiency. Though the long term use of prednisone carry a risk of potential side effects (see list above) the safety profile of prednisone is acceptable.

## **2 STUDY OBJECTIVE(S), DESIGN AND VARIABLE**

### **2.1 Study Objectives**

#### **2.1.1 Primary Objective**

To explore the safety, and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone.

#### **2.1.2 Secondary Objectives**

- To explore the effect of enzalutamide in combination with abiraterone acetate plus prednisone on androgen receptor signaling and androgen levels.
- To explore the antitumor activity of enzalutamide in combination with abiraterone acetate plus prednisone as assessed by serum prostate-specific antigen (PSA), imaging of soft tissue and bone metastases, and markers of bone metabolism.

#### **2.1.3 Exploratory Objectives**

To measure pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional).

## **2.2 Study Design and Dose Rationale**

### **2.2.1 Study Design**

This is an open label study to determine the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone in CRPC subjects with bone metastases by clinical evaluations at protocol specified intervals. The study will also determine the modulation of androgen receptor (AR) signaling in bone marrow biopsy and androgen levels as measured by testosterone concentration in bone marrow aspirate and blood by Liquid Chromatography Mass spectrometry, expression of AR and its subcellular localization by immunohistochemistry (IHC), presence of known and assessable splice variants and CYP17 expression in epithelial and host compartment of the cancer by IHC. Tumor tissue will be collected to determine AR signaling and candidate pathways that may be part of a signaling network implicated in therapy resistance. The baseline determination and subsequent

assessment of AR signaling will be correlated with progression-free survival (radiographic progression, PSA progression, and/or clinical deterioration).

Approximately 60 subjects will receive enzalutamide 160 mg daily, abiraterone acetate 1,000 mg daily, and prednisone 5 mg twice daily to be taken orally.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs).

The occurrence of an adverse event or toxicity, where continued administration of study drug is deemed to be not in the subject's best interest by the investigator and/or the sponsor, will result in the removal of the subject from therapy.

For the study duration, all subjects will maintain androgen deprivation with a GnRH agonist or antagonist or orchiectomy.

Study drug will be administered until disease progression. Disease progression is defined as a composite endpoint, consisting of clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria.

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 (abdominopelvic CT/MRI [lung when applicable] and bone scan) should be read on site.

Optional PK blood samples for determination of plasma concentrations of abiraterone will be collected pre-dose on Day 4 and Day 29. In addition optional PK blood sampling for determination of plasma concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 will be collected on Day 29.

Archival tumor tissue samples will be collected to allow for tumor profiling. Samples will be obtained and stored until qualified assays become available.

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.

### **2.2.2 Dose Rationale**

This study will utilize an enzalutamide dose of 160 mg/day, which has proven safety and efficacy in the Phase 3 AFFIRM trial.

An abiraterone acetate dose of 1000 mg/day together with prednisone 5 mg twice daily will be taken. It is the FDA approved daily dose.

## 2.3 Variables

### 2.3.1 Primary Variable

- Nature, frequency and severity of adverse events
- Safety laboratory tests: chemistry and hematology
- Vital signs (blood pressure, pulse rate and temperature)
- 12 Lead ECG parameters
- Physical examination results

### 2.3.2 Secondary Variables

- Androgen receptor signaling
  - Expression and localization of AR
  - CYP17 expression
  - Splice variants
- Pathways linked with non-classical AR signaling & Bone development
- Androgens
  - Testosterone concentration in bone marrow aspirate and blood
  - DHT concentration in bone marrow aspirate and blood
- Androgen pre-cursors and other associated metabolites. For example:
  - Cortisol
  - Androstenedione
  - Pregnenolone
  - Progesterone
- PSA levels
- Progression-free Survival (PFS)
- Objective response according to RECIST 1.1
- Bone scan results
- Markers of bone metabolism (bone specific alkaline phosphatase and urine N-telopeptides)

### 2.3.3 Exploratory Variables

Pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional). Other variables may be explored.

## 3 STUDY POPULATION

### 3.1 Selection of Study Population

The study population will include approximately 60 men with castration-resistant prostate cancer and bone metastasis.

### 3.2 Inclusion Criteria

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

1. 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).
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
3. Presence of metastatic disease to the bone at the Screening visit.
4. Ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue or orchiectomy (i.e., surgical or medical castration).
5. Serum testosterone level  $\leq 50$  ng/dL at the Screening visit.
6. Subject receiving bisphosphonate or denosumab therapy must have been on stable doses for at least 4 weeks prior to Day 1.
7. Progressive disease defined as one or more of the following three criteria (Note: subjects who received an antiandrogen must demonstrate disease progression following discontinuation of antiandrogen):
  - PSA progression defined by a minimum of two rising PSA levels with an interval of  $\geq 1$  week between each determination. The PSA value at the Screening visit should be  $\geq 2$  ng/mL.
  - Soft tissue disease progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).
  - Bone disease progression defined by PCWG2 criteria (two or more new lesions on bone scan compared with prior scan).
8. Subject previously treated with chemotherapy must have no more than two prior chemotherapy regimens for the treatment of metastatic prostate cancer.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
10. Estimated life expectancy of  $\geq 6$  months.
11. Able to swallow the study drug and comply with study requirements.
12. Agree to use a double-barrier method of contraception which involves the use of a condom in combination with one of the following: contraceptive sponge, diaphragm, or cervical ring with spermicidal gel or foam, if having sex with a woman of child-bearing potential during the length of the study and for one week after abiraterone is discontinued and for at least three months after enzalutamide is discontinued.
13. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will not be allowed.

### 3.3 Exclusion Criteria

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

1. Known allergy to the study drugs or any of its components.
2. Severe, concurrent disease, infection, or co-morbidity that, in the judgment of the investigator, would make the subject inappropriate for enrollment.
3. Medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated.
4. Known or suspected metastases in the brain.
5. Absolute neutrophil count < 1,000/ $\mu$ L, platelet count < 75,000/ $\mu$ L, and hemoglobin < 9 g/dL at the Screening visit; (NOTE: subject may not have received any growth factors or blood transfusions within seven days of the hematologic laboratory values obtained at the Screening visit).
6. Total bilirubin (TBL), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal at the Screening visit.
7. Creatinine (Cr) > 2 mg/dL at the Screening visit.
8. History of another malignancy within the previous 2 years other than curatively treated non-melanomatous skin cancer.
9. Treatment with androgen receptor antagonists (bicalutamide, flutamide, nilutamide), 5- $\alpha$  reductase inhibitors (finasteride, dutasteride), estrogens, chemotherapy, or biologic therapy within 4 weeks of Day 1 visit.
10. Radiation therapy within 3 weeks (if single fraction of radiotherapy within 2 weeks) of Day 1 visit, or radionuclide therapy within 8 weeks of Day 1.
11. Planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery.
12. Structurally unstable bone lesions suggesting impending fracture.
13. History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumors, brain metastases, or alcoholism. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrollment (Day 1 visit)
14. Clinically significant cardiovascular disease including:
  - Myocardial infarction within 6 months of Screening visit;
  - Uncontrolled angina within 3 months of Screening visit;
  - Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past, or history of anthracycline or anthracenedione (mitoxantrone) treatment, unless a

screening echocardiogram or multi-gated acquisition scan (MUGA) performed within three months of the Screening visit results in a left ventricular ejection fraction that is  $\geq 45\%$ .

- History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsade de pointes).
  - Prolonged corrected QT interval by the Fridericia correction formula (QTcF) on the screening Electrocardiogram (ECG)  $> 470$  msec.
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
  - Hypotension (systolic blood pressure  $< 86$  mmHg or bradycardia with a heart rate of  $< 50$  beats per minute on the Screening ECG., unless pharmaceutically induced and thus reversible (i.e. beta blockers).
  - Uncontrolled hypertension as indicated by a resting systolic blood pressure  $> 170$  mmHg or diastolic blood pressure  $> 105$  mmHg at the Screening visit.
15. Prior use of ketoconazole, abiraterone acetate or enzalutamide, or participation in a previous clinical trial of ketoconazole, abiraterone acetate or enzalutamide.
16. Use of an investigational agent within 4 weeks of Day 1.
17. Gastrointestinal disorder that may affect absorption (e.g., gastrectomy) of study drug.
18. Major surgery within 4 weeks prior to Day 1.
19. History of significant bleeding disorder unrelated to cancer, including:
- Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease).
  - Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies) of Screening visit.
  - History of GI bleeding within 6 months of Screening visit.
20. Active or symptomatic viral hepatitis or chronic liver disease.
21. Known history of pituitary or adrenal dysfunction.

Waivers to the exclusion criteria will not be allowed.

### **3.4 Discontinuation Criteria for Individual Subjects**

A discontinuation is a subject who enrolled in the study and for whom study treatment is terminated 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. Discontinued subjects will not be replaced. The investigator is also free to terminate a subject's involvement in the study at any time if in the opinion of the investigator the subject's clinical condition warrants it.

Discontinuation criteria for individual subjects:

- Subject develops disease progression defined as a composite endpoint, consisting of clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria. Subject with PSA progression alone will not be withdrawn from the study.
- Subject develops an adverse event or toxicity, where continued administration of study drug is deemed not in the subject's best interest by the Investigator.
- Abnormal lab values defined as: creatinine  $> 305 \mu\text{mol/L}$  (4.0 mg/dL), an absolute neutrophil count of  $\leq 750 /\mu\text{L}$  and platelet count of  $< 50,000/\mu\text{L}$ .
- LFTs that meet one of the following:
  - a. An ALT or AST value of  $> 8x$  ULN
  - b. An ALT or AST value of  $> 5x$  ULN for more than 2 weeks
  - c. An ALT or AST value of  $> 3x$  ULN and TBL  $> 2x$  ULN or INR  $> 1.5$
  - d. If close monitoring for a subject with moderate (defined in Appendix 3 as ALT or AST  $> 3x$  ULN or total bilirubin  $> 2x$  ULN) hepatic laboratory tests is not possible, study drug should be discontinued.
  - e. ALT or AST  $> 3x$  ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ( $> 5\%$ ).
- Any seizure.
- Investigator or study Medical Monitor decision that study drug continuation is not in the best interest of the subject.
- Subjects who is, in the opinion of the Investigator or the Medical Monitor, grossly non-compliant with the protocol's requirements.
- Subject is unable to continue in the study, if one of the study drugs is discontinued.
- 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.

## 4 STUDY DRUGS

### 4.1 Description of Study Drugs

#### 4.1.1 Enzalutamide

Enzalutamide has the chemical name 4- $\{3-[4\text{-cyano-3-(trifluoromethyl)phenyl}]-5,5\text{-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}\}$ -2-fluoro-N-methylbenzamide. It is a white to off-white solid that is insoluble in water and no salt forms are available at ~pH 2 to 10.

Enzalutamide capsules are white to off-white oblong capsules, printed with either “MDV” or “ENZ” in black ink. The soft gelatin capsules are filled with a clear, yellowish solution which contains the two antioxidants, butylated hydroxyanisole, and butylated hydroxytoluene, and enzalutamide active ingredient (40 mg), all dissolved in the non-ionic surfactant, Labrasol® (Caprylocaproyl Polyoxylglycerides). Enzalutamide capsules are provided in white, opaque, high-density polyethylene (HDPE) bottles with child-resistant induction seal closure.

#### 4.1.2 Abiraterone Acetate

Abiraterone acetate is designated chemically as (3 $\beta$ )-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate. It is a white to off-white, non-hygroscopic, crystalline powder, its molecular formula is C<sub>26</sub>H<sub>33</sub>NO<sub>2</sub> and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water.

Abiraterone acetate 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side and provided in bottles with child-resistant induction seal closure.

#### 4.1.3 Prednisone

Prednisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. The molecular formula for prednisone is C<sub>21</sub>H<sub>26</sub>O<sub>5</sub>. Chemically, it is 17,21-dihydroxypregna-1,4-diene-3,11,20-trione. Prednisone is a white to practically white, odorless, crystalline powder and has a molecular weight of 358.44. It melts at about 230°C with some decomposition. Prednisone is very slightly soluble in water, slightly soluble in alcohol, chloroform, dioxane, and methanol.

Prednisone inactive ingredients are: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and talc.

Prednisone 5 mg tablets are white round-shaped tablets and provided in bottles with child-resistant induction seal closure.

## 4.2 Packaging and Labeling

Enzalutamide used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person at Astellas US Technologies, Inc. (AUST) in accordance

with AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Abiraterone acetate and prednisone will be labeled and supplied to the study subjects through the site designated pharmacy.

Enzalutamide capsules are packaged either in a white, opaque, high-density polyethylene (HDPE) bottles.

Abiraterone acetate and prednisone tablets will be supplied in bottles. Information presented on the labels for investigational product will comply with applicable local regulations.

Site pharmacist or medically qualified staff will dispense the study treatment to each subjects in accordance with this protocol.

### 4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (e.g. pharmacist), and

- that such deliveries are recorded
- that study drug is handled and stored safely and properly
- that study drug is only dispensed to study subjects in accordance with the protocol
- that any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed.

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator/pharmacist. 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/pharmacist 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 returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Used or unused study drug may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted only if agreed upon by the Sponsor. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request. Unused

study drug not destroyed at the site must be returned to the Sponsor or designee at the end of the study or upon expiration.

Enzalutamide should be stored in a secure location with limited access at 77°F (25°C), with excursions permitted to 59°F to 86°F (15°C to 30°C). Bottles will be labeled with the study protocol number, medication or bottle number, contents, directions for use, storage directions, clinical trial statement, and Medivation as sponsor. Subjects will be instructed to store study drug at room temperature out of the reach of children.

Abiraterone acetate and prednisone will be provided by the local pharmacy and will be stored and handled according to the manufactures specifications and the pharmacy standards of operation.

#### **4.4 Blinding**

Not applicable.

#### **4.5 Assignment and Allocation**

##### **4.5.1 Registration**

This is an open-label study, 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. A unique subjects/treatment number will be assigned to each subjects enrolled in the study. Discontinued subjects will not be replaced.

### **5 TREATMENTS AND EVALUATION**

#### **5.1 Dosing and Administration of Study Drugs and Other Medications**

##### **5.1.1 Dose/Dose Regimen and Administration Period**

Enzalutamide: Subjects will be instructed to take 4 capsules (40 mg each) per day orally. Enzalutamide may be taken with or without food. Enzalutamide should be taken as close to the same time each day as possible.

Abiraterone acetate: Subjects will be instructed to take 4 tablets (250 mg each) orally (PO) at least 2 hour before a meal or 1 hour after a meal. Treatment with abiraterone acetate will continue throughout the duration of participation.

Prednisone: Subjects will be instructed to take 5-mg oral prednisone, twice daily. Treatment with prednisone will continue throughout the duration of participation.

All subjects who meet the inclusion/exclusion criteria are therefore assigned to begin treatment as follows:

<b>Drug</b>	<b>Dose</b>	<b>Frequency</b>	<b>Route of Administration</b>
enzalutamide	160mg	QD	oral
abiraterone acetate	1000mg	QD	oral
prednisone	5mg	BID	oral

All subjects will be treated until disease progression or meets one of the discontinuation criteria (see section 3.4).

### **5.1.2 Reduction in Dose or Discontinuation of the Study Drugs**

In subjects who experience toxicity which cannot be ameliorated by the use of adequate medical intervention, dose reductions can be performed. In these cases dose reductions of abiraterone acetate should be performed first, followed by reduction in enzalutamide doses (if needed).

For abiraterone acetate, 2 dose reductions are allowed. At each dose reduction, one tablet of abiraterone acetate will be removed, e.g., 4→3 tablets, and 3→2 tablets. Any return to protocol dose level after dose reduction or after treatment interruption must follow documentation of adverse event resolution and a discussion between the Principal Investigator and the sponsor.

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 follow a discussion between the Principal Investigator and the sponsor. Subjects will remain on abiraterone acetate and prednisone during enzalutamide dose interruption.

No dose reductions for prednisone are allowed. Subjects experiencing toxicity considered to be related to the use of prednisone for which a dose reduction is needed cannot participate in the study any longer.

Subjects should be able to take all three study drugs (enzalutamide, abiraterone acetate and prednisone) to participate in the study. An interruption of one of these drugs is allowed as per instruction above. Permanent discontinuation of one of the drugs, while continuing the two other drugs, is not allowed.

### **5.1.3 Previous and Concomitant Medication (Drugs and Therapies)**

Medication taken within four weeks prior to Screening visit must be captured on the case report form (CRF).

At each visit, all concomitant treatments, including blood and blood products, must be reported on the source documentation and on the concomitant medications page of the CRF.

Concomitant medications must also be documented at the time of discontinuation and at the 30 day follow-up visit. Please refer to Appendix 1 (list of excluded concomitant medication).

The dosage and regimen of the following medications and any chronic permitted concomitant medications should be stabilized for 4 weeks prior to Day 1 and held constant throughout the study:

- Bisphosphonates
- Denosumab
- GnRH agonist/antagonist

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

The following medications are prohibited while the subject is on study drug:

- Chemotherapeutic, biologic, or other agents with anti-tumor activity against prostate cancer other than assigned study drug.
- Anti-androgens(steroidal or non-steroidal) such as cyproterone acetate, flutamide, nilutamide, bicalutamide, etc. other than assigned study drug.
- 5- $\alpha$  reductase inhibitors such as finasteride, dutasteride, anabolic steroids, etc.
- Estrogens, progestational agents such as megestrol, medroxyprogesterone, DES, cyproterone, spironolactone > 50 mg/kg.
- Androgens such as testosterone, dehydroepiandrosterone [DHEA].
- Ketoconazole.
- Herbal products that may decrease PSA levels (e.g., saw palmetto).

Caution is advised when considering the concomitant use of the following medications:

- Medications known to lower the seizure threshold. These include but are not limited to:
  - Aminophylline/theophylline.
  - Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone).
  - Bupropion.
  - Lithium.
  - Pethidine.
  - Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine).
  - Tricyclic and tetracyclic antidepressants (e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine).
- Sensitive P-gp substrates (e.g., digoxin, fexofenadine).Medications that inhibit platelet function and anticoagulants should be used with caution while the subject is on study drug:

Src-family kinase inhibitors potentially reduce platelet aggregation. Caution should thus be exercised if subjects are required to take one of the following medications that inhibit platelet function or anticoagulants.

- aspirin or aspirin-containing combinations.

- clopidogrel, dipyridamole, tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol.
- abciximab, ticlopidine, cilostazol warfarin.
- heparin/low molecular weight heparin [eg, danaparoid, dalteparin, tinzaparin, enoxaparin].

Low-dose warfarin for prophylaxis to prevent catheter thrombosis and heparin for flushes of intravenous lines are allowed.

- Cytochrome P 450 inhibitors, inducers, and substrates.

It is currently unknown which CYP enzyme pathways are responsible for clearing enzalutamide. To limit the risk of unpredictable increases or decreases in circulating concentrations of enzalutamide, potent inhibitors or inducers should be taken with caution, and alternative products used when available. In vitro data suggest that enzalutamide may have the potential to induce CYP3A4 and inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5; therefore, concomitant medications that are substrates of any of these enzymes should be used with caution, and relevant monitoring should be considered, especially for substrates known to cause seizure, because the possibility of drug-drug interactions cannot be fully excluded. To determine if a particular drug is a potent CYP inhibitor or inducer, the investigator should consult the product label.

Drugs metabolized through the CYP2D6 and CYP1A2 pathways should be used with caution while participating in this study.

In vitro studies showed that enzalutamide is an inhibitor of CYP2C8 and CYP2C19 with lesser inhibitory effects on CYP2B6 and CYP2C9. Substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 that have a narrow therapeutic index (e.g., phenytoin, warfarin) should be used with caution.

In vitro studies showed that enzalutamide may be an inducer of CYP3A4. Co-administration of enzalutamide with CYP3A4/5 substrates may affect oral bioavailability and/or elimination of the CYP3A4/5 substrate. Substrates of CYP3A4/5 that have a narrow therapeutic index should be used with caution. Co-administration of enzalutamide and abiraterone may lower circulating levels of abiraterone acetate. An optional evaluation in this study will be performed to explore the effect of enzalutamide on the PK of abiraterone.

In vitro studies showed that enzalutamide is metabolized by CYP2C8 and CYP3A4/5. Use caution when co-administering a strong CYP2C8 inhibitor (e.g., gemfibrozil) or strong CYP3A4/5 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, grapefruit juice) during enzalutamide treatment.

Use caution when co-administering a CYP2C8 inducer (e.g., rifampin) or strong CYP3A4/5 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) during enzalutamide administration.

Please refer to the following link for an up to date list of CYP inhibitors and inducers.

<http://medicine.iupui.edu/clinpharm/ddis/>

#### **5.1.4 Treatment Compliance**

Study drug accountability will be performed to document compliance with the dosing regimen. Subjects will be asked to bring back all remaining study drug at each study visit for drug accountability.

#### **5.1.5 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.

In case of abiraterone acetate overdose, there is no specific antidote; treatment of an overdose should be symptomatic.

#### **5.1.6 Restrictions During the Study**

Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

### **5.2 Demographics and Baseline Characteristics**

#### **5.2.1 Demographics**

Demographic information is to be obtained at screening and will include date of birth, ethnicity, race as described by the subject, height and weight.

#### **5.2.2 Medical History**

Medical history will include any significant conditions or diseases other than prostate cancer that occurred prior to informed consent.

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

A complete medical history of the target disease will be recorded at screening. This includes 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.

### **5.3 Efficacy Assessment**

#### **5.3.1 CT/MRI and Bone Scan (Radiographic Assessments)**

Imaging will be performed as per the schedule of assessment. Imaging performed prior to informed consent may be used as baseline assessment if it was performed within 6 weeks prior to study drug administration (Day 1).

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

Additional 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 is based on CT or MRI scan and is defined by RECIST 1.1. Radiographic disease progression for bone lesions is based on bone scan and is defined when a minimum of two new lesions are observed [Scher, 2008]. The total number of lesions will be collected on the eCRF.

Soft tissue 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 radiographic response to the study regimen will be characterized (Please refer to Appendix 5).

At screening, a chest X-ray or a chest CT will be performed. If the chest X-ray is performed and demonstrates metastatic chest disease, a chest CT is required. In the case of metastatic chest disease, additional chest CT's should be performed as follow-up at Week 13 (Day 85) and end of treatment (ET) visit.

Study films (abdominopelvic CT/MRI[lung when applicable]and bone scan) should be read on site. The principal investigator or a sub-investigator will evaluate the images for all subjects for the duration of the study.

The same imaging method used for an individual subjects at baseline should be used throughout the entire study for that subjects, unless for medical reasons that the method must be changed (e.g. inability to receive contrast agent).

If a subject is unable to return for restaging scans due to symptoms of progressive disease, the subject may have scans done by a local facility. These scans should be sent to the investigator for review. Total number of bone lesions will be recorded on the eCRF.

PET scans should not be used to determine disease progression.

### **5.3.2 PSA**

Samples for PSA will be collected and analyzed at the local laboratory. PSA testing will be performed as per the schedule of assessment. 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 screening.

## **5.4 Safety Assessment**

### **5.4.1 Adverse Events**

Adverse events will be assessed regularly as per schedule of assessments.

Adverse event collection will begin at the time the informed consent form is signed and continue up to 30 days following last dose of study drug.

Baseline conditions that worsen during the study will be recorded as adverse events.

Adverse events ongoing at the final visit will be followed up for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes.

#### **5.4.1.1 Adverse Events of Possible Hepatic Origin**

Subjects with AE's of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored. See Appendix 12.3 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment.

#### **5.4.2 Vital Signs**

Vital signs including blood pressure, pulse rate, and temperature will be assessed at Screening, at every clinic visit while on study drug, and at the safety follow-up visit.

Per schedule of assessment vital signs will be obtained prior to and 1 to 2 hours after study drug administration. Subjects should withhold dosing of study medication on clinic visit days. Study drug will be administered in clinic.

Vital signs should be assessed after 3 minutes rest, preferably supine position or in semi-recumbent, if supine is not tolerated.

#### **5.4.3 Laboratory Assessments**

Routine laboratory assessments for hematology, chemistry and PT/PTT and INR will be collected and analyzed at the local laboratory and will be obtained as per schedule of assessment. The laboratory assessments performed at the screening visit do not need to be repeated on Day 1 if the Day 1 visit occurs within 3 days of screening.

Laboratory assessments must be obtained prior to study drug administration.

Please refer to Appendix 2 for the specification of the laboratory tests.

Please refer to Appendix 3 (Liver Safety Monitoring and Assessment) for additional DILI laboratory testing requirements and timing.

#### **5.4.3.1 Abnormal Liver Function Tests**

If laboratory testing for a subject enrolled in a study and receiving study drug reveals an increase of serum aminotransferases (AT)  $> 3 \times$  ULN, or bilirubin  $> 2.5 \times$  ULN, at least all four of the usual serum measures (ALT, AST, ALP, and TBL) should be repeated within 48 – 72 hours of notification of the test results. See Appendix 3 (Liver Safety Monitoring and Assessment) for additional information on monitoring and assessment of abnormal liver function tests.

#### **5.4.4 Physical Examination**

Standard, full physical examinations will be performed to assess weight, general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal,

neurologic status, mental status, lymphatic, and genitourinary system. Any clinically significant abnormalities will be collected as medical history or adverse events. Weight will be recorded at each visit. Height will be recorded at the screening visit only. 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 Screening visit.

#### 5.4.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed on all subjects. Parameters that include heart rate, PR interval, RR interval, QRS interval, QT interval will be collected on the (e)CRF. Abnormalities and clinical significance as judged by the Investigator will be reported as well.

An ECG will be performed as per schedule of assessment. All ECGs will be performed prior to study drug administration. The subject should have rested in supine position (or semi-recumbent, if supine is not tolerated) for 5-10 minutes.

#### 5.4.6 Imaging

A MUGA scan or echocardiogram showing LVEF  $\geq 45\%$  is required at Screening 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, or the subject has a history of congestive heart failure NYHA class 3 or 4.

#### 5.4.7 Performance Status

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

**Table 3: 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

## 5.5 Adverse Events and Other Safety Aspects

### 5.5.1 Definition of Adverse Events (AEs)

An adverse event (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.

Adverse event terms should include a diagnosis, as available, in preference to the listing of individual signs and symptoms.

Examples of AEs include:

- A change, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition.
- Development of an intercurrent illness during the study.
- Development of symptoms which may or may not be related to the use of a concomitant medication or study drug.
- Injury or accidents: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate medical events (e.g., for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately).

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.

An AE **does not** include:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event.
- Pre-existing diseases or conditions present or detected prior to the start of study drug administration that do not worsen.
- Situations where an untoward medical event has not occurred (e.g., planned hospitalization for an elective procedure as known at the time of signing of the informed consent; hospitalization for social reasons).
- Overdose of either study drug or concomitant medication without any signs or symptoms.

An adverse event observed after starting administration of the test drug/comparative drug is called “treatment emergent adverse event” Treatment-emergent adverse events will be analyzed and discussed in the clinical study report for this study.

Non-serious adverse event collection will begin at the time of signing the informed consent and continue through study completion. The subject will be questioned in a general way and no specific symptoms will be suggested. Any non-serious adverse events occurring during the screening period up until the initial dose of study drug should be reported on the medical history CRF.

All adverse events, whether or not related to the study drug, must be fully and completely documented on the adverse event page of the CRF and in the subject’s clinical chart. In the event that a subject is withdrawn from the study because of an adverse event, this must be recorded on the CRFs.

All subjects who experience an adverse event will be followed at appropriate time intervals until the event has resolved or until the event has stabilized and/or reached a new baseline. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and Medical Monitor whether continued follow up of the adverse event is warranted.

An event which recurs after resolution should generally be handled as a new adverse event. However, adverse events that occur intermittently can be recorded as one adverse event.

### **5.5.2 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.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

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

The Sponsor has a list of events that they classify as "always serious" events. If an adverse event is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

If the subjects died, the report should include the cause of death as the event term (with fatal outcome) and whether or not the death was related to study drug, as well as autopsy findings if available.

Serious adverse events will be collected and reported on the adverse event CRF from the time the subject signs the ICF until 30 days following last dose of study drug.

### 5.5.3 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".

<b>Causal relationship to the study drug</b>	<b>Criteria for causal relationship</b>
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).

#### 5.5.4 Criteria for Defining the Severity of an Adverse Event

Severity of adverse events (toxicity) will be graded according to the Cancer Therapy and Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events v4.03. A copy of the CTC Version 4.03 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>).

For terms not specified within NCI-CTCAE, the following guideline should be used to determine grade:

**Table 4: Criteria for Severity of Adverse Event Terms Not Specified Within NCI-CTCAE**

Grade	Description
1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

#### 5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact the delegated CRO by telephone 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 the delegated CRO by fax immediately (within 24 hours of awareness). 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. Please email or fax the SAE Worksheet to:

Astellas Pharma Global Development – United States  
Email : [Safety-us@us.astellas.com](mailto:Safety-us@us.astellas.com)  
Fax number: (847) 317-1241

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Director/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) as necessary.

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.

You may contact the sponsor's Medical Director/Expert for any other problem related to the safety, welfare, or rights of the study participant (subject/patient).

Full details of the SAE should also be recorded on the medical records and on the 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)
- Causal relationship to the study drug

The period for SAE reporting after the last intake of the study drug should be specified.

In accordance with local regulation either sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission to their IRB/IEC / head of the study site within timelines set by regional/country regulations (by MHLW, European Clinical Trial Directives or FDA).

Expedited Safety Reports: An unexpected adverse event is one for which the nature or severity is not consistent with the current Investigator's Brochure. The Sponsor will make this assessment for all reported serious adverse events. An adverse event which is serious, related, and unexpected may be termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). The Investigator will ensure that all relevant information is provided as soon as possible to Astellas in order that the Sponsor may meet their obligations to report any SUSAR. The Sponsor will notify all Investigators responsible for ongoing clinical studies with the study drug of all serious adverse events which require submission to their IRB within timelines set by regional regulations.

### **5.5.6 Follow-up to Adverse Events**

All adverse events occurring during 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 adverse event 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 3 (Liver Safety Monitoring and Assessment) for detailed instructions on DILI follow-up responsibilities related to history of symptoms, concomitant drug use, alcohol use, and recreational drug use.

### **5.5.7 Monitoring of Common Serious Adverse Events**

Included in Appendix 4 (Common Serious Adverse Events) is a list of SAEs commonly anticipated to occur in the study population independent of drug exposure that will be monitored by the Sponsor 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 [Section 5.5.5].

### **5.5.8 Procedure in Case of Pregnancy**

If during the conduct of the clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the investigator. The investigator should report the pregnancy 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 fertility date, pregnancy result and neonatal data etc., should be included in this information.

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 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.
- “Normality” of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

The effect of enzalutamide in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Subjects receiving enzalutamide in clinical trials are advised to use a double barrier method of birth control during the course of enzalutamide treatment and for at least three months after enzalutamide is discontinued. A double-barrier method of contraception involves the use of a condom in combination with one of the following: contraceptive sponge, diaphragm, or cervical ring with spermicidal gel or foam. Subjects who have had a vasectomy at least six months prior to starting enzalutamide and those whose female sexual partner(s) are more than 55 years of age and postmenopausal for at least two years or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) should use at minimum a condom.

Study subjects will be informed that abiraterone acetate may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection (e.g., gloves). Subjects will also be informed that it is not known

whether abiraterone acetate or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The subject should use a condom and another effective method of birth control, if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with abiraterone acetate.

### **5.5.9 Supply of New Information Affecting the Conduct of the Study**

When new information becomes available, including “Dear Doctor Letters” but not limited to that, necessary for conducting the clinical study properly will lead to a protocol amendment, the sponsor should inform regulatory authorities, as well as all investigators involved in the clinical study, who will then inform the IRB/IEC of such information, and when needed, should amend the subject information.

## **5.6 Test Drug Concentration**

### **5.6.1 Optional PK Sample Collection for Enzalutamide and Metabolites (MDPC0001 and MDPC0002)**

A 2 mL pre-dose blood sample for PK will be collected into an EDTA tube at Day 29. Centrifuge the sample to yield plasma and freeze the plasma at approximately  $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The sample will be packaged and shipped per sponsor instructions.

The PK samples may be assayed for study drug, metabolites, and/or concomitant medications at the discretion of the Sponsor using a validated analytical method.

### **5.6.2 Optional PK Sample Collection for Abiraterone**

A 4 mL pre-dose blood sample for PK will be collected into an EDTA tube at Day 4 and Day 29. Centrifuge the sample within 1 hour to yield plasma and freeze the plasma at approximately  $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The sample will be packaged and shipped per sponsor instructions.

The PK samples may be assayed for study drug, metabolites, and/or concomitant medications at the discretion of the Sponsor using a validated analytical method.

## **5.7 Other Measurements, Assessments, or Methods**

### **5.7.1 Bone Marrow Aspirate and Bone Marrow Biopsy**

Bone marrow aspirate and biopsy will be collected at the Screening, Week 9, and at the End of Treatment (EOT) visits. If the End of Treatment visit falls between Week 9 and Week 13, and the Week 9 bone marrow biopsy and aspiration was performed, then an EOT bone marrow biopsy and aspiration will not be required.

### **5.7.2 Urine N-telopeptide**

A 30 mL random urine sample will be collected at Screening, Week 9, and at the End of Treatment (EOT) visits. If the End of Treatment visit falls between Week 9 and Week 13, and the Week 9 Urine N-telopeptide was collected, then an EOT collection will not be required.

### **5.7.3 Blood sample for androgen and androgen precursors levels and bone markers**

A separate blood sample will be collected for measuring serum levels of androgens (testosterone and DHT) and androgen precursors. Bone alkaline phosphatase (a marker for bone metabolism) will be measured from the same tube of the chemistry parameters (see Appendix 2).

### **5.7.4 Archival Prostate Tumor Sample**

Archival primary or metastatic prostate tumor tissue will be obtained at the Screening visit and used for molecular profiling.

### **5.7.5 Whole Blood Sample for Optional Genotype Analysis**

A whole blood sample (5 mL) for biobanking will be collected at Day 1. In the event of unusual pharmacokinetic/pharmacodynamic (PK/PD) patterns or safety findings, genotype analysis of relevant metabolism, trans-porter, pharmacodynamic, and/or safety genes will be conducted. If there is no requirement for analysis, the whole blood sample will be destroyed. Separate subject consent is required. Samples will be collected, prepared and shipped to a central laboratory per vendor instructions.

Please refer to Appendix 6 (Optional Pharmacogenomic Sub-study) for detailed instructions.

## **5.8 Total Amount of Blood**

The total amount of blood collected for each subjects will vary depending on how long the subjects stays on the study. The maximum amount of blood collected for a subject at each visit point during the treatment period is approximately 50 mL. However, if a subject is found to have laboratory abnormalities or adverse events, additional blood may be drawn for evaluation and/or monitoring. Additional diagnostic blood for routine work may also be drawn.

In addition for pharmacokinetics samples the total amount of blood collected for each subject is approximately 10 mL.

## **6 TERMINATION OF THE CLINICAL STUDY**

When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the investigator.

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor of the discontinuation and the reason for it.

For details on early discontinuation of the clinical study please refer to section 3.4.

## **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 lock. Any deviations from the SAP will be justified in the clinical study report.

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.

### **7.1 Sample Size**

A total of 60 subjects will provide sufficient data to assess the safety of the drug combination.

The sample size and power calculation are based on the change of testosterone concentration or gene expressions (i.e. AR and CYP17) before and after therapy, which can be characterized base on effect size (i.e. mean difference of testosterone concentration or gene expression divided by standard deviation). Considering subjects with baseline and Week 9 laboratory results derived from bone marrow samples, a sample of 30 subjects provides 82% power to detect a change of testosterone concentration or gene expression with an effect size of at least 0.55, using a two sided paired t-test at a 0.05 significance level. A total of 60 subjects will be accrued to obtain at least 30 evaluable patients based on the prediction that the yield of evaluable bone marrow samples with prostate cancer cells is approximately 50%.

### **7.2 Analysis Set**

#### **7.2.1 Safety Analysis Set (SAF)**

The Safety Analysis Set will consist of all subjects who received at least one dose of any drug of the study combination treatment defined in section 1.3.

The SAF will be used to report all safety and efficacy analyses.

#### **7.2.2 Biomarker Evaluable Set**

The Biomarker Evaluable Set will consist of all subjects with baseline and Week 9 laboratory results derived from bone marrow samples. The number of subjects with evaluable results may differ for each parameter.

The Biomarker Evaluable Set will be used to assess the effect of treatment on Testosterone/DHT and androgen receptor signaling in the bone marrow.

### **7.2.3 Pharmacokinetic Analysis Set (PKAS)**

The PKAS will include the subjects from the SAF population for whom at least one PK pre-dose concentration is available. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokinetics.

The PKAS will be used for all tabular and graphical summaries of the PK data.

## **7.3 Demographics and Other Baseline Characteristics**

Demographic information is to be obtained at screening and will include date of birth, race/ethnicity as described by the subject, height and weight. Continuous baseline variables will be summarized by dose using descriptive statistics (number of observations [n], mean, standard deviation [SD], minimum, median, and maximum). Categorical baseline variables will be described using absolute and relative frequencies. Data will be listed as appropriate.

## **7.4 Analysis of Efficacy**

All efficacy analyses are carried on secondary variables.

Unless otherwise specified, categorical variables will be summarized as counts and percentages, and continuous variables will be summarized using descriptive statistics, number of subjects, mean, standard deviation [SD], median, minimum and maximum.

- **Anti-tumor Activity**

Summary statistics will be produced for the SAF.

Progression-free survival is defined as the time interval from the date of starting treatment until the date of documented progression or death in absence of progression. Progression, as a composite endpoint, consisting of clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria. Kaplan-Meier curves will be presented. The median and 25th and 75th percentiles will be tabulated, including the corresponding 95%CI calculated by use of the Brook Meyer and Crowley method. The number of events and subjects at risk over time will be tabulated.

For PSA level over time, descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for baseline value and post-baseline values, as well as absolute and percent change from baseline.

The objective response according to RECIST 1.1 and bone scan results will be reported through descriptive summaries as described by PCWG2, including the proportion of patients showing RECIST 1.1 objective response (partial or complete response).

Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.

- **Androgen, androgen receptor signaling, androgen pre-cursors and other associated metabolites**

Summary statistics will be produced for the Biomarker Evaluable Set.

The effect of enzalutamide on bone and serum biomarkers (including androgen pre-cursors and androgen expression signaling, androgen pre-cursors and other associated metabolites) will be analyzed based on change from baseline to Week 9.

For each biomarker (androgen, androgen expression signaling, androgen pre-cursors and other associated metabolites), descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for baseline value, post-baseline value, change from baseline, and percent change from baseline. Graphical display using box-plot, histogram and scatter plot will be generated as appropriate.

Biomarker results collected at baseline assessment and at each post-baseline assessment, if appropriate, will be compared using paired t-test to evaluate the effect of enzalutamide. The change from baseline in each biomarker will also be summarized by PSA response category, where PSA response is a function of percentage improvement from baseline to Week 13. The correlation between each biomarker and PSA level will be estimated using Spearman's method.

## **7.5 Analysis of Safety**

All safety analyses are carried on primary variables. Summary statistics will be produced for the SAF. Unless otherwise specified, categorical variables will be summarized as counts and percentages, and continuous variables will be summarized using descriptive statistics, number of subjects, mean, standard deviation [SD], median, minimum and maximum.

Descriptive statistics will be tabulated for the Adverse Events along with their severity evaluated by the investigator based on the NCI CTCAE (version 4.03) and coded to preferred term, higher level term, and system organ class using MedDRA. The number and percentage of subjects with adverse events will be presented by MedDRA system organ class and preferred term. Also safety will be assessed through summaries of laboratory evaluations, vital signs, physical examinations, and ECGs. Safety analyses will be based on the SAF.

## **7.6 Analysis of Pharmacokinetics**

Summary statistics will be presented for each pre-dose plasma concentration of abiraterone, and enzalutamide and its metabolites MDPC0001 and MDPC0002 by scheduled visit. Summary statistics for the concentration data will include number of subjects, mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum. Further details will be specified in the SAP.

Pre-dose concentrations of abiraterone obtained on Day 4 and on Day 29 will be compared to assess the potential effect of enzalutamide on the PK of abiraterone. Further details will be specified in the SAP.

## 7.7 Protocol Deviations and Other Analyses

Drug exposure, including data on dose reduction will be summarized by descriptive statistics based on study drug accountability.

Protocol deviations as defined in Section 8.1.6 Protocol Deviations will be summarized for all randomized subjects by treatment group and total 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)

Although no formal interim analysis is planned, safety monitoring will be conducted on ongoing basis during the trial conduct.

If the probability of Grade 4 due to treatment toxicity is likely to be greater than 10%, based on the toxicity information in a 3-month treatment time interval, the trial will be put on hold and the data will be reviewed. The trial can be stopped early if the risk of severe toxicity (defined as any grade 4 toxicity that is possibly attributed to the study agents) has been confirmed. Formally, denoting the grade 4 toxicity probability by  $p_{TOX}$  and assuming this follows a  $\text{beta}(1, 1)$  prior distribution, the trial will be held if  $\text{Prob}\{p_{TOX} > 0.10 \mid \text{data}\} > 0.95$ . Following this rule, starting with the 15<sup>th</sup> subjects, the trial will be held if  $[\# \text{ subjects with TOX due to treatment}] / [\# \text{ subjects evaluated}]$  is greater than or equal to 4/15, 6/30, 8/45 or 10/60. The operating characteristics of this design based on 10,000 simulations per case are summarized in the following table.

True Prob(tox)	Pr(stop)	Mean # Pts
0.02	<0.001	59.9
0.05	0.01	59.7
0.10	0.13	55.8
0.20	0.75	34.3
0.30	0.98	20.7

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

Imputations for missing data, if applicable, will be addressed in the SAP.

## **8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS**

### **8.1 Procedure for Clinical Study Quality Control**

#### **8.1.1 Data Collection**

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.

The investigator or designee will enter data collected using an Electronic Data Capture (EDC) system.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

For screening failures, the minimum demographic data (sex, birth date or age, race and informed consent date) and reason for screening failure will be collected in screening failure log (SFL), if applicable.

#### **8.1.2 Specification of Source Documents**

Source data must be available at the site to document the existence of the study subjects and 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 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 (if applicable)
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug detail
- Reason for premature discontinuation (if applicable)
- Randomization number (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 Department 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. CRF completion and correction process will be referenced in the CRF instructions. Coding of medical terms will be performed using MedDRA.

The study database will be soft-locked when all data that are specified in the study protocol to be collected have been received and cleaned according to applicable SOPs. It will be hard-locked when a data review meeting has been held, and all data related decisions have been made and reflected in the database.

#### **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)**

The investigator shall make accurate and adequate written progress reports to the 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-sponsored studies, or for APEB/APEL-sponsored studies within one year after last patient out (LPO) or termination of the study.

### **8.2.2 Ethical Conduct of the Study**

The investigator(s) and all parties involved in this study should conduct the study in adherence to GCP, ICH Guidelines and the applicable laws and regulations.

### **8.2.3 Informed Consent of Subjects**

#### **8.2.3.1 Subject Information and Consent**

Prior to execution of the clinical study, the investigator should prepare the written informed consent form and other written information in collaboration with the sponsor and revise the information whenever necessary. The written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

- The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will.

- The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the written information, or write down his/her name, and date the form.
- Informed consent must be obtained by the time that the first observations / examinations of the pre-investigational period are performed. Guardian consent should be obtained from the proxy consentor, before start of pre-investigational period.
- The investigator or other responsible personnel must give a copy of the signed consent form to the subject and store the original appropriately in accordance with the rules at the study site concerned.
- The investigator or other responsible personnel should note the following when obtaining consent from subjects:
  - No subject may be subjected to undue influence, such as compulsory enrollment into a study.
  - The language and expressions used in the written information should be as plain and understandable as possible. Subjects should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor 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/sub-investigator 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 participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented in the subject's medical records, and it should be confirmed whether the subject is willing to remain in the study or not.
2. If the investigator recognizes the necessity to revise the written information in the terms and conditions applicable to paragraph 1, the written information should be revised immediately based upon the newly available information, and be re-approved by the IRB/IEC.
3. The investigator/sub-investigator should obtain written informed consent to continue participation with the revised written information defined in paragraph 2, even if subjects are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the informed consent form, or write down his/her name and date the form. The investigator or other

responsible personnel should give a copy of the signed informed consent form to the subject who had given consent with the written information and store the original appropriately as done for the previous informed consent.

#### **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).

For US sites, the HIPAA Privacy Rule provides federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in sponsored clinical trials. "Authorization" is required from each research subject, i.e. specific permission granted by an individual to a covered entity for the use or disclosure of an individual's PHI. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined into the Informed Consent document (approved by the IRB/IEC) or it may be a separate document (approved by the IRB/IEC or designed PB) or provided by the investigator or sponsor (without IRB/IEC or PB approval). It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

### **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.

The study will be considered for publication or presentation at (scientific) symposia and congresses. The investigator will be entitled to publish or disclose the data generated at their respective study site only after submission to the sponsor all transcripts, texts of presentations, and abstracts related to the study at least 90 days prior to the intended submission for publication or any other disclosure for API and/or APEB/APEL-sponsored studies or 30 days prior for APGD-sponsored studies. This is necessary to confirm whether any inventive knowledge should be protected by a patent or not and to prepare and file a patent application accordingly. In addition this is in no way intended to restrict publication of facts or opinions formulated by the investigator. The sponsor will inform the investigator in writing of any objection or question arising within 30 days of receipt of the proposed publication material.

### **8.3.2 Documents and Records Related to the Clinical Study**

The sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, as applicable)
- Investigator's Brochure (and amendments, as applicable)
- CRFs and SAE Report Worksheet
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54
- Signed Investigator's Statement in this protocol
- Executed Research Agreement
- Signed and dated FDA form 1572
- Copy of the approved ICF and separate authorization form, if appropriate.
- Independent Ethics Committee/IRB approval of the protocol, protocol amendments (if applicable) and ICF (and separate authorization form, if appropriate), stating clearly the sponsor's name, study number and study drug, including a membership list with names and qualifications.
- Current Curricula Vitae of all investigators (signed and dated)
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)
- Medical/Laboratory/Technical procedures/tests certifications or accreditations or established quality control or other validation, where required.

At the end of the study, the sponsor is responsible for the collection of:

- Unused CRFs and other study documentation,
- Unused study drug

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). It is recommended, however, that records be retained for at least five years in the event follow-up is necessary to help determine any potential hazards to subjects who took part in the study. The sponsor will notify the site/investigator if the NDA is approved or if the IND 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 CRFs supplied for each subject.

Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

The investigator and sponsor will mutually agree upon the storage format for the retention of electronic data.

### **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 is 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 (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to inspect/audit the clinical study at any or all investigational sites. The auditor is independent from the clinical monitoring and project management team at the Sponsor. 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 Data and Safety Monitoring Board (DSMB) | Data Monitoring Committee (DMC)**

Not applicable.

### **10.2 Other Evaluation Committee(s)**

Not applicable.

### **10.3 Other Study Organization**

Not applicable.

## 11 REFERENCES

- Abiraterone acetate, ZYTIGA (Package Insert). Horsham, PA: Centocor Ortho Biotech Inc.; April 2011.
- 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; 346, 21.
- Duc I, Bonnet P, Duranti V, Cardinali S, Rivière A, De Giovanni A, et al. In vitro and in vivo models for the evaluation of potent inhibitors of male rat 17 $\alpha$ -hydroxylase/C17,20 lyase. *J Steroid Biochem Mol Biol* 2003; 84(5):537-42.
- Efstathiou E, Titus M, Tsavachidou D, Vassiliki Tzelepi, Wen S, Hoang A, et al. Effects of Abiraterone Acetate on Androgen Signaling in Castrate-Resistant Prostate Cancer in Bone. *J Clin Oncol* 2011.
- Efstathiou E, Logthetis CJ. A New Therapy Paradigm for Prostate Cancer Founded on Clinical Observations. *Clin Cancer Res* 2010; 16(4):1100-1107.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228-247.
- Foster WR, Car BD, Shi H et al. Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. *Prostate* 2011; 71(5):480-488.
- Haidar S, Ehmer PB, Barassin S, Batzl-Hartmann C, Hartmann RW . Effects of novel 17 $\alpha$ -hydroxylase/ C17, 20 lyase (P45017 $\alpha$ , CYP 17) inhibitors on androgen biosynthesis in vitro and in vivo. *J Steroid Biochem Mol Biol* 2003; 84(5):555-62.
- Ideyama Y, Kudoh M, Tanimoto K, Susaki Y, Nanya T, Nakahara T, et al. Novel nonsteroidal inhibitor of cytochrome P45017 $\alpha$  (17 $\alpha$ -hydroxylase/C17-20 lyase), YM116, decreased prostatic weights by reducing serum concentrations of testosterone and adrenal androgens in rats. *Prostate* 1998; 37(1):10-8.
- Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649-655.
- Prednisolone 5 mg (Package Insert). Devon, UK: Actavis UK Ltd.; July 2011.
- Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, et al. Antitumor activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. *Lancet* 2010; 375: 1437–46.
- Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; 26:1148-5.

### *Company Reports*

Investigator's Brochure. MDV3100 for the treatment of cancer. 5th edition. Medivation, Inc., 23 March 2012.

## 12 APPENDICES

### 12.1 Appendix 1: List of Excluded Concomitant Medication

Prohibited drugs		
cyproterone acetate	finasteride	testosterone
flutamide	dustasteride	dehydroepiandrosterone
nilutamide	estrogens	ketoconazole
bicalutamide	megestrol	saw Palmetto
	medroxyprogesterone	
	DES	
	cyproterone	
	spirinolactone	

Note that this drug list is not all inclusive, please contact the Medical Monitor with questions.  
Please reference section 5.1.3.

## 12.2 Appendix 2: Laboratory Tests

Test	Visit	Collecting Tube	Parameters to be Analyzed
Hematology	All visits, except Day 4	EDTA tube	Hemoglobin Hematocrit Erythrocytes (RBC) Leukocytes (WBC) Differential WBC Platelets
PT/PTT & INR	All visits, except Day 4	Citrate tube	PT/PTT & INR
Chemistry	All visits, except Day 4	Serum tube	Sodium Potassium Calcium Chloride Magnesium Phosphorus Glucose Creatinine Alkaline phosphatase LDH AST ALT Direct bilirubin Total bilirubin Total protein Albumin CO <sub>2</sub> BUN Bone alkaline phosphatase
PSA	All visits, except for Day 4	Serum tube	PSA
Urine N-telopeptide	Screening, Week 9 and at the end of treatment (ET). If the ET visit falls between Week 9 and Week 13, and the Week 9 Urine N-telopeptide was collected, then an ET collection will not be required.	30 mL random urine sample	Urine N-telopeptide
Androgen, androgen expression signaling, androgen pre-cursors and other associated metabolites	Screening, Week 9 and at the end of treatment (ET). If the ET visit falls between Week 9 and Week 13, and the Week 9 sample was collected, then an ET collection will not be required.	Serum tube (red top, no additive), Sodium Heparin tube	androgen, androgen expression signaling, androgen pre-cursors and other associated metabolites
Blood sample for genotype analysis	Day 1	K3EDTA tube	Genotype analysis
Blood sample for PK analysis	Day 4 and Week 5	K2EDTA tube	PK analysis

### 12.3 Appendix 3: Liver Safety Monitoring and Assessment

If laboratory testing for a subject enrolled in study and receiving study drug reveals an increase of serum aminotransferases (AT) to  $> 3X$  ULN, or bilirubin  $> 2X$  ULN, at least all four of the usual serum hepatic measures (ALT, AST, ALP, and TBL) should be repeated. 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 marked 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 marked where ULN:

<b>Moderate</b>	<b>ALT or AST</b> $> 3 \text{ x ULN}$	or	<b>Total Bilirubin</b> $> 2 \text{ x ULN}$
<b>Marked</b>	$> 3 \text{ x ULN}$	and	$> 2 \text{ x ULN}$

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

- ALT or AST  $> 8X$  ULN
- ALT or AST  $> 5X$  ULN for more than 2 weeks
- ALT or AST  $> 3X$  ULN and INR  $> 1.5$
- ALT or AST  $> 3X$  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 marked abnormalities and require additional monitoring and follow-up.

#### Follow-up Procedures

Confirmed moderate and marked 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 an 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.

Marked hepatic liver function abnormalities, in the absence of another etiology, may be considered an important medical event and reported as a Serious Adverse Event (SAE). The sponsor should be contacted and informed of all subjects for whom marked 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 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 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:
  1. acute viral hepatitis (A,B, C, D, E or other infectious agents).
  2. ultrasound or other imaging to assess biliary tract disease
  3. 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 LFTs, such as viral hepatitis, pre-existing or acute liver disease 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 must occur if:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and (TBL > 2X ULN or INR > 1.5)

Discontinuation of treatment should be considered if:

ALT or AST > 3X 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 marked hepatic laboratory tests is not possible, drug should be discontinued.

### **Reference**

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

## 12.4 Appendix 4: 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 5.5.2 Definition of Serious Adverse Event (SAE).** 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 **5.5.5 Reporting of Serious Adverse Events (SAE).**

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

## 12.5 Appendix 5: Soft Tissue Assessment (RECIST 1.1)

**Table 1 – Time point response: patients with target (+/- non-target) disease.**

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

**Table 2 – Time point response: patients with non-target disease only.**

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD <sup>a</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.  
 a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

## **12.6 Appendix 6: Optional Pharmacogenomic Sub-study**

### **INTRODUCTION**

Pharmacogenomics research aims to provide medical information regarding how variations in a subject's gene function and/or expression based on their genetic polymorphism may impact what treatment options are best suited for that subject. Through investigation of pharmacogenomics via such technologies as gene sequencing, statistical genetics and gene expression analysis, the relationship between gene profiles and a drug's efficacy or toxicity may be better understood.

Because many diseases may develop as a result of one or more genetic mutations, pharmacogenomics research may identify the genes that are involved in determining whether a subject may or may not respond to a drug.

### **STUDY OBJECTIVES**

The pharmacogenomic research that will be conducted in the future with acquired blood samples is exploratory. The objective of this research is to comprehensively analyze:

- Suspected disease-related genes;
- Genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues, to be identified in a precautionary/retrospective setting.

By analyzing differing genetic polymorphisms, it may be possible to predict genetic effect on an individual subject's response to enzalutamide.

### **STUDY POPULATION**

Subjects who have consented to participate in the 9785-CL-0011 study may also participate in this optional sub-study. As part of this sub-study, subjects must provide written consent prior to providing any blood samples that will be used at a later time for the genetic analysis.

### **SITE SAMPLE COLLECTION**

Subjects who consent to participate in this sub-study will provide one 5 mL sample of whole blood on visit Day 1 per vendor preparation instructions. Each sample will be identified with a unique subject identifier. Sample will be shipped to a Sponsor designated central laboratory.

Samples will be anonymized prior to analysis.

### **CENTRAL LABORATORY AND PHARMACOGENOMIC RESEARCH LABORATORY PROCESSING AND STORAGE / SAMPLE ANONYMIZATION**

Upon receipt, the central laboratory will identify each sample by subject number and initials utilizing the shipment documents accompanying each sample. Samples will be stored frozen until prompted by Astellas. When prompted, the central laboratory will ship the samples to a separate laboratory for prolonged storage.

When samples are shipped from the central laboratory to the prolonged storage laboratory, they will be identified solely by subject number. Once received at the prolonged storage laboratory,

the samples will be assigned a unique sample code and stored frozen. A table linking the subject number with newly-assigned sample code will be provided to the Astellas' code administrator.

Once the table is provided to Astellas and receipt acknowledged, the link between the subject number and sample code held at the prolonged storage laboratory will be broken.

### **ASSOCIATING CLINICAL DATA WITH SAMPLE CODES**

Before the pharmacogenomics research begins, the Astellas' code administrator will provide Astellas with the linkage table. Astellas will associate clinical data related to finding with each subject number and corresponding sample code. The clinical data with the corresponding sample codes (without associated subject numbers) will be provided to the Astellas Research Laboratory, who will be responsible for the genetic analysis. After which, the original linkage table and any copies containing the subject number and sample code provided to Astellas will be destroyed by Astellas. No pharmacogenomics data will be traceable back to the original subject number.

### **PHARMACOGENOMIC ANALYSIS**

The detailed content of the pharmacogenomic analysis has not been determined. Astellas will initiate the pharmacogenomic research after the targeted genes have been identified. In the event of unusual PK/PD patterns or safety findings, genotype analysis or relevant metabolism, transporter, pharmacodynamic and/or safety genes will be conducted. If there is no requirement for analysis, the whole blood sample will be destroyed.

### **DISPOSAL OF PHARMACOGENOMIC SAMPLES/DATA**

All collected pharmacogenomic samples will be maintained for a period of up to 15 years following database hardlock. In addition, the Astellas Research Laboratory will retain all raw data and records pertaining to the study for the period of at least 15 years or unless otherwise notified by the Sponsor. At the conclusion of the retention period, Astellas will instruct the central or pharmacogenomics research laboratory to destroy all remaining samples, data and records.

### **SUBJECT INFORMED CONSENT**

This pharmacogenomic sub-study is independent of the clinical study. Each subject participating in the clinical study may choose whether or not to consent to provide pharmacogenomic blood samples. Refusal to consent to the pharmacogenomic research or withdrawal of pharmacogenomic consent will not result in any penalty in regards to participation in the clinical study or further treatment received.

Prior to providing any blood samples as part of the pharmacogenomic sub-study, separate written informed consent must be obtained. A subject has the irrevocable right to withdraw consent from solely the pharmacogenomic research at any point during or after completion of the clinical study. Once pharmacogenomic consent is withdrawn, the subject's samples will be

destroyed. However, any genetic analysis data which had been obtained from the subject's analyzed samples at the time of withdrawal may be used after withdrawal.

### **INFORMATION DISCLOSURE TO THE SUBJECTS**

The exploratory pharmacogenomics research will be conducted following the conclusion of the clinical study. The results of the genetic analysis will not be provided to any Investigators or subjects nor can the results of the genetic analysis be requested at a later date. Any information that is obtained from the pharmacogenomic research in relation to the contents of the pharmacogenomic research protocol, results of the correlation between genetic data and subject response or toxicity, etc. belong to Astellas.

### **SITE PARTICIPATION IN THE PHARMACOGENOMICS SUB-STUDY**

Participation in the pharmacogenomic sub-study at a given site is contingent on the site's Institutional Review Board/Ethics Committee/Regulatory Authority approval and on specific local regulations when applicable. If a site's IRB/EC/Regulatory Authority does not approve the sampling for the pharmacogenomic research, this section will not be applicable to that site.

## 13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 2

### I. The purpose of this amendment is:

<b>Substantial Changes</b>
<b>1. Secondary Variables</b>
DESCRIPTION OF CHANGE:
Re-organized the presentation of the secondary variables into groups and added variables that will that will be included in the analysis.
RATIONALE:
To provide clarification on the secondary variables in the analysis.
<b>2. Statistical Methods</b>
DESCRIPTION OF CHANGE:
Reclassified the testosterone and DHT as androgens and added androgen pre-cursors and other associated metabolites to the efficacy analysis.
RATIONALE:
To provide details on the efficacy analysis and align with the changes in the secondary variables.
<b>3. Description of the Study Drug</b>
DESCRIPTION OF CHANGE:
Amended the description of the study drug to include the capsules that are marked with "ENZ".
RATIONALE:
To update the description of the study drug.

<b>Non-Substantial Changes</b>
<b>1. Update Contact Details of Key Sponsor's Personnel</b>
DESCRIPTION OF CHANGE:
Contact information of the Clinical Research Contact and Medical Monitor are updated
RATIONALE:
To update Sponsor personnel assigned to the study and to update Medical Monitor's contact information.

<b>2. Update Planned Study Period</b>
DESCRIPTION OF CHANGE:
The planned study period used projected quarter and is being modified to use the actual study start date and a planned completion date.
RATIONALE:
To update the study period to reflect current estimates.
<b>3. Add Footnote to Table 2</b>
DESCRIPTION OF CHANGE:
Added a footnote to the table instructing the reader to refer to the Investigator's Brochure for up to date information.
RATIONALE:
To provide a reference to the Investigator's Brochure for the current safety information.
<b>4. Update Study Design</b>
DESCRIPTION OF CHANGE:
Removed the statement that subjects with only PSA progression will not be removed from the study
RATIONALE:
To allow subjects with only PSA progression to discontinue from the study if it is in their best interest.
<b>5. Update Exploratory Variables</b>
DESCRIPTION OF CHANGE:
Added a statement that other variables that have not been identified yet may be explored during the study.
RATIONALE:
To provide flexibility in the options for performing exploratory analyses.
<b>6. Update Discontinuation Criteria</b>
DESCRIPTION OF CHANGE:
Removed the word "either" from the first discontinuation criteria.
RATIONALE:
To correct the grammatical error.

<b>7. Change in Adverse Event Reporting</b>
DESCRIPTION OF CHANGE:
The statement on the adverse event reporting period was modified to including the reporting of adverse events for 30 days post last dose of study drug. Duplicate and incorrectly placed information was also deleted or moved to an appropriate section.
RATIONALE:
To clarify the adverse event reporting period.
<b>8. Change to Adverse Events of Possible Hepatic Origin</b>
DESCRIPTION OF CHANGE:
Moved the reference to Appendix 12.3, Liver Safety Monitoring and Assessment, to this section of the protocol.
RATIONALE:
To place the reference in a more appropriate location
<b>9. Definition of Serious Adverse Events</b>
DESCRIPTION OF CHANGE:
Clarified the reporting period of SAEs by removing the term “termination of the study” and replacing it with a more specific description.
RATIONALE:
To clarify the SAE reporting period.
<b>10. Procedure in Case of Pregnancy</b>
DESCRIPTION OF CHANGE:
Removed the incorrect reference that the pregnancy should be reported within 30 days of discontinuing study drug.
RATIONALE:
To correct the reporting period for a pregnancy.
<b>11. Blood Sample for Androgen Levels</b>
DESCRIPTION OF CHANGE:
Added a reference to testing the blood for androgen precursors.
RATIONALE:
To align the text with the new secondary variables.

## 12. Analysis of Efficacy

### DESCRIPTION OF CHANGE:

The text was revised to match the changes in the secondary variables by adding androgen, androgen precursors, and associated metabolites. References to testosterone and DHT was removed since they are covered under the term androgen. Other small changes were made to fix grammatical error

### RATIONALE:

To align the analysis with the new secondary variable and to correct grammatical errors

## 13. Laboratory Tests

### DESCRIPTION OF CHANGE:

Replaced references to testosterone and DHT with Androgen, androgen expression signaling, androgen pre-cursors and other associated metabolites.

### RATIONALE:

To align the laboratory test descriptions with the new secondary variables.

## 14. Common Adverse Events

### DESCRIPTION OF CHANGE:

Added text based on standards to further describe the process for handling common serious adverse events

### RATIONALE:

To update the text to reflect standard language.

## 15. Other Minor Administrative-type Corrections

### DESCRIPTION OF CHANGE:

Include minor administrative corrections, e.g., spelling, grammar, consistency.

### RATIONALE:

To ensure accuracy and clear understanding of protocol content.

## II Amendment Summary of Changes:

### II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Page 9

WAS:

Clinical Research Contact:	[REDACTED] BS Astellas Pharma Global Development Office: [REDACTED] Email: [REDACTED]
Medical Monitor:	[REDACTED] MD Astellas Pharma Global Development Office: [REDACTED] Cell: [REDACTED] Fax: [REDACTED] Email: [REDACTED]

IS AMENDED TO:

Clinical Research Contact:	[REDACTED] Astellas Pharma Global Development Office: [REDACTED] Email: [REDACTED] [REDACTED] <del>Astellas Pharma Global Development</del> Office: [REDACTED] Email: [REDACTED]
Medical Monitor:	[REDACTED] MD Astellas Pharma Global Development Office: [REDACTED] Cell: [REDACTED] Fax: [REDACTED] Email: [REDACTED]

### IV. SYNOPSIS, Planned Study Period

Page 13

WAS:

From 2Q2012 to 4Q2013

IS AMENDED TO:
From <b>10 July 2012</b> Q2012 to <b>17 June 2014</b> Q2013

**IV. SYNOPSIS, Secondary Variables**

*Page 19*

WAS:

- Testosterone concentration in bone marrow aspirate and blood
- DHT concentration in bone marrow aspirate and blood
- Expression and localization of AR
- Splice variants
- CYP17 expression
- PSA levels
- Progression Free Survival (PFS)
- Objective response according to RECIST 1.1
- Bone scan results
- Markers of bone metabolism (bone specific alkaline phosphatase and urine N-telopeptides)

IS AMENDED TO:

- **Androgen receptor signaling**
  - **Expression and localization of AR**
  - **CYP17 expression**
  - **Splice variants**
- **Pathways linked with non-classical AR signaling & Bone development**
  - Androgens**
    - **Testosterone concentration in bone marrow aspirate and blood**
    - **DHT concentration in bone marrow aspirate and blood**
- **Androgen pre-cursors and other associated metabolites. For example:**
  - **Cortisol**
  - **Androstenedione**
  - **Pregnenolone**
  - **Progesterone**
- PSA levels
- Progression-free Survival (PFS)
- Objective response according to RECIST 1.1
- Bone scan results
- Markers of bone metabolism (bone specific alkaline phosphatase and urine N-telopeptides)
- ~~Testosterone concentration in bone marrow aspirate and blood~~
- ~~DHT concentration in bone marrow aspirate and blood~~
- ~~Expression and localization of AR~~
- ~~Splice variants~~
- ~~CYP17 expression~~

#### IV. SYNOPSIS, Statistical Methods

Page 20

WAS:

Efficacy analysis will be conducted on all enrolled subjects who received any amount of study drug. Progression free survival (PFS) is defined as the time interval from the date of starting treatment until the date of documented progression or death in absence of progression. PFS will be reported using Kaplan-Meier methods, including the median and its 95% CI. PSA and PSA change from baseline over time will be descriptively summarized.

Proportion of patients showing RECIST 1.1 objective response (partial or complete response) will be descriptively summarized. Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.

Proportion of patients showing RECIST 1.1 objective response (partial or complete response) will be descriptively summarized. Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.

- Testosterone/DHT and Androgen Receptor Signaling

Considering subjects with baseline and Week 9 laboratory results derived from bone marrow samples, testosterone, DHT, and androgen receptor signaling will be summarized by descriptive statistics and a paired t-test at a 0.05 level of significance will be performed on the change from baseline at Week 9.

IS AMENDED TO:

Efficacy analysis will be conducted on all enrolled subjects who received any amount of study drug. Progression-free survival (PFS) is defined as the time interval from the date of starting treatment until the date of documented progression or death in absence of progression. PFS will be reported using Kaplan-Meier methods, including the median and its 95% CI. PSA and PSA change from baseline over time will be descriptively summarized.

Proportion of patients showing RECIST 1.1 objective response (partial or complete response) will be descriptively summarized. Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.

Proportion of patients showing RECIST 1.1 objective response (partial or complete response) will be descriptively summarized. Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.

- **Androgens, ~~Testosterone/DHT~~ and Androgen Receptor Signaling, Androgen precursors and other associated metabolites**

Considering subjects with baseline and Week 9 laboratory results derived from bone marrow samples, ~~testosterone, DHT~~ **androgens, and** androgen receptor signaling, **androgen precursors and other associated metabolites** will be summarized by descriptive statistics and, **if appropriate**, a paired t-test at a 0.05 level of significance will be performed on the change from baseline at Week 9.

### 1.3.1 Enzalutamide

Page 29

WAS:

Table 2: Summary of Study Drug Exposure, Adverse Events, and Deaths (CRPC2)

Treated (Safety Population)	enzalutamide (n = 800)	Placebo (n = 399)
Discontinued Treatment	569 (71.1%)	380 (95.2%)
Treatment Duration (median months)	8.3	3.0
Patients with $\geq 1$ Treatment Emergent Adverse Event	785 (98.1%)	390 (97.7%)
Patients with $\geq 1$ Treatment Emergent Adverse Event (Grade 3 or Higher)	362 (45.3%)	212 (53.1%)
Patients with $\geq 1$ Serious Treatment Emergent Adverse Event	268 (33.5%)	154 (38.6%)
Patients with an Adverse Event Leading to Death	23 (2.9%)	14 (3.5%)
Patients with Adverse Events Leading to Study Drug Discontinuation	61 (7.6%)	39 (9.8%)
SUSARs (all in unique patients)	10	6
Deaths	308 (38.5%)	212 (53.1%)

IS AMENDED TO:

Table 2: Summary of Study Drug Exposure, Adverse Events, and Deaths (CRPC2)\*

Treated (Safety Population)	enzalutamide (n = 800)	Placebo (n = 399)
Discontinued Treatment	569 (71.1%)	380 (95.2%)
Treatment Duration (median months)	8.3	3.0
Patients with $\geq 1$ Treatment Emergent Adverse Event	785 (98.1%)	390 (97.7%)
Patients with $\geq 1$ Treatment Emergent Adverse Event (Grade 3 or Higher)	362 (45.3%)	212 (53.1%)
Patients with $\geq 1$ Serious Treatment Emergent Adverse Event	268 (33.5%)	154 (38.6%)
Patients with an Adverse Event Leading to Death	23 (2.9%)	14 (3.5%)
Patients with Adverse Events Leading to Study Drug Discontinuation	61 (7.6%)	39 (9.8%)
SUSARs (all in unique patients)	10	6
Deaths	308 (38.5%)	212 (53.1%)

**\*For up to date study information refer to the current edition of the Investigator's Brochure**

### 1.3.2 Abiraterone Acetate

Page 31, Paragraph 4

WAS:

Hepatotoxicity: Increases in liver enzymes have lead to drug interruption, dose modification and/or discontinuation. Liver function should be monitored and modify, interrupt, or discontinue abiraterone acetate dosing as recommended. Study subjects will have liver function tests (including alkaline phosphatase, AST, ALT, direct and total bilirubin, and LDH) every 2 weeks for the first 12 weeks of treatment.

IS AMENDED TO:

Hepatotoxicity: Increases in liver enzymes have ~~lead~~**led** to drug interruption, dose modification and/or discontinuation. Liver function should be monitored and modify, interrupt, or discontinue abiraterone acetate dosing as recommended. Study subjects will have liver function tests (including alkaline phosphatase, AST, ALT, direct and total bilirubin, and LDH) every 2 weeks for the first 12 weeks of treatment.

### 2.2.1 Study Design

Page 34

WAS:

This is an open label study to determine the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone in CRPC subjects with bone metastases by clinical evaluations at protocol specified intervals. The study will also determine the modulation of androgen receptor (AR) signaling in bone marrow biopsy and androgen levels as measured by testosterone concentration in bone marrow aspirate and blood by Liquid Chromatography Mass spectrometry, expression of AR and its subcellular localization by immunohistochemistry (IHC), presence of known and assessable splice variants and CYP17 expression in epithelial and host compartment of the cancer by IHC. Tumor tissue will be collected to determine AR signaling and candidate pathways that may be part of a signaling network implicated in therapy resistance. The baseline determination and subsequent assessment of AR signaling will be correlated with progression free survival (radiographic progression, PSA progression, and/or clinical deterioration).

Approximately 60 subjects will receive enzalutamide 160 mg daily, abiraterone acetate 1,000 mg daily, and prednisone 5 mg twice daily to be taken orally.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs).

The occurrence of an adverse event or toxicity, where continued administration of study drug is deemed to be not in the subject's best interest by the investigator and/or the sponsor, will result in the removal of the subject from therapy.

For the study duration, all subjects will maintain androgen deprivation with an GnRH agonist or antagonist or orchiectomy.

**IS AMENDED TO:**

This is an open label study to determine the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone in CRPC subjects with bone metastases by clinical evaluations at protocol specified intervals. The study will also determine the modulation of androgen receptor (AR) signaling in bone marrow biopsy and androgen levels as measured by testosterone concentration in bone marrow aspirate and blood by Liquid Chromatography Mass spectrometry, expression of AR and its subcellular localization by immunohistochemistry (IHC), presence of known and assessable splice variants and CYP17 expression in epithelial and host compartment of the cancer by IHC. Tumor tissue will be collected to determine AR signaling and candidate pathways that may be part of a signaling network implicated in therapy resistance. The baseline determination and subsequent assessment of AR signaling will be correlated with progression-free survival (radiographic progression, PSA progression, and/or clinical deterioration).

Approximately 60 subjects will receive enzalutamide 160 mg daily, abiraterone acetate 1,000 mg daily, and prednisone 5 mg twice daily to be taken orally.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs).

The occurrence of an adverse event or toxicity, where continued administration of study drug is deemed to be not in the subject's best interest by the investigator and/or the sponsor, will result in the removal of the subject from therapy.

For the study duration, all subjects will maintain androgen deprivation with an GnRH agonist or antagonist or orchiectomy.

**2.3.2 Secondary Variables**

Page 36

WAS:

- Testosterone concentration in bone marrow aspirate and blood
- DHT concentration in bone marrow aspirate and blood
- Expression and localization of AR
- Splice variants
- CYP17 expression
- PSA levels
- Progression Free Survival (PFS)
- Objective response according to RECIST 1.1
- Bone scan results
- Markers of bone metabolism (bone specific alkaline phosphatase and urine N-telopep`tides)

**IS AMENDED TO:**

- **Androgen receptor signaling**
  - **Expression and localization of AR**
  - **CYP17 expression**
  - **Splice variants**

- **Pathways linked with non-classical AR signaling & Bone development**
- **Androgens**
  - **Testosterone concentration in bone marrow aspirate and blood**
  - **DHT concentration in bone marrow aspirate and blood**
- **Androgen pre-cursors and other associated metabolites. For example:**
  - **Cortisol**
  - **Androstenedione**
  - **Pregnenolone**
  - **Progesterone**
- PSA levels
- Progression-free Survival (PFS)
- Objective response according to RECIST 1.1
- Bone scan results
- Markers of bone metabolism (bone specific alkaline phosphatase and urine N-telopeptides)
- ~~Testosterone concentration in bone marrow aspirate and blood~~
- ~~DHT concentration in bone marrow aspirate and blood~~
- ~~Expression and localization of AR~~
- ~~Splice variants~~
- ~~CYP17 expression~~

### 2.3.3 Exploratory Variables

Page 36

WAS:

Pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional).

IS AMENDED TO:

Pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional). **Other variables may be explored.**

### 3.4 Discontinuation Criteria for Individual Subjects

Page 39

WAS:

Subject develops disease progression defined as a composite endpoint, consisting of either clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria. Subject with PSA progression alone will not be withdrawn from the study.

IS AMENDED TO:

Subject develops disease progression defined as a composite endpoint, consisting of ~~either~~ clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria. Subject with PSA progression alone will not be withdrawn from the study.

#### 4.1.1 Enzalutamide

Page 40, Paragraph 2

WAS:

Enzalutamide capsules are white to off-white oblong capsules, printed with “MDV” in black ink. The soft gelatin capsules are filled with a clear, yellowish solution which contains the two antioxidants, butylated hydroxyanisole, and butylated hydroxytoluene , and enzalutamide active ingredient (40 mg), all dissolved in the non-ionic surfactant, Labrasol® (Caprylocaproyl Polyoxylglycerides). Enzalutamide capsules are provided in white, opaque, high-density polyethylene (HDPE) bottles with child-resistant induction seal closure.

IS AMENDED TO:

Enzalutamide capsules are white to off-white oblong capsules, printed with **either** “MDV” **or** “ENZ” in black ink. The soft gelatin capsules are filled with a clear, yellowish solution which contains the two antioxidants, butylated hydroxyanisole, and butylated hydroxytoluene , and enzalutamide active ingredient (40 mg), all dissolved in the non-ionic surfactant, Labrasol® (Caprylocaproyl Polyoxylglycerides). Enzalutamide capsules are provided in white, opaque, high-density polyethylene (HDPE) bottles with child-resistant induction seal closure.

#### 5.1.2 Reduction in Dose or Discontinuation of the Study Drugs

Page 44, Paragraph 5

WAS:

Subjects should be able to take all three study drugs (enzalutamide, abiraterone acetate and prednisone) to participate in the study. Interruptions of one of these drugs is allowed as per instruction above. Permanent discontinuation of one of the drugs, while continuing the two other drugs, is not allowed.

IS AMENDED TO:

Subjects should be able to take all three study drugs (enzalutamide, abiraterone acetate and prednisone) to participate in the study. **An interruption** ~~Interruptions~~ of one of these drugs is allowed as per instruction above. Permanent discontinuation of one of the drugs, while continuing the two other drugs, is not allowed.

#### 5.4.1 Adverse Events

Page 48

WAS:

Adverse events will be assessed regularly as per schedule of assessments.  
Adverse event collection will begin at the time the informed consent form is signed and continue through to the last assessments.  
Baseline conditions that worsen during the study will be recorded as adverse events.  
Adverse events beginning after subjects have completed end of study procedures will be

<p>recorded up to 30 days following last dose of study drug.</p> <p>Adverse events ongoing at the final visit will be followed up for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes.</p> <p>Please refer to Appendix 3 (Liver Safety Monitoring and Assessment) for DILI adverse event assessment.</p>
<p>IS AMENDED TO:</p> <p>Adverse events will be assessed regularly as per schedule of assessments.</p> <p>Adverse event collection will begin at the time the informed consent form is signed and <b>continue up to 30 days following last dose of study drug</b> <del>continue through to the last assessments.</del></p> <p>Baseline conditions that worsen during the study will be recorded as adverse events. <del>Adverse events beginning after subjects have completed end of study procedures will be recorded up to 30 days following last dose of study drug.</del></p> <p>Adverse events ongoing at the final visit will be followed up for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes.</p> <p><del>Please refer to Appendix 3 (Liver Safety Monitoring and Assessment) for DILI adverse event assessment.</del></p>

<p><b>5.4.4.1 Adverse Events of Possible Hepatic Origin</b></p>
<p><u>Page 49</u></p>
<p>WAS:</p> <p>Subjects with AE's of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.</p>
<p>IS AMENDED TO:</p> <p>Subjects with AE's of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored. <b>See Appendix 12.3 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment.</b></p>

<p><b>5.5.2 Definition of Serious Adverse Events (SAEs)</b></p>
<p><u>Page 53, Paragraph 7</u></p>
<p>WAS:</p> <p>Serious adverse events will be collected and reported on the adverse event CRF from the time the subject signs the ICF until termination from the study.</p>
<p>IS AMENDED TO:</p> <p>Serious adverse events will be collected and reported on the adverse event CRF from the time the subject signs the ICF until <b>30 days following last dose of study drug</b> <del>termination from the study.</del></p>

### 5.5.8 Procedure in Case of Pregnancy

Page 56, Paragraph 1

WAS:

If during the conduct of the clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the investigator. The investigator should report the pregnancy to the sponsor as an SAE within 30 days from discontinuation of dosing. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

IS AMENDED TO:

If during the conduct of the clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the investigator. The investigator should report the pregnancy to the sponsor **as if it is an SAE** ~~within 30 days from discontinuation of dosing~~. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

### 5.7.3 Blood sample for androgen levels and bone markers

Page 58

WAS:

5.7.3 Blood sample for androgen levels and bone markers

A separate blood sample will be collected for measuring serum levels of androgens (testosterone and DHT). Bone alkaline phosphatase (a marker for bone metabolism) will be measured from the same tube of the chemistry parameters (see Appendix 2).

IS AMENDED TO:

5.7.3 Blood sample for androgen **and androgen precursors** levels and bone markers

A separate blood sample will be collected for measuring serum levels of androgens (testosterone and DHT) **and androgen precursors**. Bone alkaline phosphatase (a marker for bone metabolism) will be measured from the same tube of the chemistry parameters (see Appendix 2).

### 7.4 Analysis of Efficacy

Page 60

WAS:

Progression free survival is defined as the time interval from the date of starting treatment until the date of documented progression or death in absence of progression. Progression, as a composite endpoint, consisting of either clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria. Subjects with PSA progression alone will not be withdrawn from the study. Kaplan-Meier curves will be presented. The median and 25% and 75% percentiles will be tabulated, including the corresponding 95%CI

calculated by use of the Brook Meyer and Crowley method. The number of events and subjects at risk over time will be tabulated.

For PSA level over time, descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for baseline value and post-baseline values, as well as absolute and percent change from baseline.

The objective response according to RECIST 1.1 and bone scan results will be reported through descriptive summaries as described by PCWG2, including the proportion of patients showing RECIST 1.1 objective response (partial or complete response).

Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.

- Testosterone/DHT and Androgen Receptor Signaling

Summary statistics will be produced for the Biomarker Evaluable Set.

The effect of enzalutamide on bone and serum biomarkers (including androgen expression signaling) will be analyzed based on change from baseline to Week 9.

For each biomarker (testosterone, DHT and androgen receptor signaling), descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for baseline value, post-baseline value, change from baseline, and percent change from baseline. Graphical display using box-plot, histogram and scatter plot will be generated as appropriate.

Biomarker results collected at baseline assessment and at each post-baseline assessment will be compared using paired t-test to evaluate the effect of enzalutamide. The change from baseline in each biomarker will also be summarized by PSA response category, where PSA response is a function of percentage improvement from baseline to Week 13. The correlation between each biomarker and PSA level will be estimated using Spearman's method.

IS AMENDED TO:

Progression-free survival is defined as the time interval from the date of starting treatment until the date of documented progression or death in absence of progression. Progression, as a composite endpoint, consisting of either clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria. ~~Subjects with PSA progression alone will not be withdrawn from the study.~~ Kaplan-Meier curves will be presented. The median and 25<sup>th</sup>% and 75<sup>th</sup>% percentiles will be tabulated, including the corresponding 95%CI calculated by use of the Brook Meyer and Crowley method. The number of events and subjects at risk over time will be tabulated.

For PSA level over time, descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for baseline value and post-baseline values, as well as absolute and percent change from baseline.

The objective response according to RECIST 1.1 and bone scan results will be reported through descriptive summaries as described by PCWG2, including the proportion of patients showing RECIST 1.1 objective response (partial or complete response).

Bone specific alkaline phosphatase and urine N-telopeptides will be descriptively summarized.

• **Androgen, Testosterone/DHT and Androgen Receptor Signaling, androgen pre-cursors and other associated metabolites**

Summary statistics will be produced for the Biomarker Evaluable Set.

The effect of enzalutamide on bone and serum biomarkers (including **androgen pre-cursors and androgen expression signaling, androgen pre-cursors and other associated metabolites**) will be analyzed based on change from baseline to Week 9.

For each biomarker (**androgen, androgen expression signaling, androgen pre-cursors and other associated metabolites**~~testosterone, DHT and androgen receptor signaling~~), descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for baseline value, post-baseline value, change from baseline, and percent change from baseline. Graphical display using box-plot, histogram and scatter plot will be generated as appropriate.

Biomarker results collected at baseline assessment and at each post-baseline assessment, **if appropriate**, will be compared using paired t-test to evaluate the effect of enzalutamide. The change from baseline in each biomarker will also be summarized by PSA response category, where PSA response is a function of percentage improvement from baseline to Week 13. The correlation between each biomarker and PSA level will be estimated using Spearman’s method.

**12.2 Appendix 2: Laboratory Tests**

Page 73

WAS:

Testosterone and DHT	Screening, Week 9 and at the end of treatment (ET). If the ET visit falls between Week 9 and Week 13, and the Week 9 DHT and Testosterone was collected, then an ET collection will not be required.	Serum tube (red top, no additive), Sodium Heparin tube	Testosterone and DHT
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IS AMENDED TO:

<b>Androgen, androgen expression signaling, androgen pre-cursors and other associated metabolites</b> <del>Testosterone and DHT</del>	Screening, Week 9 and at the end of treatment (ET). If the ET visit falls between Week 9 and Week 13, and the Week 9 <b>sample</b> <del>DHT and Testosterone</del> was collected, then an ET collection will not be required.	Serum tube (red top, no additive), Sodium Heparin tube	<b>androgen, androgen expression signaling, androgen pre-cursors and other associated metabolites</b> <del>Testosterone and DHT</del>
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## 12.4 Appendix 4: Common Serious Adverse

Page 76

WAS:

The following list of serious adverse events are considered common for the study population defined in this protocol and should be reported by the investigator as described in Section 5.5. For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to FDA.

IS AMENDED TO:

~~The following list of serious adverse events are considered common for the study population defined in this protocol and should be reported by the investigator as described in Section 5.5. For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to FDA.~~

**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 5.5.2 Definition of Serious Adverse Event (SAE). 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 5.5.5 Reporting of Serious Adverse Events (SAE).**

**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.**

## 14 SPONSOR'S SIGNATURES

**1. SPONSOR'S SIGNATURES**

**A Phase 2 Study Determining Safety and Tolerability of Enzalutamide (formerly MDV3100) in Combination with Abiraterone Acetate in Bone Metastatic Castration-Resistant Prostate Cancer Patients**

**ISN/Protocol 9785-CL-0011 / Version 3.0, Incorporating Substantial Amendment 2  
18 June 2014**

Signature: [Redacted]	[Redacted]
[Redacted]	Date
Signature: [Redacted]	[Redacted]
[Redacted]	Date
Signature: [Redacted] MD	[Redacted]
[Redacted]	Date

**1. SPONSOR'S SIGNATURES**

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18 June 2014**

Signature: _____ [Redacted]	Date _____
Signature: _____ [Redacted]	[Redacted]
Signature: _____ [Redacted] MD	Date _____

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**A Phase 2 Study Determining Safety and Tolerability of Enzalutamide (formerly MDV3100) in Combination with Abiraterone Acetate in Bone Metastatic Castration-Resistant Prostate Cancer Patients**

**ISN/Protocol 9785-CL-0011 / Version 3.0, Incorporating Substantial Amendment 2  
18 June 2014**

Signature: _____ [Redacted]	Date _____
Signature: _____ [Redacted]	Date _____
Signature: _____ [Redacted] MD	Date _____ [Redacted]