

**Janssen Research & Development \*****Clinical Protocol**

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**Abiraterone acetate in patients with Metastatic Castration-Resistant Prostate Cancer, Chemo-naive, who received a prior Diethylstilbestrol therapy**

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**Protocol 212082PCR2036; Phase: 2**  
Amendment INT-2**JNJ-212082 (abiraterone acetate)**

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**Prepared by:** Janssen Research & Development, LLC

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**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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## LIST OF ATTACHMENTS

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## PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	10 Feb 2014
Amendment INT-1	05 Dec 2014
Amendment INT-2	18 Jan 2018

Amendments are listed beginning with the most recent amendment.

### Amendment INT-2 (18 January 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** The overall reason for the amendment is to finalize follow-up/study, eliminating any unnecessary burden on the [REDACTED]

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> Original protocol visits and follow-up period were decided under assumptions made at the time of sample size calculation (ie: before trial start). A medium time of 8.5 months was assumed to PSAP of Abiraterone plus prednisone in CRPC patients, which had failed to DES therapy, and a 5-month time to PSAP as the minimum effect to consider drug activity in this setting such as first-line chemotherapy.
	Janssen has performed an interim statistical analysis with proven efficacy of study drug and therefore accomplishing the primary objective of this protocol. Having reached the necessary number of events, additional patient visits or follow-up of the remaining 3 patients are not necessary for final statistical analysis. Therefore, this amendment is being proposed to finalize follow-up, eliminating any unnecessary burden on patients.
Synopsis: Study design	Change the sentence to clarify that treatment will continue until PSA progression, clinical progression, consent withdrawal, occurrence of unacceptable toxicity or study termination. Inclusion of sentence: In case of early study termination, any patients still receiving study drug will continue to do so, if the physician considers beneficial to the patient, under a Continued Access Program, following the applicable regulations. Investigators will be trained on Janssen and regulatory pharmacovigilance requirements and patients will be followed for safety until 30 days after the last study drug dose.

Applicable Section(s)	Description of Change(s)
5.1. Planned dose	Inclusion of sentence: In case of early study termination, any patients still receiving study drug will continue to do so, if the physician considers beneficial to the patient, under a Continued Access Program, following the applicable regulations. Investigators will be trained on Janssen and regulatory pharmacovigilance requirements and patients will be followed for safety until 30 days after the last study drug dose.
8.1.4. PSA Progression/Early Withdrawal	Inclusion of sentence: There is an expected data collection period of up to 24 months per patient after enrollment to monitor survival status and, if applicable, subsequent prostate cancer therapy.
8.1.5. Post-PSA Progression (Follow-up)	Inclusion of sentence: In case of early study termination, any patients still receiving study drug will continue to do so, if the physician considers beneficial to the patient, under a Continued Access Program, following the applicable regulations. Investigators will be trained on Janssen and regulatory pharmacovigilance requirements and patients will be followed for safety until 30 days after the last study drug dose.
9.1. Study Completion	Change the sentence to clarify expected data collection period. Inclusion of sentence: There is an expected data collection period of up to 24 months per patient after enrollment to monitor survival status and, if applicable, subsequent prostate cancer therapy.
16.9.2. Study termination	Inclusion of additional reason for the early closure of investigational site: patients do not reach PSAP after at least 24 months of treatment and do not show clinical progressive results for more than 12 months.

### **Amendment INT-1 (05 December 2014)**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** The overall reason for the amendment is correct the Permitted Supportive Care and Interventions List.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarify that laboratory documents are the source data. Only actual dates of sample collection will be collected in eCRF.	
8.4. Sample Collection and Handling	Change the sentence to clarify that laboratory documents are the source data and only actual dates of sample collection will be collected in eCRF
<b>Rationale:</b> Spironolactone is a prohibited medication.	

Applicable Section(s)	Description of Change(s)
7.1. Permitted Supportive Care and Interventions	Exclusion of spironolactone of Permitted Supportive Care and Interventions list.

## SYNOPSIS

### Abiraterone acetate in patients with Metastatic Castration-Resistant Prostate Cancer, Chemo-naive, who received a prior Diethylstilbestrol therapy

## STUDY DRUG

ZYTIGA® (abiraterone acetate) is a prodrug of abiraterone, an irreversible inhibitor of 17 $\alpha$  hydroxylase/C17, 20-lyase (cytochrome P450c17 [CYP17]), a key enzyme required for testosterone synthesis. Marketing authorization for ZYTIGA and prednisone/prednisolone was granted in April 2011 in the United States and in September 2011 in the European Union. Treatment with ZYTIGA improves survival in patients with metastatic castration-resistant prostate cancer.

## OBJECTIVES

### Primary

The primary objective is to evaluate the efficacy, based on Prostate-specific antigen (PSA) progression, of Abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC), chemo-naive, who received a prior Diethylstilbestrol Therapy (DES).

### Secondary

The secondary objectives are to evaluate the clinically relevant Prostate-specific antigen (PSA) and survival improvements, safety of abiraterone acetate plus low-dose prednisone, as well as to explore the relationship between serum androgen levels and response to therapy.

## HYPOTHESIS

Abiraterone acetate could be clinically effective and delay the start to chemotherapy in mCRPC patients who have progressed on DES therapy.

## STUDY DESIGN

This is a phase II, multicenter, open-label, single arm study to determine if mCRPC patients who failed to prior DES therapy will benefit from the addition of abiraterone acetate and low-dose prednisone to androgen deprivation therapy (ADT). In this study, ADT refers specifically to luteinizing hormone releasing hormone (LHRH) agonists or orchiectomy. Approximately 45 subjects will be enrolled. The study population includes mCRPC adult men that might have undergone to a complete androgen blockage (CAB) and had failed to DES therapy.

The study will consist of a Screening Phase of up to 28 days before enrollment to establish study eligibility and document baseline measurements; a PSA Evaluation Phase; and a Follow-up Phase of up to 24 months to monitor survival status and subsequent prostate cancer therapy. Each cycle of abiraterone therapy is 28 days. Treatment will continue until PSA progression, clinical progression, consent withdrawal, occurrence of unacceptable toxicity or study termination. Patients experiencing PSA progression might be offered continuation on abiraterone treatment at the discretion of the investigator. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled to receive abiraterone acetate [1,000

mg once daily] plus low-dose prednisone [5 mg once daily]. Patients need to be under ADT [LHRH agonist or orchiectomy] as per discretion of attending physician.

Subjects will be monitored for safety throughout the study. Adverse events including laboratory adverse events will be graded and summarized using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Dose modification guidelines are provided.

In case of early study termination, any patients still receiving study drug will continue to do so, if the physician considers beneficial to the patient, under a Continued Access Program, following the applicable regulations. Investigators will be trained on Janssen and regulatory pharmacovigilance requirements and patients will be followed for safety until 30 days after the last study drug dose.

## **SUBJECT SELECTION**

### **Inclusion**

1. Willing and able to provide written informed consent;
2. Men age 18 years and older;
3. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology;
4. Prior therapy with DES for castration resistant prostate cancer. Patients should demonstrate evidence of progression (see below definitions) on DES or evidence of grades 3/4 toxicities on DES;
5. Progressive disease: PSA progression per PCWG2 criteria (sequence of rising PSA values at least 1 week apart and minimum PSA level of 2 ng/mL) or radiographic progression per RECIST (version 1.1);
6. Metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI;
7. Ongoing ADT (LHRH agonist or orchiectomy), with serum testosterone level of less than 50 ng per deciliter (1.7 nmol per liter). Eligible patients must maintain ADT;
8. Could have received prior androgen blockage (bicalutamide or flutamide) but must have been discontinued for least 28 days;
9. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0, 1 or 2;
10. Adequate hematologic, hepatic, and renal function:
  - hemoglobin  $\geq$  9.0 g/dL independent of transfusions;
  - neutrophils  $\geq$  1.5  $\times$  10<sup>9</sup>/L;

- platelets  $\geq 100 \times 10^9/L$ ;
- total bilirubin  $\leq 1.5X$  upper limit of normal (ULN) [except for subjects with documented Gilbert's disease in which case total bilirubin not to exceed 10X ULN];
- alanine (ALT) and aspartate (AST) aminotransferase  $\leq 2.5X$  ULN;
- serum creatinine  $<1.5X$  ULN or calculated creatinine clearance  $\geq 50$  mL/min;
- serum potassium  $\geq 3.5$  mM;
- serum albumin  $\geq 3.0$  g/dL;

11. Ability to swallow study medication tablets;

12. Agrees to use a condom and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant during the treatment period and for 1 week after the last dose of abiraterone acetate.

### **Exclusion**

1. Active infection or other medical condition that would make prednisone use contraindicated,
2. Any chronic medical condition requiring a higher systemic dose of corticosteroid than 5 mg prednisone per day,
3. Pathological finding consistent with small cell carcinoma of the prostate,
4. Known brain metastasis,
5. Has had prior cytotoxic chemotherapy or biologic therapy for the treatment of mCRPC,
6. Any prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer. The following exceptions are permitted:
  - Prior use of anti-androgens (e.g. bicalutamide) in combination with ADT (LHRH agonists or orchiectomy) as part of CAB;
  - Subjects may have one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (eg, impending cord compression or obstructive symptoms) if it was administered at least 28 days prior to Cycle 1 Day 1. All adverse events associated with these procedures must be resolved at least to Grade 1 by Cycle 1 Day 1.
7. Uncontrolled hypertension (systolic blood pressure (BP)  $\geq 160$  mmHg or diastolic BP  $\geq 95$  mmHg). Subjects with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment,

8. Active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction,
9. History of adrenal dysfunction,
10. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events or history of cardiac failure in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease,
11. Atrial fibrillation or other cardiac arrhythmia requiring pharmacotherapy,
12. Other malignancy (within 5 years), except non-melanoma skin cancer,
13. Administration of an investigational therapeutic or invasive surgical procedure (not including surgical castration) within 28 days of Cycle 1 Day 1 or currently enrolled in an investigational study,
14. Any condition or situation which, in the opinion of the investigator, would put the subject at risk, may confound study results, or interfere with the subject's participation in this study.

NOTE: Each subject will be reviewed by sponsor before enrollment to ensure that select eligibility criteria have been met.

## **DOSAGE AND ADMINISTRATION**

Abiraterone acetate 1,000 mg (four 250 mg tablets) should be taken orally once daily, concomitantly with oral low-dose prednisone 5mg. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. Tablets should be swallowed whole with water. If an abiraterone acetate dose is missed, it should be omitted and will not be made up.

All subjects should remain on a stable regimen of ADT (LHRH agonists) or have had surgical castration. The choice of the LHRH agonist will be at the investigator's discretion and is to be selected prior to enrollment. Dosing (dose and frequency of administration) will be consistent with the prescribing information and should only be adjusted if clinically indicated to achieve and maintain subcastrate concentrations of testosterone (50 ng/dL or 1.7 nM).

## **EVALUATIONS**

### **Efficacy**

- Time to PSA progression is calculate from the time of enrollment to the PSA progression defined as  $\geq 25\%$  and  $\geq 2$  ng/mL after 12 weeks (in case of no decline in PSA from baseline), or first PSA increase that is  $\geq 25\%$  and  $\geq 2$  ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (in case of decline of PSA from baseline);

- PSA response rate ( $\geq 50\%$  decline in PSA level from baseline at 12 weeks and at any time);
- Maximal PSA post-therapy change from baseline (maximal at 12 weeks or at any time point PSA post-therapy change from baseline presented in waterfalls);
- Overall survival (OS) (time from enrollment to death due to any cause);
- Patients' reports of pain (as measured by the average of the pain scores on the BPI-SF (range, 0 to 10, with higher scores indicating worse average pain). An increase in pain is defined as an increase in the baseline pain score at two consecutive visits by 30% or more, as measured by the average of the pain scores on the BPI-SF (range, 0 to 10, with higher scores indicating worse average pain), without a decrease in analgesic use.

## Biomarkers

Biomarker analyses are designed to confirm previously identified markers predictive of response (or resistance) to abiraterone acetate or correlated with poor prognosis (e.g. low SA levels at baseline). Serum samples will be collected at baseline, week 12 and PSA Progression Visit to allow for related analyses.

## Safety

Safety evaluations include adverse events, vital signs measurements, physical examinations, and clinical laboratory tests.

## ENDPOINTS

### Primary

Time to PSA progression (PSAP)

### Secondary

PSA response rate, Maximal PSA post-therapy change from baseline, Overall Survival (OS), safety and Patients' reports of pain.

### Exploratory

Investigate the relationship between baseline serum androgen (SA) levels (Androstenedione, Testosterone, dehydroepiandrosterone (DHEA), Dehydroepiandrosterone sulfate (DHEAS)) and PSA response and time to PSA progression. Analyze SA variability from baseline to time to PSAP. To collect plasma for future correlative translational research to investigate other serum androgens, and biomarkers that may be discovered during the study.

## STATISTICAL METHODS

### Sample Size Determination

We assumed that the medium time to PSAP of Abiraterone plus prednisone in CRPC patients, which had failed to DES therapy, would be 8.5 months as in historical data with DES and ketoconazole<sup>1-3</sup>. A 5 months time to PSAP is the minimum effect to consider drug activity in

this setting such as first-line chemotherapy<sup>4,5</sup>. Considering a uniform accrual over 1 year enrollment period, 6 months follow-up time and exponentially distributed PSAP times, a two-sided test for the median<sup>7</sup> with an alpha level of 0.05 and a power of 80%, 40 patients would need to be enrolled. In addition, considering a drop-out rate of 10%, a total sample size of 45 patients is planned for the study.

### **Efficacy Analysis**

The primary analysis population will use the efficacy population, which includes all eligible enrolled subjects. The efficacy population will be used for the analysis of subject disposition and efficacy. The safety population includes all subjects who received at least 1 dose of study drug.

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects, mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. The baseline measurement will be the last value on or before the date of first study treatment.

### **Biomarkers Analysis**

The associations of the above biomarkers with clinical response or survival endpoints will be assessed using appropriate statistical methods (logistic regression model or survival model), depending on the endpoint.

### **Safety Analyses**

The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

## TIME AND EVENTS SCHEDULE

	Screening Phase	Cycles (28 days)					Subsequent cycles	PSA progression visit / Early Withdrawal <sup>§</sup>	Follow-up Phase
		1 <sup>§</sup>	1	2	3				
<b>Visit no. (at the end of each cycle ± 2 days)</b>	1	1 <sup>§</sup>	1	2	3		From cycle 4 until PSA progression	15-30 days after confirmation of PSA progression	Every 3 months, up to 2 years
<b>Day of cycle</b>	-28 to -1	1	28	28	28	28			
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history/Demographics	X								
Diagnosis/extent of cancer/ Prior antineoplastic therapy	X								
Vital signs (HR and blood pressure) <sup>1</sup>	X	X	X	X	X	X		X	
Height	X								
Weight	X	X	X	X	X	X		X	
Physical examination	X		X	X	X	X		X	
ECOG Performance Status	X	X	X	X	X	X		X	
ECG	X								
PSA	X	X	X	X	X <sup>2</sup>	X		X	
Hematology <sup>3</sup>	X	X	X	X	X	X		X	
Serum Biochemistry <sup>4</sup>	X	X	X	X	X	X		X	
Liver function <sup>5</sup>	X	X	X	X	X	X		X	
Serum Androgens <sup>6</sup>		X			X <sup>2</sup>			X	
BPI-SF Questionnaire <sup>7</sup>			X		X	every 2 cycles		X	
Prior/concomitant medications	X	Continuous until 30 days after last study drug dose							
Adverse events	X	Continuous from ICF to 30 days after last study drug dose							
Reason of discontinuation of study drug, if applicable								X	X
Survival Status and subsequent therapies								X	X
Blood collection for exploratory biomarkers <sup>8</sup>		X			X <sup>2</sup>			X	

**Table legend**

§ Highlight in grey - do not repeat exams and data collection if done at screening (for cycle 1) / at the end of last cycle (for PSA Progression visit)

1. HR (heart rate) and BP (blood pressure) at screening; afterwards only blood pressure.
2. This exam should be performed on 12 weeks from baseline. If C3D28 is delayed, perform the exam on the week 12 and do not repeat on later visit.
3. Hemoglobin, White Blood Counts (including neutrophil), Platelet
4. Potassium, creatinine, fasting glucose, lactate dehydrogenase, INR
5. ALT (alanine aminotransferase), AST (aspartate aminotransferase), total bilirubin, albumin (screening only)
6. Testosterone, Androstenedione, DHEA, DHEAS. To be collected before abiraterone and prednisone administration.
7. BPI-SF (Brief Pain Inventory – Short Form): at cycle 1 day 1, at day 28 (+/- 2) of every 2 cycles (cycle 2, 4, 6, 8, etc.) and at PSA progression visit
8. For subjects participating in the correlative translational study, the blood volumes will be 5 to 10 mL per study visit. Freeze and Store according “Sample Collection and Handling Manual”.

## ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
BPI-SF	Brief Pain Inventory - Short Form
CAB	complete androgen blockade
CRPC	castration resistant prostate cancer
CT	computerized tomography
CYP	Cytochrome
DES	diethylstilbestrol
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
FDA	food and drug administration
GCP	good clinical practice
GnRH	Gonadotropin-releasing hormone
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IDMC	independent data monitoring committee
IRB	Institutional Review Board
ITT	intention-to-treat
LHRH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	overall survival
PCWG2	Prostate Cancer Clinical Trials Working Group
PQC	Product Quality Compliant
PSA	prostate-specific antigen
PSAP	prostate-specific antigen progression
QD	once a day ( <i>quaque die</i> )
RECIST	response evaluation criteria in solid tumors
rPFS	radiographic progression free survival
SA	serum androgen
SAE	serious adverse event
SD	stable disease
ULN	upper limit of normal

## 1. INTRODUCTION

### 1.1. Background

#### 1.1.1. The Rationale for Abiraterone Acetate in the Management of Castration-Resistant Prostate Cancer (CRPC)

Testosterone production is a key element in the control of prostate cancer growth. In the testis and adrenals, C17,20-lyase converts the C21 precursors to the corresponding C19 androgens. Testosterone, a C19 androgen, is further converted to the more potent androgen dihydrotestosterone (DHT) by 5 $\alpha$ -reductase in the prostate<sup>6,7</sup>. Both testosterone and DHT stimulate prostatic growth, although DHT plays a much more important role than testosterone in the organogenesis and homeostasis of the prostate. Inhibitors of the enzyme 17 $\alpha$  hydroxylase/C17,20- lyase, such as abiraterone acetate and abiraterone, block testosterone production both in the testis and adrenal gland. Standard androgen deprivation therapies, such as orchectomy and treatment with gonadotropin-releasing hormone (GnRH) analogues, ablate androgen production by the testis but do not affect androgen production by the adrenals, which continue to supply androgens to the prostate cancer and, thereby, promote disease progression<sup>8</sup>. In castrated men, as much as 10% of baseline circulating testosterone remains because of conversion of adrenal androgens to testosterone<sup>9</sup>. In addition, more than 10% of baseline concentrations of the androgens testosterone, DHT, dehydroepiandrosterone sulfate (DHEAS), and androstenedione remain in recurrent prostate cancer tissue after castration<sup>10</sup>. Autocrine synthesis may contribute to these high prostate tumor androgen concentrations since high concentrations of CYP17 messenger ribonucleic acid (mRNA) are found in high Gleason score prostate tumors of subjects who experience metastasis. Furthermore, the androgen receptor (AR) becomes amplified in prostate tumor cells, and the amplified AR is activated by extremely low androgen concentrations<sup>11</sup>. The sensitivity of the AR is also increased by the overexpression of 2 nuclear coactivators, which enhances activation of the AR at lower testosterone concentrations<sup>12,13</sup>. Together, the increased sensitivity of AR with persistent androgens after castration results in tumor progression in many men with CRPC. Therefore, even though the progression of prostate cancer may be slowed in the absence of testicular androgens, the tumor remains responsive to stimulation from extratesticular or autocrine androgens. Because of this responsiveness, anti-androgen therapy with abiraterone acetate may still be effective after medical or surgical castration. The term hormone refractory prostate cancer should now be replaced with the more accurate name, CRPC, to reflect the continued sensitivity of men after castration to ultra low level androgen deprivation by abiraterone acetate. Current second-line hormone therapies include anti-androgens such as flutamide, bicalutamide, and nilutamide, estrogens including diethylstilbestrol, or adrenal androgen synthesis inhibitors such as hydrocortisone alone, ketoconazole, and aminoglutethimide<sup>14</sup>. The adverse events (AEs) observed in subjects receiving ketoconazole or aminoglutethimide were thought to be related to the nonspecific nature of enzyme inhibition. Since abiraterone acetate, and its chief metabolite abiraterone, is selective inhibitors of 17 $\alpha$  hydroxylase/C17,20-lyase, administration is expected to reduce the risk of nonspecific enzyme inhibition affecting the synthesis of glucocorticoids and mineralocorticoids, improving efficacy and minimizing AEs.

### **1.1.2. Abiraterone Acetate**

ZYTIGA® (abiraterone acetate) is a prodrug of abiraterone, an irreversible inhibitor of 17 $\alpha$  hydroxylase/C17,20-lyase (cytochrome P450c17 [CYP17]), a key enzyme required for testosterone synthesis. This enzyme is found in the testis, adrenals, and prostate tumors<sup>15-17</sup>. Marketing authorization for ZYTIGA and prednisone/prednisolone was granted in April 2011 in the United States and in September 2011 in the European Union. Treatment with ZYTIGA improves survival in patients with metastatic castration-resistant prostate cancer.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of abiraterone acetate, refer to the latest version of the Investigator's Brochure for abiraterone acetate. The term sponsor used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

### **1.1.3. Clinical Experience with Abiraterone Acetate**

In healthy subjects after single dose administration of 1,000 mg abiraterone acetate, there is a substantial food effect and absorption of abiraterone acetate increases greatly with increasing fat content of a meal (Study COU-AA-009)<sup>18</sup>. Compared to administration after an overnight fast, geometric mean maximum concentration (C<sub>max</sub>) and the area under the concentration-time curve (AUC) of abiraterone increased approximately 7-fold and 5-fold, respectively, when administered following a low-fat meal (estimated 2% of calories from fat) and increased by approximately 17-fold and 10-fold, respectively, when administered following a high-fat meal (estimated 56% of calories from fat).

In the two large phase 3 randomized studies (COU-AA-301 and COU-AA-302), treatment with abiraterone acetate and prednisone had an acceptable safety profile and resulted in a favorable benefit/risk ratio. The safety profile of abiraterone acetate plus prednisone was distinct from that of cytotoxic agents. Adverse events usually did not interfere with administration of abiraterone acetate. In the combined dataset of safety for studies COU-AA-301 and COU-AA-302, the most frequently reported adverse events were fatigue (43.8%), back pain (32.6%), nausea (28.4%), arthralgia (29.5%), constipation (26.1%), bone pain (24.2%), peripheral edema (26.0%), hot flush (20.6%) and diarrhea (20.5%). Most events were Grade 1 or 2 in severity. Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia (eg, those on cardiac glycosides), or fluid retention (eg, those with heart failure), severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia, and those with severe renal impairment.

Study COU-AA-301 was a Phase 3, multinational, randomized, double-blind, placebo-controlled study of oral abiraterone acetate and oral prednisone in 1,195 subjects with mCRPC whose disease had progressed on or after 1 or 2 chemotherapy regimens, at least one of which contained docetaxel. The study conclusively demonstrated that further lowering testosterone concentrations below those achieved with standard therapy to suppress androgen production

(LHRH agonists or orchiectomy) using CYP17 inhibition with abiraterone acetate improves survival in patients with mCRPC<sup>19</sup>.

#### **1.1.4. Clinical Experience with Abiraterone Acetate in CRPC chemo-naïve patients**

Study COU-AA-302 was a Phase 3, multinational, randomized, double-blind, placebo-controlled study of abiraterone acetate and oral prednisone in 1,088 asymptomatic or mildly symptomatic subjects with mCRPC who had not received chemotherapy<sup>20</sup>. This study had co-primary endpoints of radiographic progression free survival (rPFS) and overall survival. Treatment with abiraterone acetate plus prednisone decreased the risk of radiographic progression or death by 57% compared with placebo plus prednisone (HR=0.425; p<0.0001). The study met its nominal significance level (0.01) for the co-primary endpoint of rPFS by independent review. There was a 25% decrease in the risk of death in the abiraterone acetate and prednisone group compared with the placebo plus prednisone group (HR=0.752; p=0.0097) when the Independent Data Monitoring Committee (IDMC) unanimously recommended unblinding the treatment and allowing subjects in the placebo group to receive abiraterone acetate. The median OS had not been reached for the abiraterone acetate group and was 27.2 months in the placebo group. The safety profile was similar, although the duration of treatment was longer, to that observed with abiraterone acetate plus prednisone in subjects in the post-docetaxel setting (COU-AA-301).

#### **1.2. Overall Rationale for the Study**

Although advanced prostate cancer is initially sensitive to androgen deprivation, most patients invariably develop progressive disease, and most deaths occur after the cancer has progressed to castration-resistant status. Historically, second-line hormonal therapy after maximum androgen blockade (e.g. diethylstilbestrol (DES), ketoconazole, steroids) has demonstrated clinical benefit among patients with chemo-naïve castration-resistant prostate cancer. Despite of secondary hormonal therapy being used in clinical practice, none of these drugs are approved by regulatory agencies in this indication and do not show survival benefit.

Abiraterone was recently approved as for metastatic castration-resistant prostate cancer patients who had not received cytotoxic chemotherapy. In the pivotal study COU-AA-302, patients with visceral metastatic disease and prior treatment with subsequent hormonal therapy lines were excluded. A preliminary data from a phase 2 ongoing study showed that a substantial number of patients with prior ketoconazole exposure respond to Abiraterone indicative of the greater CYP 17 inhibition induced by Abiraterone and retained CYP 17 dependence in mCRPC. The lower responses observed in this study compared to keto naïve mCRPC suggests the potential for overlapping mechanisms of resistance to Abiraterone and ketoconazole<sup>21</sup>. In a retrospective study, patients with mCRPC, chemo-naïve and that failed to DES, the treatment with, abiraterone resulted in ≥ 50% PSA declines in 20/27 (74.1%) and 8.5 months median time to PSA progression. This study suggests that Abiraterone has significant antitumour activity in men with mCRPC even after DES exposure<sup>3</sup>.

Thus, Abiraterone has not been well investigated in patients with prostate cancer progressing on secondary hormone therapy (especially DES) and that strategy could delay the start of chemotherapy. In addition, the evaluation of SA as a predictor of treatment benefit with

Abiraterone after DES exposure was not yet described. This phase II trial studies the efficacy of Abiraterone in patients with metastatic hormone-resistant prostate cancer that have progressed to DES therapy.

## 2. OBJECTIVE AND HYPOTHESIS

### 2.1. Objectives

#### Primary Objective

The primary objective is to evaluate the efficacy, based on Prostate-specific antigen (PSA) progression, of Abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC), chemo-naïve, who received a prior Diethylstilbestrol Therapy (DES).

#### Secondary Objective

The secondary objectives are to evaluate the clinically relevant Prostate-specific antigen (PSA) and survival improvements, safety of abiraterone acetate plus low-dose prednisone, as well as to explore the relationship between serum androgen levels and response to therapy.

### 2.2. Hypothesis

Abiraterone acetate could be clinically effective and delay the start to chemotherapy in mCRPC patients who have progressed on DES therapy.

## 3. STUDY DESIGN AND RATIONALE

### 3.1. Overview of Study Design

This is a phase II, multinational, multicenter, open-label, single arm study to determine if mCRPC patients who failed to prior DES therapy will benefit from the addition of abiraterone acetate and low-dose prednisone to androgen deprivation therapy (ADT). In this study, ADT refers specifically to luteinizing hormone releasing hormone (LHRH) agonists or orchietomy. Approximately 45 subjects will be enrolled. Subjects must have metastatic disease as documented by positive bone scan or metastatic lesions on CT or MRI to be eligible. Need to have PSA progression according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria<sup>22</sup> or radiographic progression per RECIST version 1.1. Eligible subjects must maintain ADT, with serum testosterone level of less than 50 ng per deciliter (1.7 nmol per liter) and Eastern Cooperative Oncology Group (ECOG) performance status grade 0, 1 or 2. Selection of the LHRH agonist is by Investigator's choice provided that the dosing (dose and frequency of administration) is consistent with prescribing information. Abiraterone acetate and low-dose prednisone will be considered as study drugs.

The study will consist of a Screening Phase of up to 28 days before enrollment to establish study eligibility and document baseline measurements; a PSA Evaluation Phase; and a Follow-up Phase of up to 24 months to monitor survival status and subsequent prostate cancer therapy. Each cycle of abiraterone therapy is 28 days. Treatment will continue until PSA progression, clinical progression, consent withdrawal, occurrence of unacceptable toxicity or study termination. Patients experiencing PSA progression might be offered continuation on abiraterone treatment at the discretion of the investigator. Subjects who meet all of the inclusion

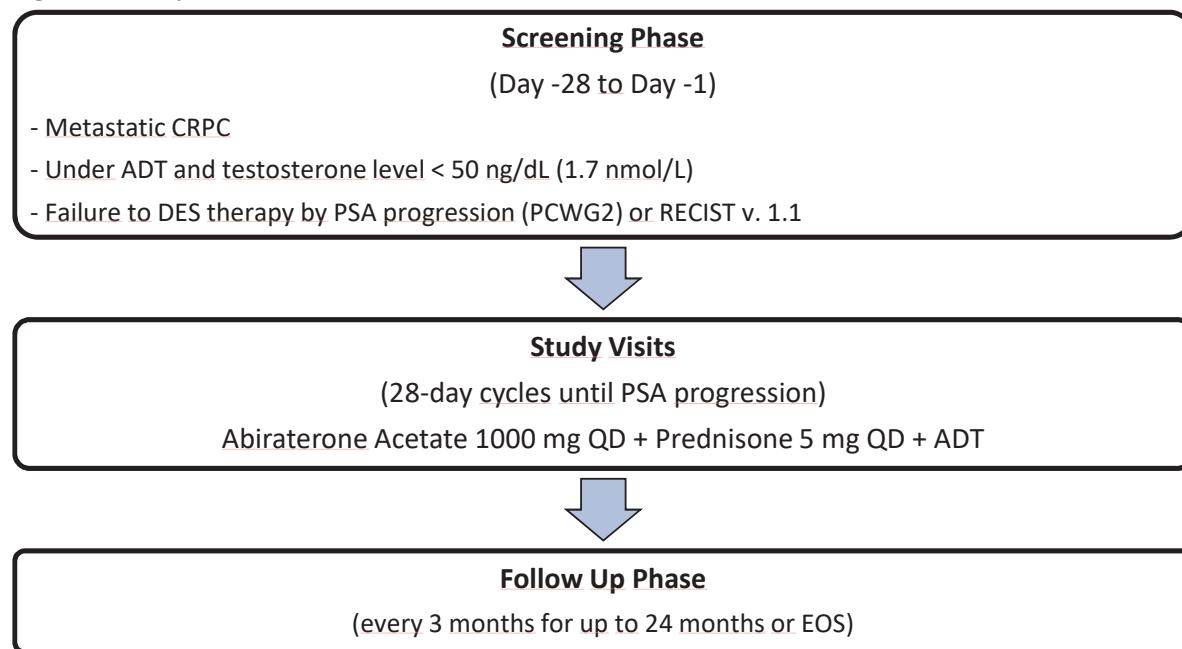
criteria and none of the exclusion criteria will be enrolled to receive abiraterone acetate [1,000 mg once daily] plus low-dose prednisone [5 mg once daily]. Patients need to be under ADT [LHRH agonist or orchiectomy] as per discretion of attending physician.

Serum samples collected at multiple time points during the study. Other samples could be obtained from subjects for biomarker evaluations.

Subjects will be monitored for safety throughout the study. Adverse events including laboratory adverse events will be graded and summarized using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Dose modification will be made as required according to dose modification rule.

A study flowchart is provided in Figure 1.

**Figure 1 – Study Flowchart 1**



ADT: androgen deprivation therapy (LHRH agonist or orchiectomy); DES: Diethylstilbestrol; EOS: end of study; QD: once a day

#### **4. SUBJECT POPULATION**

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections.

##### **4.1. Inclusion Criteria**

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Willing and able to provide written informed consent;

2. Men age 18 years and older;
3. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology;
4. Prior therapy with DES for castration resistant prostate cancer. Patients should demonstrate evidence of progression (see below definitions) on DES or evidence of grades 3/4 toxicities on DES;
5. Progressive disease: PSA progression per PCWG2 criteria (sequence of rising PSA values at least 1 week apart and minimum PSA level of 2 ng/mL) or radiographic progression per RECIST (version 1.1);
6. Metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI;
7. Ongoing ADT (LHRH agonist or orchiectomy), with serum testosterone level of less than 50 ng per deciliter (1.7 nmol per liter). Eligible patients must maintain ADT;
8. Could have received prior androgen blockage (bicalutamide or flutamide) but must have been discontinued for at least 28 days;
9. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0, 1 or 2 (Attachment 2);
10. Adequate hematologic, hepatic, and renal function:
  - hemoglobin  $\geq$  9.0 g/dL independent of transfusions;
  - neutrophils  $\geq$  1.5 x 10<sup>9</sup>/L;
  - platelets  $\geq$  100 x 10<sup>9</sup>/L;
  - total bilirubin  $\leq$  1.5X upper limit of normal (ULN) [except for subjects with documented Gilbert's disease in which case total bilirubin not to exceed 10X ULN];
  - alanine (ALT) and aspartate (AST) aminotransferase  $\leq$  2.5X ULN;
  - serum creatinine  $< 1.5X$  ULN or calculated creatinine clearance  $\geq$  50 mL/min;
  - serum potassium  $\geq$  3.5 mM;
  - serum albumin  $\geq$  3.0 g/dL;
11. Ability to swallow study medication tablets;
12. Agrees to use a condom and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having

sex with a woman who is pregnant during the treatment period and for 1 week after the last dose of abiraterone acetate.

#### **4.2. Exclusion Criteria**

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Active infection or other medical condition that would make prednisone use contraindicated;
2. Any chronic medical condition requiring a higher systemic dose of corticosteroid than 5 mg prednisone per day;
3. Pathological finding consistent with small cell carcinoma of the prostate;
4. Known brain metastasis;
5. Has had prior cytotoxic chemotherapy or biologic therapy for the treatment of mCRPC;
6. Any prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer; The following exceptions are permitted:
  - Prior use of anti-androgens (e.g. bicalutamide) in combination with ADT (LHRH agonists or orchiectomy) as part of CAB;
  - Subjects may have one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (e.g., impending cord compression or obstructive symptoms) if it was administered at least 28 days prior to Cycle 1 Day 1. All adverse events associated with these procedures must be resolved at least to Grade 1 by Cycle 1 Day 1;
7. Uncontrolled hypertension (systolic blood pressure (BP)  $\geq$ 160 mmHg or diastolic BP  $\geq$ 95 mmHg). Subjects with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment;
8. Active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction;
9. History of adrenal dysfunction;
10. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events or history of cardiac failure in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease (Attachment 3);
11. Atrial fibrillation or other cardiac arrhythmia requiring pharmacotherapy;
12. Other malignancy (within 5 years), except non-melanoma skin cancer;

13. Administration of an investigational therapeutic or invasive surgical procedure (not including surgical castration) within 28 days of Cycle 1 Day 1 or currently enrolled in an investigational study;
14. Any condition or situation which, in the opinion of the investigator, would put the subject at risk, may confound study results, or interfere with the subject's participation in this study.

NOTE: Each subject will be reviewed by sponsor before enrollment to ensure that select eligibility criteria have been met.

## **5. DOSAGE AND ADMINISTRATION**

### **5.1. Planned Dose**

Abiraterone acetate 1,000 mg (four 250 mg tablets) should be taken orally once daily, concomitantly with oral low-dose prednisone 5mg. Abiraterone must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. Tablets should be swallowed whole with water. If an abiraterone dose is missed, it should be omitted and will not be made up.

All subjects should remain on a stable regimen of ADT (LHRH agonists) or have had surgical castration i.e. orchiectomy. The choice of the LHRH agonist will be at the Investigator's discretion and is to be selected prior to enrollment. Dosing (dose and frequency of administration) will be consistent with the prescribing information and should only be adjusted if clinically indicated to achieve and maintain subcastrate concentrations of testosterone (50 ng/dL or 1.7 nM).

In case of early study termination, any patients still receiving study drug will continue to do so, if the physician considers beneficial to the patient, under a Continued Access Program, following the applicable regulations. Investigators will be trained on Janssen and regulatory pharmacovigilance requirements and patients will be followed for safety until 30 days after the last study drug dose.

### **5.2. Dose Modification and Management of Toxicity**

In clinical studies in subjects with mCRPC, the most common adverse events related to abiraterone acetate have included fatigue most likely attributable to the underlying disease; and hypertension, hypokalemia, fluid retention/edema, and due to mineralocorticoid excess caused by compensatory ACTH drive. In this study, low-dose prednisone is expected to mitigate these effects through abrogation of the ACTH drive (*see Section 5.4*).

Following prolonged therapy with corticosteroids, subjects may develop Cushings syndrome characterized by central adiposity, thin skin, easy bruising, and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise. This may occur even without evidence of adrenal insufficiency.

**In the event where dose-reduction is used for adverse event management, 2 dose reductions are allowed.** At each dose reduction, 1 tablet of abiraterone acetate will be removed, e.g., 4→3 tablets, and 3→2 tablets. Any return to protocol dose level (4 tablets) after dose reduction must follow documentation of adverse event resolution and a discussion with the sponsor.

**In case of adverse events, the next cycle can be withheld for a maximum of 4 weeks until AE resolution (grade  $\leq$  1).** If AE is not resolved and study treatment not started during this period, the patient needs to be discontinued from the study.

### **5.3. Guidelines for Abnormal Liver Function Test**

For subjects who develop liver function test abnormalities (ALT and/or AST greater than 5 X ULN but not exceeding 20 X ULN or total bilirubin greater than 3 X ULN but not exceeding 10X ULN), study drug should be interrupted. Treatment may be restarted at a reduced dose of 750 mg (3 tablets) once daily following return of liver function tests to the subject's baseline or to AST and ALT less than or equal to 2.5 X ULN and total bilirubin less than or equal to 1.5 X ULN.

For subjects with ALT and/or AST greater than 20 X ULN or total bilirubin greater than 10 X ULN, study drug should be interrupted. The decision to restart treatment at a reduced dose will be made in consultation with the sponsor medical monitor on an individual basis.

For subjects who resume treatment, serum transaminases and bilirubin should be monitored at a minimum of every 2 weeks for 3 months and monthly thereafter.

If liver function test abnormality recurs at the dose of 750 mg (3 tablets) once daily, re-treatment may be restarted at a reduced dose of 500 mg (2 tablets) once daily following return of liver function tests to the subject's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If liver function test abnormality recurs at the reduced dose of 500 mg (2 tablets) once daily, study drug should be discontinued.

### **5.4. Guidelines for Hypertension, Hypokalemia and Fluid Retention/Edema Due to Mineralocorticoid Excess**

The study drug should be used with caution in subjects with a history of cardiovascular disease. The study drug may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Caution should be exercised when treating subjects whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention.

In patients with pre-existing hypokalemia or those who develop hypokalemia on study treatment, consider maintaining the subject's potassium level at 4.0 mM or higher. If hypokalemia persists despite optimal potassium supplementation and adequate oral intake, or if any of the other mineralocorticoid effects persist, the dose of prednisone may be increased to 10 mg/day and documented in the study medication eCRF.

For subjects who develop drug-related Grade 3 or higher toxicities including hypertension, hypokalemia, edema, and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with abiraterone acetate should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline. In the event where dose reduction is used for adverse event management, please refer to Section 5.2.

## **6. TREATMENT COMPLIANCE**

Accurate records of all drug shipments as well as tablets dispensed and returned will be maintained. This inventory must be available for inspection by designated sponsor or regulatory authority representatives at any time. Drug supplies are to be used only in accordance with this protocol and under the supervision of the investigator. Study drug administration and dosing compliance will be assessed at each study visit, starting with Cycle 2. A count of all study drug provided by the sponsor will be conducted during the study.

If dosing compliance is not 100% in the absence of toxicity, then subjects should be re-instructed regarding proper dosing procedures and may continue with the study. Subsequent dosing compliance procedure will be conducted at each study visit. If the number of study drug doses taken by the subject is 75% in the absence of toxicity or disease progression, then subjects should be re-instructed regarding proper dosing procedures. Subjects who have study drug dosing compliance of 75% for 2 consecutive cycles should be discontinued from the study.

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (subject by subject accounting), and accounts of any study drug accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned to sponsor or its representative.

## **7. PRESTUDY AND CONCOMITANT THERAPY**

All pre-study therapies administered up to 28 days before first dose of study drug must be recorded at screening. All concomitant therapies must be recorded on the subject's eCRF throughout the study beginning when the first dose of study drug is administered.

Concurrent enrollment in another investigational drug or device study is prohibited. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from study drug must be recorded in the concomitant therapy section of the eCRF.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

## 7.1. Permitted Supportive Care and Interventions

- Use of as needed opioid analgesics for cancer-related pain
- Bisphosphonates and denosumab for management of bone-related metastasis according to their market authorized approved label
- LHRH agonists to maintain testosterone <50 ng/dL or <1.7 nM (for those subjects who do not have orchiectomy)
- Conventional multivitamins, selenium and soy supplements
- Prednisone dose increase up 10 mg/day is permitted to manage refractory mineralocorticoid related toxicities
- Additional systemic glucocorticoid administration such as “stress dose” glucocorticoid is permitted when clinically indicated for a life threatening medical condition, and in such cases, the use of steroids will be documented as concomitant drug
- Transfusions and hematopoietic growth factors per institutional practice guidelines
- If the permissibility of a specific drug/treatment is in question, then please contact the study sponsor
- Radiotherapy

## 7.2. Special Concomitant Therapy

The following concomitant therapies warrant special attention:

Caution is advised when abiraterone acetate is administered with medicinal products activated by or metabolized by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolized by CYP2D6 should be considered. Examples of medicinal products metabolized by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter 3 products requiring CYP2D6 to form their active analgesic metabolites).

Based on in vitro data, abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme, CYP2C8. Examples of medicinal products metabolized by CYP2C8 include paclitaxel and repaglinide. There are no clinical data on the use of abiraterone acetate with drugs that are substrates of CYP2C8.

Based on in vitro data, abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (eg, phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Strong inhibitors and inducers of CYP3A4 during treatment are to be avoided, or used with caution.

For more information see Attachment 4.

### **7.3. Prohibited Medications**

- Investigational agents other than abiraterone acetate
- Other antineoplastic agents
- 5- $\alpha$ -reductase inhibitors
- Chemotherapy
- Immunotherapy
- Anti-androgens (e.g., bicalutamide, nilutamide, flutamide, cyproterone acetate) except in situations as outlined for management of tumor flare anticipated with the initiation of continuous LHRH agonist
- Systemic ketoconazole (or other azole drugs such as fluconazole or itraconazole)
- Diethylstilbestrol (DES) or similar
- Other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
- Radiopharmaceuticals such as strontium (89Sr) or samarium (153Sm) or similar analogues such as radium-223
- Spironolactone
- Digoxin, digitoxin, and other digitalis drugs, Fludrocortisone acetate (Florinef)

## **8. STUDY EVALUATIONS**

### **8.1. Study Procedures**

#### **8.1.1. Overview**

The Time and Events Schedule included in the Synopsis summarizes the frequency and timing of efficacy, and safety assessments. All visit-specific PRO assessments during a visit should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

#### **8.1.2. Screening Phase**

A signed informed consent must be obtained before any study-specific assessments are performed. Informed consent may be obtained up to 28 days before the first dose of study drug. Screening procedures to evaluate subject eligibility for the study will be conducted within 28 days prior to Cycle 1 Day 1.

Once select eligibility criteria are confirmed, subjects will be enrolled to the study.

### **8.1.3. Study Visits**

Subjects must start taking study drug within 7 days from the study enrollment. The treatment begins on Cycle 1 Day 1 and continues until PSA progression, clinical progression, consent withdrawal, or the occurrence of unacceptable toxicity.

Study visits for each cycle will have a 2 day window. Study visits will be calculated from the Cycle 1 Day 1 date and continues until PSA Progression Visit. Subjects may have imaging performed at any time as per discretion of Investigator, but image assessments are not part of this protocol.

Investigators will review all clinical, laboratory and imaging data, and will use this information to make decisions about dose modification and study medication discontinuation. PSA results from every other cycle starting with Cycle 2 will be available to the investigators. Investigators will need to notify if testosterone results do not fall below the definition of castration concentrations (<50 ng/dL or <1.7 nM).

### **8.1.4. PSA Progression/Early Withdrawal**

The PSA Progression Visit should be scheduled between 15 to 30 days after confirmation of PSA progression to collect protocol endpoints.

There is an expected data collection period of up to 24 months per patient after enrollment to monitor survival status and, if applicable, subsequent prostate cancer therapy.

### **8.1.5. Post-PSA Progression (Follow-Up)**

After PSA progression, subject status will be monitored every 3 months for up to 24 months (2 years) or until subject death, lost to follow-up, withdrawal of consent, or study termination. Information regarding survival status and initiation of subsequent prostate cancer therapies will be collected. If patient is using abiraterone acetate, adverse events and concomitant medication should be followed. Visits to the clinic are not required; sites may collect the information by telephone interview, chart review, or other convenient methods. If the follow-up information is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents.

In case of early study termination, any patients still receiving study drug will continue to do so, if the physician considers beneficial to the patient, under a Continued Access Program, following the applicable regulations. Investigators will be trained on Janssen and regulatory pharmacovigilance requirements and patients will be followed for safety until 30 days after the last study drug dose.

## **8.2. Efficacy**

### **8.2.1. Evaluations**

Considering that image assessment is not part of this protocol, tumor assessment if performed as per institution standard of care or in case of signs or symptoms suggestive of disease progression, including escalating pain not referable to another cause, worsening ECOG

performance status grade, or physical examination findings consistent with disease progression, will be recorded.

### **8.2.2. Endpoints**

#### **8.2.2.1. Primary Endpoint**

The primary endpoint is time to PSA progression (PSAP) defined as the date from enrollment to the date of first PSA progression (as per PCWG2)<sup>22</sup>.

- PSA progression (PCWG2) is defined as  $\geq 25\%$  and  $\geq 2$  ng/mL after 12 weeks (in case of no decline in PSA from baseline), or first PSA increase that is  $\geq 25\%$  and  $\geq 2$  ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (in case of decline of PSA from baseline).

#### **8.2.2.2. Secondary Endpoints**

- PSA response rate ( $\geq 50\%$  decline in PSA level from baseline at 12 weeks and at any time).
- Maximal PSA post-therapy change from baseline (maximal at 12 weeks or at any time point PSA post-therapy change from baseline presented in waterfalls).
- Overall survival (OS) (time from enrollment to death due to any cause).
- Patients' reports of pain (as measured by the average of the pain scores on the BPI-SF (range, 0 to 10, with higher scores indicating worse average pain). An increase in pain is defined as an increase in the baseline pain score at two consecutive visits by 30% or more, as measured by the average of the pain scores on the BPI-SF (range, 0 to 10, with higher scores indicating worse average pain), without a decrease in analgesic use.

#### **Exploratory:**

To investigate the association between SA levels (Androstenedione, Testosterone, DHEA, DHEAS) and PSA response and time to PSAP. Analyze SA variability from baseline to time to PSAP.

Furthermore serum samples (plasma) will be collected and stored at the time points (baseline, week 12 and PSA Progression) indicated in the Time and Events Schedule table for potential correlative translational research projects such as other serum androgens, and others biomarkers that may be discovered during the study. Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will have no scientific value, or there are not enough samples or not enough responders to allow for adequate biomarker evaluation.

#### **8.2.2.3. Brief Pain Inventory-Short Form (BPI-SF)**

Pain will be evaluated using the BPI-SF instrument. A sample of the BPI-SF questionnaire along with detailed instructions will be provided to the sites in a separate appendix.

### 8.3. Safety Evaluations

The evaluation period for safety will start at the time a signed and dated informed consent form is obtained to at least 30 days after the last dose of study drug or recovery from all acute toxicities associated with the study drug administration. Adverse events will be reported by the subject for the duration of the study. Adverse events including laboratory adverse events will be graded and summarized according to the NCI-CTCAE, Version 4.0.

Any clinically significant abnormalities persisting at the end of the study or during early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study will include the following evaluations of safety according to the time points provided in the Time and Events Schedule.

#### Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative). Adverse events will be followed by the investigator as specified in Section 11 Adverse Event Reporting.

#### Clinical Laboratory Tests

All laboratory tests will be performed by local laboratory. Blood samples for serum chemistry and hematology will be collected. The following tests will be performed:

Hematology Panel	Serum Biochemistry Panel	Liver Function Tests
<ul style="list-style-type: none"> <li>- hemoglobin</li> <li>- platelet count</li> <li>- white blood cells including neutrophil count</li> </ul>	<ul style="list-style-type: none"> <li>- potassium</li> <li>- creatinine</li> <li>- fasting glucose</li> <li>- lactate dehydrogenase</li> <li>- INR</li> </ul>	<ul style="list-style-type: none"> <li>- alanine aminotransferase (ALT/SGPT)</li> <li>- aspartate aminotransferase (AST/SGOT)</li> <li>- total bilirubin</li> <li>- albumin (Screening only)</li> </ul>

In addition, testosterone, androstenedione, DHEA, DHEAS and PSA will be evaluated periodically throughout the study. PSA results from every other cycle starting with Cycle 2 will be available to the investigators. Investigators will need to notify if testosterone results do not fall below the definition of castration concentrations (<50 ng/dL or <1.7 nM).

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

#### Electrocardiogram

Electrocardiograms (ECGs) (12-lead) will be recorded at screening. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the investigator. If blood sampling or vital sign measurement is scheduled at the same visit as ECG recording, then it is recommended that the procedures should be performed in the following

order: ECG(s), vital signs, blood draw. ECGs should not be obtained when serum potassium is <3.5 mM/L. Hypokalemia should be corrected prior to ECG collection.

### **Vital Signs**

Heart rate and blood pressure will be measured at Screening. At all subsequent study visits, including the PSA Progression Visit, only blood pressure will be measured.

### **Physical Examination**

Physical examinations will be directed at detecting adverse events and should be completed as specified in the Time and Events Schedule. Physical examinations should be performed by the same evaluator throughout the study, whenever possible. Subject height will be measured at screening only. Weight will be measured at Screening and Study visits until PSA Progression Visit. Physical examination includes head, eyes, ears, nose and throat, chest, cardiac, abdominal, extremities, neurologic, and lymph node examinations. Any clinically significant change in physical findings noted during the study should be reported as an adverse event. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

### **8.4. Sample Collection and Handling**

The actual dates of sample collection must be recorded in the eCRF according to laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections. Instructions for the collection, handling, and shipment of biomarker samples are found in the “Sample Collection and Handling Manual” that will be provided separately for sample collection and handling.

## **9. SUBJECT COMPLETION/WITHDRAWAL**

### **9.1. Study Completion**

A subject will be considered to have completed the study if assessments have been completed until PSA Progression Visit. Subjects that have discontinued treatment for any reason will keep on the Follow-up Phase. There is an expected data collection period of up to 24 months per patient after enrollment to monitor survival status and, if applicable, subsequent prostate cancer therapy.

### **9.2. Discontinuation of Study Treatment**

Discontinuation of a study drug will not result in automatic withdrawal from the study.

A subject should ordinarily be maintained on study treatment until PSA progression as defined Section 8.2.2.1.

However, a subject's study treatment may be discontinued for:

- Radiographic progression as per RECIST v1.1
- Clinical Progression defined as:

- Deterioration in ECOG performance status to grade 3 or higher
- Need to initiate any of the following because of tumor progression (even in the absence of radiographic evidence of disease)
  - Anticancer therapy for prostate cancer
  - Radiation therapy
  - Surgical interventions for complications due to tumor progression
- Dosing noncompliance or delay the start of next cycle for more than 4 weeks (due to toxicity)
- Withdrawal of consent for continued treatment
- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to stop treatment. All attempts to obtain imaging studies at the time of treatment discontinuation should be made to assess for radiographic progression.
- Study data will continue to be collected after discontinuation of treatment, unless the subject withdraws consent for further study participation.

### **9.3. Withdrawal from the Study**

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent for subsequent data collection

If a patient is lost to follow up, all possible efforts must be made by the study site personnel to contact the subject and to determine endpoint status and the reason for the discontinuation/withdrawal. The measures taken for follow up must be documented. The informed consent will stipulate that even if a subject decides to discontinue the study drug, he will agree to be contacted periodically by the investigator to assess endpoint status.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be re-assigned to another subject. Subjects who withdraw will not be replaced.

## **10. STATISTICAL METHODS**

Statistical analysis will be performed by the sponsor or under the supervision of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects, mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and

percentages. The baseline measurement will be the last value on or before the date of first study treatment.

Interim analysis could be performed during this study.

### **10.1. Subject Information**

The ITT population will include all subjects who enter onto this multicenter, single-arm, phase II study.

Subject disposition, demographic and baseline characteristics will be performed on data from the ITT population.

The safety population will include all subjects who receive at least 1 dose of any study drug. All baseline characteristics, treatment exposure, safety, toxicity and laboratory test analysis will be run on this database.

The efficacy population will include all eligible subjects who receive at least one dose of any study drug. All efficacy tables will be run on this database.

### **10.2. Sample Size Determination**

We assumed that the medium time to PSAP of Abiraterone plus prednisone in CRPC patients, which had failed to DES therapy, would be 8.5 months as in historical data with DES and ketoconazole<sup>1-3</sup>. A 5 months time to PSAP is the minimum effect to consider drug activity in this setting such as first-line chemotherapy<sup>4,5</sup>. Considering an uniform accrual over 1 year enrollment period, 6 months follow-up time and exponentially distributed PSAP times, a two-sided test for the median<sup>7</sup> with an alpha level of 0.05 and a power of 80%, 40 patients would need to be enrolled. In addition, considering a drop-out rate of 10%, a total sample size of 45 patients is planned for the study.

### **10.3. Demographics and Baseline Characteristics**

Demographic variables will include age, race, height, and weight. Baseline disease characteristics will include time from diagnosis, number of prior hormonal therapies, and other clinical characteristics as documented in the e-CRF.

### **10.4. Efficacy Analyses**

Efficacy endpoints are described in Section 8.2.2.

All continuous variables will be summarized using number of subjects (n), mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized using frequencies and percentages. All efficacy endpoints will be analyzed using the efficacy analysis population.

Distributions of time-to-event will be estimated using the Kaplan-Meier product limit method and will be graphically displayed. The median times to event with two-sided 95% confidence intervals will be estimated. Non-stratified analysis will be conducted. Cox proportional hazards regression models will be used to evaluate potential covariates that may affect the estimates of

event-free survival time. The covariate effect will be estimated using a hazard ratio and its 95% confidence interval obtained from these models.

Response rate variable will be the proportion of patients fulfilling the respective criteria for response and will be reported with the 95% exact confidence limits for the binomial proportion.

Additional exploratory analyses may be performed if deemed necessary.

## **10.5. Biomarker Analyses**

Biomarker studies are designed to confirm prior findings in asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer. SA analyses will be conducted on blood samples from entire study population and serum samples for correlative translational research will be collected at 3 time points (baseline, week 12 and at the time of PSA progression/ end of study) from all subjects.

The associations of SA with clinical response or time-to-event endpoints will be assessed using the appropriate statistical methods (logistic regression model or survival model will be used), depending on the endpoint. Other clinical covariates (such as age, tumor burden) may also be included in the model. Correlation of baseline expression levels with response or time-to-event endpoints will identify responsive (or resistant) subgroups. Biomarker results might be reported separately from the clinical study report due to its exploratory nature.

## **10.6. Safety Analyses**

Subjects who receive at least 1 dose of any study drug will be analyzed for safety. The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

### **Adverse Events**

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the NCI-CTCAE, Version 4.0. Treatment-emergent adverse events are those events that occur or worsen on or after first dose of study drug through 30 days post last dose and will be included in the analysis. Adverse events will be summarized by system organ class and preferred term, and will be presented overall. Serious adverse events and deaths will be provided in a listing. All adverse events resulting in discontinuation, dose modification, dosing interruption, or treatment delay of study drug will also be listed and tabulated by preferred term.

### **Clinical Laboratory Tests**

Clinical laboratory test results will be collected from screening until PSA Progression Visit. Laboratory data will be summarized by type of laboratory test using descriptive statistics at each measurement time point. Parameters with predefined NCI-CTCAE, Version 4, toxicity

grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

## **Vital Signs and Physical Examination**

Descriptive statistics of BP (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized. Descriptive statistics of changes from baseline in physical examinations will be summarized at each scheduled time point.

## **11. ADVERSE EVENT REPORTING**

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

### **11.1. Definitions**

#### **11.1.1. Adverse Event Definitions and Classifications**

##### **Adverse Event**

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Committee on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 11.3.1, All Adverse Events, for time of last adverse event recording).

##### **Serious Adverse Event (SAE)**

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death should it have been more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important\*

\*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 should usually be considered serious.

### **Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An AE is considered unlisted when the nature or severity is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

### **Adverse Event Associated With the Use of the Drug**

An adverse event is considered associated with the use of the drug when the attribution is possible, probable, or very likely by the definitions listed in Section 11.1.2.

#### **11.1.2. Attribution Definitions**

##### **Not Related**

An adverse event that is not related to the use of the drug.

##### **Doubtful**

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

##### **Possible**

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

##### **Probable**

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

##### **Very Likely**

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

### **11.1.3. Severity Criteria**

The NCI-CTCAE v4.0 will be used to grade the severity of adverse events.

Any adverse event not listed in the CTCAE will be graded as follows:

**Grade 1, Mild:** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Grade 2, Moderate:** Sufficient discomfort is present to cause interference with normal activity.

**Grade 3, Severe:** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

**Grade 4, Life-threatening:** Urgent intervention indicated.

**Grade 5, Death:** Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

### **11.2. Special Reporting Situations**

Safety events of interest on a sponsor medicinal product that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor medicinal product
- Suspected abuse/misuse of a sponsor medicinal product
- Inadvertent or accidental exposure to a sponsor medicinal product
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor medicinal product, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

### **11.3. Procedures**

#### **11.3.1. All Adverse Events**

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until 30 days after last dose of study drug. Serious adverse events, including those spontaneously reported to the investigator

within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unlisted (unexpected) and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, when appropriate) must be provided with a "study card" indicating the following:

- Subject's name
- Subject number
- Subject's date of birth
- Study site number
- Investigator's name and 24-hour contact information
- Local sponsor's name and 24-hour contact information
- Statement that the subject is participating in a clinical study

### **Clinical Laboratory Adverse Events**

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the Sponsor's medical monitor (or his/her designated representative), or until a diagnosis that explains them is made. The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, or

- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting as an adverse event), or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, or
- Test result leads to any of the outcomes included in the definition of a serious adverse event, or
- Test result is considered to be an adverse event by the investigator or Sponsor.

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for Condition 4. Clinically significant laboratory results must be recorded in the subject's eCRF.

### **11.3.2. Serious Adverse Events**

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, when a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in the absence of an adverse event

- Surgery or procedure planned before entry into the study (must be documented in the eCRF)

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported when they fulfill the serious adverse event definition (see Section 11.1.1).

During the follow-up phase of the study, deaths regardless of causality and serious adverse events thought to be related to study drug will be collected and reported within 24 hours of discovery or notification of the event and documented.

### **11.3.3. Pregnancy**

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

### **11.3.4. Contacting Sponsor Regarding Safety**

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

## **12. PRODUCT QUALITY COMPLAINT HANDLING**

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

### **12.1. Procedures**

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, then the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 11.3.2). A sample of the suspected product should be maintained for further investigation when requested by the sponsor.

## **12.2. Contacting Sponsor Regarding Product Quality**

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

## **13. STUDY DRUG INFORMATION**

### **13.1. Physical Description of Study Drug(s)**

Abiraterone acetate 250 mg tablets are oval, white to off-white and contain abiraterone acetate and compendial (USP/NF/EP) grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and purified water, in descending order of concentration (the water is removed during tableting).

### **13.2. Packaging**

The study drugs will be packaged in individual subject kits. Subjects will be provided with a 30-day supply to allow for visits to occur every 28 days with a  $\pm$  2 day window. Study drug will be dispensed in child-resistant packaging.

### **13.3. Labeling**

Study drug labels will contain information to meet the applicable regulatory requirements.

### **13.4. Preparation, Handling, and Storage**

The study drugs must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol. Study drugs should be stored at room temperature. Additional information is provided in the abiraterone acetate Investigator's Brochure.

### **13.5. Drug Accountability**

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. These requirements also apply to prednisone capsules supplied by the sponsor.

All study drugs must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the drug return form.

All study drugs should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be

supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his study drug to the site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

## **14. STUDY-SPECIFIC MATERIALS**

The investigator will be provided with the following supplies:

- Investigator Brochure
- Pharmacy manual/site investigational product procedures manual
- Sample Collection and Handling manual
- eCRF
- BPI-SF Questionnaire

## **15. ETHICAL ASPECTS**

### **15.1. Study-Specific Design Considerations**

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Ongoing medical review is completed by the sponsor.

The blood volume to be collected is approximately 5 to 10 mL per study visit. For subjects participating in the correlative translational study, the blood volumes will be 5 to 10 mL per study visit.

Subjects will receive low-dose prednisone 5mg/day. The prednisone dose used in this study is lower than the prednisone 10mg/day dose used in other abiraterone acetate Phase 3 studies COU-AA-301 and COU-AA-302 that enrolled advanced symptomatic mCRPC patients. The higher prednisone dose in other Phase 3 studies was selected because it is commonly used as the standard of care in combination with approved chemotherapy agents or as monotherapy for palliation of symptoms in advanced prostate cancer patients. The required use of prednisone in combination with abiraterone acetate is to help mitigate the symptoms of mineralocorticoid excess caused by CYP17 inhibition, which is the mechanism of action of abiraterone acetate. Data from early Phase 1/2 studies with abiraterone acetate in patients with mCRPC demonstrate that dexamethasone 0.5mg once daily (equivalent to prednisone dose of 3.33 mg once daily) was effective in mitigating the mineralocorticoid effects of abiraterone acetate<sup>1-3</sup>. The protocol

allows for the dose of prednisone to be increased to 10 mg/day if required to manage mineralocorticoid toxicities.

## **15.2. Regulatory Ethics Compliance**

### **15.2.1. Investigator Responsibilities**

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

### **15.2.2. Independent Ethics Committee or Institutional Review Board**

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, when applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, when applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, any amendments, the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- When applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, when applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification when a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

### **15.2.3. Informed Consent**

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The

informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his disease. Subjects will be told that alternative treatments are available should they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up when needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject is authorizing such access, and agrees to allow his study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments or to obtain information about his survival status.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject is unable to read or write, then an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

#### **15.2.4. Privacy of Personal Data**

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

### **15.2.5. Country Selection**

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 15.1.

## **16. ADMINISTRATIVE REQUIREMENTS**

### **16.1. Protocol Amendments**

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

### **16.2. Regulatory Documentation**

#### **16.2.1. Regulatory Approval/Notification**

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, when applicable. A study may not be initiated until all local regulatory requirements are met.

#### **16.2.2. Required Prestudy Documentation**

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and any amendment(s), signed and dated by the principal investigator

- A copy of the dated and signed, written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and when applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, then a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, then documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, when applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), when applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, when applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), when applicable

### **16.3. Subject Identification, Enrollment, and Screening Logs**

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by ID and date of

birth. In cases where the subject is not randomized into the study, the date seen and the date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

#### **16.4. Source Documentation**

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, when applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

#### **16.5. Case Report Form Completion**

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (eg, pain scale information) to be recorded in the eCRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. When necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (when applicable) and complete the query.

When corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager can generate a query for resolution by the investigational staff
- Clinical data manager can generate a query for resolution by the investigational staff

### **16.6. Data Quality Assurance/Quality Control**

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.

### **16.7. Record Retention**

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 7, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period when required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, then custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, then the investigator must permit access to such reports.

## **16.8. Monitoring**

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, then the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

## **16.9. Study Completion/Termination**

### **16.9.1. Study Completion**

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject assessment at that site, in the time frame specified in the Clinical Trial Agreement.

### **16.9.2. Study Termination**

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development

- Patients do not reach PSAP after at least 24 months of treatment and do not show clinical progressive results for more than 12 months.

#### **16.10. On-Site Audits**

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees. Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor when they have been contacted by a regulatory agency concerning an upcoming inspection.

#### **16.11. Use of Information and Publication**

All information, including but not limited to information regarding abiraterone acetate or the sponsor's operations (e.g. patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of abiraterone acetate, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of exploratory biomarker results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish site-specific data after the primary data are published. If an investigator wishes to

publish information from the study, then a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, then the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

### **Registration of Clinical Studies and Disclosure of Results**

The sponsor will register or disclose the existence of and the results of clinical studies as required by law.

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**Attachment 1: SUMMARY OF RECIST CRITERIA VERSION 1.1**

The following information was extracted from Section 3, Section 4, and Appendix I of the New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) authored by Eisenhauer et al (2009). Refer to the European Journal of Cancer article (2009;45(2):228-247) for the complete publication.

**Measurability of tumor at baseline****3.1 Definitions At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:****3.1.1 Measurable**

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

The following two methods of measure are not allowed in this protocol:

- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

- 20 mm by chest X-ray

- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also 'Baseline documentation of target and non-target lesions' in section 4.2 of the RECIST guideline for information on lymph node measurement.

**3.1.2 Non-measurable** 

All other lesions, including small lesions (longest diameter  $<10$  mm or pathological lymph nodes with  $\geq 10$  to  $<15$  mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

**3.2 Specifications by methods of measurements****3.2.1 Measurement of lesions**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

### 3.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination.

## 4. Tumor response evaluation

### 4.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

### 4.2 Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al. (Reference #10 in Eisenhauer publication).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Lymph nodes merit special mention since they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II of the Eisenhauer reference). All other pathological nodes (those with short axis  $\geq 10$  mm but  $<15$  mm) should be considered non-target lesions. Nodes that have a short axis  $<10$  mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline

sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

#### 4.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

##### 4.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to  $<10$  mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

##### 4.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of  $<10$  mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis  $<10$  mm. For PR, SD and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become ‘too small to measure’. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist

may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

#### **4.3.3 Evaluation of non-target lesions**

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

**Non-CR/Non-progressive disease:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**Progressive Disease:** Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

#### **4.3.4 Special notes on assessment of progression of non-target disease**

**The concept of progression of non-target disease requires additional explanation as follows:**

When the patient also has measurable disease. In this setting, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for

unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as ‘sufficient to require a change in therapy.’ If ‘unequivocal progression’ is seen, the patient should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

#### 4.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

#### 4.4.1 Timepoint response

It is assumed that at each protocol specified timepoint, a response assessment occurs. Table 1 in this attachment provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 in this attachment is to be used.

#### 4.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of progressive disease. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion.

#### 4.4.3 Best overall response: all timepoints

**The best overall response is determined once all the data for the patient is known.**

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

**Table 1: Timepoint Response: patients with Target (+/- no target) disease 1**

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; NE = not evaluable.

Table 2: Timepoint Response: patients with non-target disease only i

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; NE = not evaluable.  
 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 studies so to assign this category when no lesions can be measured is not advised.

**Attachment 2: ECOG PERFORMANCE STATUS****ECOG Grade Scale (with Karnofsky conversion)**

0 Fully active, able to carry on all predisease performance without restriction. (Karnofsky 90-100)

1 Restricted in physically strenuous activity but ambulatory and able to carry out work on a light or sedentary nature, eg, light housework, office work. (Karnofsky 70-80)

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. (Karnofsky 50-60)

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

5 Dead. (Karnofsky 0)

Based on published in Am. J. Clin. Oncol<sup>23,24</sup>..:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

**Attachment 3: NEW YORK HEART FAILURE CRITERIA**

The following table presents the New York Heart Association classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease

Reference <sup>23,24</sup>: American Heart Association. Classes of heart failure. Available at [http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure\\_UCM\\_306328\\_Article.jsp](http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp). Accessed September 6, 2011.

**Attachment 4: ADDITIONAL INFORMATION ON CYP450 DRUG INTERACTIONS**

<http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractions/ucm093664.htm>

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

**INVESTIGATOR AGREEMENT**

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Telephone Number: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Rosemarie Gidekel \_\_\_\_\_

Institution: Janssen Research & Development \_\_\_\_\_

Signature: ROSEMARIE  
GIDEKEL \_\_\_\_\_ Date: \_\_\_\_\_  
(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.