Clinical Study Protocol

Study Title:	OPEN LABEL PHARMACODYNAMIC STUDY OF ABIRATERONE ACETATE IN THE TREATMENT OF METASTATIC, CASTRATION RESISTANT PROSTATE CANCER
Study Number:	0801 Cancer Consortium # 7639
Study Phase:	2
Product Name:	Abiraterone acetate
IND Number:	Exempt
Indication:	Treatment of metastatic, castration resistant prostate cancer
Protocol version	Current Version Date: 09/10/2015 v. 6.0

SYNOPSIS

Study Title:
Open label pharmacodynamic study of abiraterone acetate in the treatment of metastatic, castration resistant prostate cancer.

Study: Investigator-initiated, Phase II

Funding support and abiraterone acetate provided by Janssen Services

Primary Objective:

To determine the magnitude of tissue testosterone suppression by abiraterone acetate in metastatic CRPC (resistant to LHRH agonist or orchiectomy ± antiandrogen) after one month of treatment to establish tissue based mechanism of action.

Exploratory Objectives:

- To determine the ability of abiraterone acetate to suppress tumor testosterone after 12 weeks of treatment.
- To determine tissue testosterone from metastasis at time of radiographic progression during abiraterone acetate treatment.
- To determine response to dose escalation of abiraterone acetate at clinical progression
- To determine potential mechanisms of resistance to abiraterone acetate by analyzing pharmacokinetics at clinical progression, tissue androgen levels at baseline and at radiographic progression, evaluating wild type and splice variant AR levels at baseline and at time of progression and cDNA microarray at progression
- To determine if microRNA acquired from peripheral blood reflect molecular changes in tumor metastases and are a potential biomarker for mechanisms of sensitivity and resistance.
- To evaluate pharmacokinetics of dose escalated abiraterone at 1000 mg twice daily

Study Population:

Men with metastatic, castration resistant prostate cancer amenable to biopsy

- **Investigational Product, Dose and Mode of Administration:**
  Abiraterone acetate, 1000 mg/dose (4 x 250-mg tablets) given orally, at least 2 hours before a meal and 1 hour after a meal, initially given once a day, then twice a day at dose escalation.
- Abiraterone acetate will be administered with prednisone 5 mg given orally twice daily

Duration of Treatment:

All patients will undergo pretreatment metastasis biopsy. All patients will receive Lupron or orchiectomy combined with abiraterone acetate and prednisone until radiologic or clinical progression as defined by Prostate Cancer Working Group 2 criteria. Patients will be sequentially enrolled in three cohorts, to undergo repeat biopsy at 4 weeks (cohort 1), 12 weeks (cohort 2) or at progression (cohort 3). Dose escalation after initial radiographic progression for all patients is allowed until there is evidence of additional radiographic or clinical progression.

Endpoints

Primary Endpoint:

- Tissue testosterone

Exploratory endpoints

- Tissue and serum DHT, androstenedione, DHEA,
- PSA kinetics and radiologic changes by RECIST 1.1
- Androgen receptor – wild type and splice variant levels
- cDNA microarray analysis, RT-PCR
- MicroRNA
- Pharmacokinetics of abiraterone

Statistical Methods for sample size calculation

The primary endpoint is evaluation of the suppression of tissue testosterone from baseline (the last value on or before the date of first study treatment) to the 4-week time point. Sample size calculations for this endpoint are based on xenograft studies of abiraterone acetate. Planned analysis of primary and exploratory endpoints involves numerical and graphical summaries and standard statistical hypothesis tests and linear-model-based inference.

Basal tissue testosterone and testosterone after abiraterone acetate treatment at response were derived from xenograft studies of abiraterone acetate effect in castrate male mice. Baseline tissue testosterone in untreated CRPC xenografts was 0.687 ± 0.364 (mean ± SD) pg/mg, approximating that seen in human CRPC metastases. Nadir tissue testosterone after 7–21 days was 0.027 ± 0.009 pg/mg, approximating 4-week levels. Using the SD of testosterone derived from untreated observations (0.364 pg/mg), 6 patients provide 94% power to detect the anticipated 0.660 pg/mg difference in tissue testosterone relative to baseline based on a 2-sided paired t-test with alpha 5%. Ten patients per cohort will be included to account for potentially unproductive biopsies.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AR	Androgen receptor
AST	Aspartate aminotransferase (SGOT)
BUN	Blood urea nitrogen
C	Celsius
CBC	Complete blood count
CrCl	Creatinine clearance
CFR	Code of Federal Regulations
CRF	Case Report Form
CRPC	Castration resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	Dehydroepiandrosterone
ECG	Electrocardiogram
F	Fahrenheit
FDA	Food and Drug Administration
HEENT	Head, Eyes, Ears, Nose, Throat
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
LDH	Lactic dehydrogenase
LHRH	Luteinizing hormone releasing hormone

LN	Lymph Node
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
OS	Overall survival
PFS	Progression Free Survival
PR	Partial Response
PT	Prothrombin time
PTT	Partial thromboplastin time
PSA	Prostate Specific Antigen
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
WBC	White blood cell (count)

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1 INTRODUCTION

1.1 Advanced Prostate Cancer and Efficacy of Standard Androgen Deprivation

Androgen deprivation therapy (ADT) has been the primary treatment for patients with advanced prostate cancer since the seminal recognition of the disease as androgen-dependent by Huggins and Hodges in 1941 [1]. Although highly effective in stabilizing disease in hormone-naïve patients, ADT is uniformly marked by progression to recurrent, castration-resistant disease over a period of 18-20 months following the initiation of treatment, with an ensuing median survival of one to two years.

Numerous investigators have shown that despite achieving castrate serum testosterone (T) levels, intraprostatic androgen levels remain substantial, at about 20-25% of the levels found in untreated patients [2-4]. Soft tissue metastases from patients with anorchid serum testosterone contain tumoral levels of T which are higher than levels in prostate tumors in eugonadal men [5]. Transcript levels for enzymes of androgen synthesis, including CYP17, were upregulated in the same tumors from 8 to 30 fold, suggesting that tumoral synthesis from cholesterol is possible. These levels of testosterone and dihydrotestosterone (DHT) are well within the concentration of androgens able to activate the androgen receptor and to mediate proliferation and survival of prostate cancer cells. Therefore, 'castrate' levels of T and DHT are clearly capable of continuing to modulate intraprostatic androgen-regulated gene expression, protein synthesis, cell survival and proliferation, [4, 6, 7] suggesting that clinical castration defined by serum T levels cannot be equated with cellular castration at the tissue and genomic level. Intratumoral androgens, including residual T, DHT and adrenal androgens, are implicated in nearly every mechanism whereby AR-mediated signaling leads to the development of castration-resistant disease [8-11]. These mechanisms include: 1) AR hypersensitivity due to AR gene amplification, over-expression, increased AR stability, or co-regulator alterations that modulate ligand sensitivity [12-14]; 2) AR mutations that broaden ligand specificity and confer sensitivity to adrenal androgens [15]; 3) nongenomic mechanisms whereby residual T and DHT modulate signaling cascades (11); and 4) tumor-specific dysregulation of steroid metabolic pathways effectively potentiating the intraprostatic conversion of adrenal androgens to T and DHT. [16-18].

The next generation of effective agents in the treatment of prostate cancer leverage the ability to block tissue androgen synthesis more completely. Abiraterone acetate is a specific CYP17 inhibitor with activity demonstrated against CRPC. The proposed mechanism of action is suppression of androgen levels in tumor tissue as a result of suppression of testicular, adrenal and tumoral CYP17 activity. Clinical studies have demonstrated suppression of serum androgen levels [19] and xenograft studies from our group demonstrate suppression of tumor tissue androgens in preclinical models even in the setting of castrate serum levels [20]. Phase I and II studies have been published and demonstrated safety of the agent as well as efficacy of the drug in men with CRPC both before and after docetaxel therapy [21, 22]. These studies led to the definitive phase III registration study, COU-AA-301 in men with metastatic CRPC. In this study, 1195 men with CRPC previously treated with docetaxel based chemotherapy were randomized to abiraterone acetate with prednisone or prednisone alone [23]. The study demonstrated a 3.9 month median survival advantage, with a hazard ratio of 0.65, favoring abiraterone acetate therapy. Systemic effects attributable to abiraterone acetate were primarily related to increased mineralocorticoid levels (hypertension,

hypokalemia, edema). The improvement in relative risk of death is better than other drugs used in the treatment of advanced disease and led to FDA approval of abiraterone acetate for the treatment of metastatic, CRPC in patients treated with docetaxel. Abiraterone acetate is an effective hormonal therapy which directly targets steroidogenesis and suppresses serum hormone levels while improving survival. As the first in a new generation of agents targeting androgen receptor signaling, critical questions remain to be answered regarding mechanisms of effect in tissue and relevant mechanisms of de novo and acquired resistance.

Previous work cited above demonstrated that despite the ability of standard androgen deprivation to suppress serum androgens, there is limited effect on tissue androgens and resistance is associated with augmented signaling through the androgen receptor [5, 13, 24]. Our group has performed detailed analysis of the effects of abiraterone acetate in two human CRPC xenografts grown in castrate murine hosts. These studies demonstrate that; 1) Abiraterone acetate suppresses tissue hormone levels and improves survival in two human prostate cancer xenografts, in an animal model lacking adrenal androgens; 2) Exposure to abiraterone acetate induced upregulation of both wild type androgen receptor (AR) and oncogenic splice variant AR's lacking ligand binding domain. These data suggest that abiraterone acetate suppresses de novo androgen synthesis by tumor and that resistance to abiraterone acetate therapy is mediated by upregulation of AR in an attempt to bypass the decrease in tissue androgens. In addition, a subset of tumors recurred with elevated tissue androgen and CYP17 levels, suggesting breakthrough of CYP17 inhibition. These mechanisms of resistance would provide potentially important points of inflection for either preventing or treating abiraterone acetate resistance in human tumors. There have been no studies evaluating abiraterone acetate effect on tumor tissue from patients. This study is designed to evaluate abiraterone acetate effect on tissue androgen levels in metastases from patients with metastatic CRPC, while evaluating tumoral AR and androgens over the course of treatment as a potential point of inflection for determining optimal combinations and sequential therapy. Dose escalation will be explored to determine if 1000 mg twice daily will improve tumor control. Those studies noted above show that there is no additional toxicity at 2000 mg daily compared to the standard dosing of 1000 mg daily and the lower dose was used because there was serum androgens were equally suppressed and there was no clear improvement in initial response in the phase I cohorts in patients who had never been treated with abiraterone acetate. Induction of abiraterone metabolism resulting in suboptimal pharmacokinetics and pharmacodynamic effect on tumor is an additional potential mechanism of secondary resistance to abiraterone therapy. There is limited data available regarding abiraterone pharmacokinetics after prolonged dosing of abiraterone and there is evidence that ability of other, less effective CYP17 inhibitors such as ketoconazole, to suppress androgen levels wanes with time due either to incomplete CYP17 block or altered pharmacokinetics [31, 32]. The addition of formal pharmacokinetic evaluations before and after dose escalation would provide important information about secondary resistance to abiraterone therapy.

1.2 Abiraterone acetate (JNJ212082)

Abiraterone acetate is a steroidal irreversible inhibitor of CYP17 (17α hydroxylase/C17,20-lyase), blocking 2 important enzymatic activities in the synthesis of testosterone (Figure 1), based on the observation that nonsteroidal 3 pyridyl esters improved selectivity for inhibition of 17α-hydroxylase/C17,20 lyase. Abiraterone acetate is a potent inhibitor with an apparent inhibition constant of 0.5 nM. In patients with castration resistant prostate cancer which was chemotherapy

naïve, PSA response rates were 65%, and in those with previously treated with docetaxel, the PSA response rate was 50% with an objective response rate of 22% [25]. These response rates are significantly better than any agent in chemotherapy naïve or pretreated patients. Pharmacodynamic studies demonstrated that its effects on adrenal steroid synthesis were consistent with its mechanism of action. Antitumor effects were evident with PSA response and durable objective responses using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [26]. In the initial phase I study there were no grade 3 or 4 toxicities reported. In a heavily pretreated patient population who had received prior docetaxel, the incidence of grade 3 and 4 toxicity was 25%, with 4 % grade 4 toxicity. The grade 4 toxicities were a single episode of pneumonia and a second malignancy. Thee adverse events from two phase III studies, study 1 (COU-301) and study 2 (COU-302) were as follows

Table 1: Adverse Reactions due to ZYTIGA in Study 1

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542) All Grades[1] %	 Grade 3-4 %	Placebo with Prednisone (N=540) All Grades %	 Grade 3-4 %
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

Abiraterone may cause fetal harm when administered to a pregnant woman. Abiraterone is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug the patient should be apprised of the potential hazard to the fetus. Women who are pregnant or women who may be pregnant should not handle abiraterone without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with abiraterone.

1.2.1 Dosing Rationale

The dose of abiraterone acetate to be used in this study is 1000 mg daily based on results of the phase III study, COU-AA-301. In the first Phase 1 study with capsule formulation (COU-AA-001) [26], abiraterone acetate was evaluated for safety, pharmacokinetics, and its effects on adrenal steroid synthesis at dose levels ranging from 250 mg to 2000 mg. Consistent with abiraterone acetate's mechanism of action, hypertension (HTN), hypokalemia, and edema were the most commonly-observed drug-related adverse events, which were manageable with medication. Adrenal metabolite analysis showed inhibition of CPY17 even at low doses of abiraterone acetate and a compensatory increase of corticosterone and deoxycorticosterone. Analysis showed that abiraterone acetate was well tolerated at all dose levels, including 2000 mg daily, with no grade 3 or greater toxicity at 2000 mg daily. There were no hospital admissions related to study drug or any evidence of clinically significant adrenal insufficiency. Pharmacokinetic (PK) studies showed increased systemic drug exposure at higher doses. Responses to abiraterone acetate were seen at similar rates for all doses of drug which substantially suppressed serum androgen levels. Because no clear difference in response in these chemotherapy and abiraterone acetate naïve patients was discernible at higher doses, further dose escalation was stopped beyond 2000 mg daily and the 1000 mg daily dose was used as there was no clear additional effect on serum androgen levels. Higher dose levels have not been tested in patients with tumor progression while receiving abiraterone acetate. The potential that tumors in patients might escape abiraterone acetate effect by upregulating CYP17, as demonstrated in our recently published data in preclinical models (section 1.1), provides rationale for increasing dose in the event of tumor progression.

1.2.2 Concurrent Prednisone

In ongoing studies, patients receiving abiraterone acetate are being treated concurrently with glucocorticoids, including prednisone. Based on the mechanism of abiraterone acetate action and observations in patients with congenital deficiency of CYP17, it was anticipated that a state of mineralocorticoid excess could occur after pharmacologic inhibition of CYP17. Resulting reduced cortisol levels may lead to a compensatory ACTH surge thereby resulting in hypertension, hypokalemia, and fluid retention. Notably, patients with the rare syndrome of congenital CYP17 deficiency do not develop adrenocortical insufficiency as corticosterone synthesis is unaffected. However, as corticosterone is a weaker glucocorticoid than cortisol, interruption of negative feedback control of adrenocorticotrophic hormone (ACTH) occurs, resulting in high levels of ACTH and steroid precursors upstream of CYP17 [27]. As expected, when abiraterone acetate was used as a single agent in Phase 1 and 2 studies, hypertension, hypokalemia, and fluid retention were observed and were primarily CTC grade 1-2 in severity. These side effects were readily managed with potassium supplementation, eplerenone (selective mineralocorticoid antagonist), antihypertensive agents, and low dose corticosteroids. Grade 1-2 fatigue was observed in some patients and was associated with discontinuation of corticosteroids as required per Phase 2 protocol entry criteria and extended duration of treatment with abiraterone acetate. Although there was no evidence of a dose-response relationship, administration of low dose corticosteroids as specified in the study improved symptoms of fatigue and tolerability of abiraterone acetate, including symptoms of mineralocorticosteroid excess. The improved tolerability of abiraterone acetate after concomitant administration of low-dose corticosteroids was associated with suppression of ACTH surge and upstream adrenal

steroids, suggesting that this combination may be a better tolerated and safer regimen in this older and frail patient population. Prednisone was selected over other corticosteroids because it is commonly used as standard of care in combination with approved chemotherapy agents. The regimen of abiraterone acetate 1000 mg daily and low dose prednisone 5-mg twice daily, as tested in the phase III study has been chosen for subjects in this study. When dose of abiraterone is escalated to 1000 mg twice daily, the dose of prednisone will be maintained at 5 mg twice daily. The primary reason for maintaining the dose of prednisone is that in phase I with higher dose abiraterone, there was no increase in the risk of adverse events related to increased mineralocorticoids or decreased cortisol. Adrenal insufficiency is not seen as a result of increased corticosterone levels with CYP17 blockade, which will be unchanged with higher dose abiraterone. .

1.3 Rationale for Study Design

The studies cited demonstrate that the androgen axis remains the most important determinant of progression and probably the most important target to prevent progression of prostate cancer. Moreover, the evidence suggests that current treatment strategies lack optimal efficacy in achieving androgen ablation and tumor cell apoptosis, and that the adequacy of interrupting the AR pathway cannot be determined from serum androgen levels, but must be ascertained at the tissue and molecular level [4, 5]. The hypothesis of this study is that abiraterone acetate achieves more effective tumor control through suppression of adrenal and tumoral androgen production and will result in lower intratumoral levels of DHT and testosterone. Confirming tissue suppression of tumor androgens is critical as the limited ability of standard LHRH agonist therapy to suppress tissue androgens has only recently been recognized more than 60 years after the treatment was described. Similarly, delineating whether tissue based mechanisms of ligand production or receptor regulation are operative at resistance is critical to designing more effective therapy. Tissue androgen levels and components of the AR signaling axis can only be assessed from tumor tissue. All patients in the current study will undergo pretreatment biopsy of metastasis amenable to biopsy, including bone, node or soft tissue. The Genitourinary oncology group has participated in multiple studies which require pretreatment tumor biopsy using CT guided tissue acquisition, with successful tissue acquisition in 70% of the biopsy sessions. Patients unable to undergo metastasis biopsy may undergo biopsy of primary prostate instead, as resistant primary prostate cancer also upregulates androgens. The standard operating procedure for tissue acquisition and processing is contained in the separate lab manual (Tissue Acquisition and Processing). Tissue from the six core biopsies will be collected and analyzed for tissue DHT, testosterone, DHEA and androstenedione, as well as AR and AR splice variants. These assays are well established within our group [5, 28, 29]. Serum androgens drawn at the same time intervals will be compared with the tissue androgens measured above. Three cohorts of patients will be treated with LHRH agonist or orchiectomy, Abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily in order to allow evaluation of tissue androgens and mechanisms of resistance to abiraterone acetate. The total cohort size will be 10 patients per cohort with successful acquisition of tumor at initial biopsy. Repeat biopsy will be performed at 4 weeks (cohort 1), 12 weeks (cohort 2) or at progression as defined by radiographic progression (cohort 3). We will sequentially assign patients to repeat biopsy at 4 weeks or 12 weeks until both cohorts are complete. Patients who progress prior to planned biopsy will be considered part of cohort 3 and undergo biopsy at progression. Once cohorts 1 and 2 are full, all patients will be assigned to cohort 3. All patients will be offered elective participation in evaluation of pharmacokinetics at progression at 1000 mg daily. For patients in all cohorts, there will be the

option of dose escalation of abiraterone acetate to 1000 mg twice daily. In the phase I studies cited, there were no grade 3 or 4 toxicities seen at 2000 mg daily. The rationale for dose escalation to 1000 mg twice daily compared to 2000 mg once daily is that previous data indicated that there was minimal increase in abiraterone PK exposure when the dose increased from 1000 mg QD to 2000 mg QD. Given the poor solubility of abiraterone acetate, this less than dose proportional increase in PK exposure was most likely caused by solubility-limited absorption. Administering the total daily dose (2000 mg per day) in two divided doses (1000 mg BID) may help circumvent this issue by increasing the soluble fraction of abiraterone acetate thereby enhancing overall absorption. Dose escalation will test the hypothesis generated from preclinical studies that more effective CYP17 inhibition may provide additional benefit in the face of tumor progression.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is;

To determine the magnitude of tissue testosterone suppression by abiraterone acetate in metastatic CRPC (resistant to LHRH agonist or orchiectomy ± antiandrogen) after one month of treatment to establish tissue based mechanism of action.

2.2 Exploratory Objectives

The exploratory objectives of this study are:

- To determine the ability of abiraterone acetate to suppress tumor testosterone after 12 weeks of treatment.
- To determine tissue testosterone from metastasis at time of progression during abiraterone acetate treatment.
- To determine response to dose escalation of abiraterone acetate at clinical progression
- To determine potential mechanisms of resistance to abiraterone acetate by analyzing pharmacokinetics at clinical progression, tissue androgen levels at baseline and at radiographic progression, evaluating wild type and splice variant AR levels at baseline and at time of progression and cDNA microarray at progression
- To determine if microRNA acquired from peripheral blood reflect molecular changes in tumor metastases and are a potential biomarker for mechanisms of sensitivity and resistance.
- To evaluate pharmacokinetics of dose escalated abiraterone at 1000 mg twice daily

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label study with 30 patients with metastatic prostate cancer resistant to LHRH agonist, or orchiectomy ± antiandrogen. All patients will be treated with continued Lupron (or have prior orchiectomy), and abiraterone acetate with prednisone as therapy during study enrolled from 1 study center. This is a study assessing the primary endpoint of suppression of tissue androgens at 4 weeks, After informed consent, all patients will undergo successful biopsy of a metastatic lesion

and then be enrolled alternating between the first cohort of patients undergoing repeat biopsy at 4 weeks (cohort 1), or repeat biopsy at 12 weeks (cohort 2) until 10 patients are in each cohort. If any patients experience progression prior to planned biopsy they will be included in cohort 3 (biopsy at progression) and the patient will be replaced in cohort 1 or 2. After cohorts 1 and 2 have been filled, patients will be assigned to cohort 3, with all patients undergoing biopsy at the time of progression, with a total of 10 patients enrolled in cohort 3 cohort. At the time of progression, patients may have pharmacokinetics performed at the dose of 1000 mg daily (elective study). All patients will have the dose of abiraterone acetate escalated to 1000 mg twice daily. Repeat pharmacokinetics at the higher dose will be performed 7-14 days after dose escalation (elective). All patients in all cohorts will be treated to clinical or radiographic progression, or until another intervening reason for withdrawal from study (Section 6.9).

3.1.1 Primary Endpoint

The primary efficacy endpoint (testosterone) will be assayed from the tumor biopsy procured at baseline, and at approximately Week 4. Tissue androgen measurements will be performed by the Nelson and Mostaghel laboratories at Fred Hutchinson Cancer Research Center using previously published techniques. Assumptions regarding basal tissue androgens and androgens after abiraterone acetate treatment at response and progression are derived from xenograft studies of abiraterone acetate effect in castrate male mice. Baseline tissue testosterone in untreated CRPC xenografts is 0.687 ± 0.364 pg/mg, approximating that seen in human CRPC metastases. Nadir tissue testosterone at 7 and 21 days is 0.027 ± 0.009 pg/mg (approximating one and three month levels) which rise to 0.222 ± 0.246 pg/mg at progression.

3.1.2 Exploratory Endpoints

- To determine the ability of abiraterone acetate to suppress tumor testosterone after 12 weeks of treatment.
- To determine tissue testosterone from metastasis at time of progression during abiraterone acetate treatment.
- To determine PSA response to dose escalation of abiraterone acetate (PSA response by PCWG2 criteria) and associate response to tumor androgen levels prior to dose escalation
- To determine potential mechanisms of resistance to abiraterone acetate by analyzing tissue androgen levels at baseline and at progression, evaluating wild type and splice variant AR levels at baseline and at time of progression, pharmacokinetics at progression and cDNA microarray at progression
- To determine if microRNA acquired from peripheral blood reflect molecular changes in tumor metastases and are a potential biomarker for mechanisms of sensitivity and resistance.
- To evaluate pharmacokinetics of dose escalated abiraterone at 1000 mg twice daily

1. Tissue and serum testosterone, DHT, androstenedione and DHEA will be analyzed from collection at baseline, at approximately weeks 4, 12 and progression) in the different cohorts of patients as described. This will address the exploratory objects assaying the various androgens at defined time points and progression.

2. Response to dose escalation will be defined as PSA and RECIST response.

- PSA response as defined as decline from the PSA at initiation of therapy and then with dose escalation of abiraterone acetate will be evaluated per PCWG2 criteria. This will be determined by PSA's performed at monthly intervals. The subsequent response to dose escalation (if any) will be correlated with tumor androgens.
- RECIST - participants with measurable disease will be assessed by RECIST (1.1), bone scan and PSA criteria. For the purposes of this study, participants should be re-evaluated every 4 weeks by PSA and every 12 week with CT and bone scan. PCWG2 recommendations for response and progression definitions will be followed for PSA progression and RECIST criteria for progression on imaging. Patients should not be taken off treatment for PSA progression alone but should remain on treatment until documented progression by imaging

3. Mechanisms of resistance will be evaluated by assaying;

   - Tissue androgens – as described above
   - AR levels – tumor tissue will be evaluated by RT-PCR for wild type and splice variant (AResdel567 and ARv7) at initiation of therapy, 4 weeks, 12 weeks and progression.
   - cDNA microarray – microdissected tumor from biopsies taken at progression will be processed and analyzed as previously described in order to identify signaling pathways relevant in progression (Risk, Clin Cancer Res. 2010 16:5414-23.)
   - Pharmacokinetics – plasma samples drawn as described at progression and after dose escalation will be analyzed by liquid chromatography followed by tandem mass spectrometry (LC-MS/MS) with subsequent calculation of Cmax, Tmax, and AUC(0-24)

4. MicroRNA analysis - Plasma will be collected for miRNA analysis by the Tewari lab, Fred Hutchinson Cancer Research Center. In these analyses a panel of miRNA's will be assessed at baseline, 4 weeks, 12 weeks and progression in the cohorts undergoing biopsy at these time points. Plasma samples will be profiled for the relative abundance of 375 miRNAs by using miRNA Ready-to-Use PCR, Human Panel I, V2.M qRT-PCR arrays. Candidate miRNA strongly associated with response or progression will be quantitated in biopsy tissue as possible.

4 STUDY POPULATION SELECTION

4.1 Study Population

Patients for the study will be recruited from within the Seattle Cancer Care Alliance (SCCA) and University of Washington, which are separate practice sites within the same practice and share a single IRB. Patients will be identified by their oncologist as eligible for the study and the study will be discussed with the patient by the provider. If patients are interested in participating, they will be counseled and informed consent will be obtained by one of the investigators. A total of 30 subjects will be enrolled into the study, with consideration that additional patients may be enrolled in order to acquire 30 sets of informative biopsies.

4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Have signed an informed consent document indicating that the subjects understands the purpose of and procedures required for the study and are willing to participate in the study
2. Written Authorization for Use and Release of Health and Research Study Information has been obtained
3. Be willing/able to adhere to the prohibitions and restrictions specified in this protocol
4. Male aged 18 years and above
5. Able to swallow the study drug whole as a tablet
6. Willing to take abiraterone acetate on an empty stomach; no food should be consumed at least two hours before and for at least one hour after the dose of abiraterone acetate is taken.
7. Patients who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 1 week after last dose of abiraterone acetate
8. Histologically proven adenocarcinoma of the prostate.
9. ECOG performance status ≤ 2
10. Metastatic castration resistant prostate cancer as defined by serum testosterone < 50 ng/ml and one of the following:
    a. PSA level of at least 2 ng/ml that has risen on at least 2 successive occasions at least 1 week apart.
    b. Evaluable disease progression by modified RECIST (Response Evaluation Criteria in Solid Tumors)
    c. Progression of metastatic bone disease on bone scan with > 2 new lesions
11. Maintenance of Lupron or antagonist unless previously treated with orchiectomy.
12. The presence of metastatic disease amenable to CT or ultrasound guided biopsy. This may include thoracolumbar vertebral bodies, pelvis, femur or humerus, or soft tissue or nodal metastasis amenable to biopsy (excluding lung or pleural lesions).
13. Patients may have received secondary hormonal manipulations (excluding prior Abiraterone acetate, MDV3100 or TAK700) or up to two lines of chemotherapy. All prior therapy except Lupron must have been discontinued for more than 4 weeks before enrollment.
14. Baseline laboratory values must be as follows:
    - Serum potassium of ≥ 3.5 mEq/L
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels < 1.5 x ULN
    - Serum albumin of ≥ 3.0 g/dL
    - Total bilirubin ≤ 1.5 x ULN
    - Calculated creatinine clearance ≥ 60 mL/min
    - Platelet count of $\geq 100{,}000/\mu L$
    - Absolute neutrophil count of > 1500 cell/mm3
    - Hemoglobin of ≥ 9.0 g/dL

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Active infection or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
2. Patients who are currently receiving active therapy for other neoplastic disorders will not be eligible.
3. Patients with histologic evidence of small cell carcinoma of the prostate will not be eligible.
4. Known brain metastasis
5. Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg) Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment
6. Active or symptomatic viral hepatitis or chronic liver disease
7. History of pituitary or adrenal dysfunction
8. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of < 50 % at baseline
9. Atrial fibrillation, or other cardiac arrhythmia requiring medical therapy
10. Administration of an investigational therapeutic within 30 days of screening.
11. Patients with dementia/psychiatric illness/social situations that would limit compliance with study requirements or would prohibit the understanding and/or giving of informed consent will not be eligible
12. Patients with any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements
13. Patients requiring therapeutic anticoagulation (e.g., warfarin, Dabigatran, heparin, or low molecular weight heparins (Lovenox, dalteparin))
14. Patients with poorly controlled diabetes
15. Patients with a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents
16. Patients with a pre-existing condition that warrants long-term corticosteroid use in excess of study dose
17. Patients with known allergies, hypersensitivity, or intolerance to abiraterone acetate or prednisone or their excipients.
18. Child-Pugh class B or C hepatic impairment

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Abiraterone acetate

Abiraterone acetate is an oral, selective, steroidal inhibitor of the steroidogenic cytochrome CYP17 that serves as an androgen antagonist. Abiraterone acetate has been evaluated in two phase III, randomized, placebo controlled studies. The first study treated 1195 patients who had previously received docetaxel (COU-301). This study showed that abiraterone acetate improved overall survival by 4 months compared to prednisone alone with a hazard ratio of 0.65 for patients receiving abiraterone acetate. The secondary endpoints of PSA response and time to progression also favored abiraterone acetate. Based on this study abiraterone acetate was approved for use in men with metastatic, CRPC after prior docetaxel therapy. The second study treated 1088 patients with metastatic castration-resistant prostate cancer who had not received previous chemotherapy.(COU-302). This study showed that abiraterone acetate improved radiographic progression free survival compared to prednisone alone with a hazard ratio of 0.53 for patients receiving abiraterone acetate. Based on this study abiraterone acetate was approved for use in men with metastatic, CRPC prior to docetaxel therapy. 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). Abiraterone acetate for this study will be provided by Janssen Services.

5.1.2 Prednisone

Prednisone is a corticosteroid. It is used in the study to suppress the compensatory increase in mineralocorticoid which occurs after CYP17 inhibition. Prednisone is supplied as a 5 mg tablet. Commercial supplies of prednisone will be used for this trial.

5.2 Treatments Administered

5.2.1 Abiraterone acetate

Starting on study Day 1, patients will be instructed to take 1000mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. Abiraterone Cmax and AUC0-∞ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone are taken with food has not been assessed. Treatment will continue until there is evidence of clinical or radiologic progression or intolerance to drug (Grade 3 or 4). . Patient compliance will be tracked through interview and pill count at study visit. If an abiraterone acetate dose is missed, it should be omitted and will not be made up. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures and continue in the protocol. After progression by radiographic or clinical criteria patients in all cohorts are eligible to have the dose of abiraterone escalated to 1000 mg twice daily taken in the same manner.

5.2.2 Prednisone

Starting on study Day 1, patients will be instructed to take 5-mg prednisone PO twice daily. Treatment duration of prednisone will be for the duration of study concurrent with abiraterone acetate. In the abiraterone acetate dose escalation cohort at progression, prednisone dose will not be changed. At discontinuation of study, after abiraterone acetate is discontinued, prednisone will be decreased to 5 mg every other day for one week and then discontinued. If a prednisone dose is missed, it should be omitted and will not be made up.

Although not considered a study agent, subjects will also receive their regularly prescribed Leuprolide (to be administered as prescribed). If patients have undergone orchiectomy, use of Leuprolide is not necessary.

5.3 Concomitant Therapy

Concurrent treatment with Leuprolide is mandatory at screening and must be continued unless the subject has undergone orchiectomy.

The use of any concurrent drug from screening and while on study (other than those listed in Section 5.2), prescription or over-the-counter, is to be recorded on the patient's CRF along with the reason the drug was taken.

Concurrent enrollment in another clinical investigational drug or device study is prohibited. Supportive care medications are permitted with their use following institutional guidelines.

The following supportive care medications are considered permissible during the study:

- Conventional multivitamins, selenium and soy supplements
- Additional systemic glucocorticoid administration such as “stress dose” glucocorticoid is permitted if clinically indicated and in such cases, the use of steroids will be documented as concomitant drug
- If the permissibility of a specific drug/treatment is in question, please contact the study investigator-sponsor.

5.4 Restrictions

The concurrent administration of other anticancer therapy, including cytotoxic or hormonal agents (except LHRH agonists), or immunotherapy, is prohibited therapy. Use of other investigational drug therapy for any reason is prohibited. The decision to administer a prohibited drug/treatment will be made by the investigator based on the consideration of the safety of study participant.

5.5 Potential for Drug-Drug Interactions

Effects of Abiraterone on Drug Metabolizing Enzymes
Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone

acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000mg abiraterone acetate. Therefore, patient should be monitored closely for signs of toxicity related to CYP2C8 substrate with a narrow therapeutic index if used concomitantly with Zytiga.

Drugs that Inhibit or Induce CYP3A4 Enzymes
In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC∞ of abiraterone was decreased by 55%. Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during treatment with ZYTIGA are to be avoided, or used with careful evaluation of clinical efficacy.

In a separate clinical pharmacokinetic interaction study of healthy subjects, coadministration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

5.6 Treatment Compliance

A dosing compliance check will be conducted at each study visit while subject is taking abiraterone acetate. If a patient misses 14 or more doses within a single 28-day cycle, the patient should be discontinued from the study treatment Phase. All End-of-Study treatment procedures should be followed. The patient will be followed for PSA progression.

A current and accurate account of the number of investigational tablets will be maintained including the amount of investigational tablets received by the investigator, amount dispensed each patient, the number of units returned to the investigator by each patient, and the number of units destroyed on site, after full reconciliation at the completion of the study. A detailed inventory must be completed and maintained for the study treatment.

5.7 Packaging and Labeling

Abiraterone acetate tablets will be provided to the site with marketing packaging and labeling. Tablets will be packaged for dispensing 4-week supplies of 250 mg tablets on a per patient basis. Patients will be provided with no more than a 4-week supply of abiraterone acetate at any one time.

Lupron and prednisone will be provided or prescribed to each patient in accordance with this protocol and under the guidelines of the site or pharmacy's dispensation standard operating procedure.

5.8 Storage

5.8.1 Pharmacy Storage Requirements

Study medication must be stored in a secure area and administered only to patients entered into the clinical study in accordance with the conditions specified in this protocol.

Bottles of abiraterone acetate should be stored at a room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) with the cap on tightly and should not be refrigerated. Additional information is provided in the abiraterone acetate Investigator's Brochure or US prescribing information (www.zytiga.com).

Lupron and prednisone should be stored according to manufacturer instructions as indicated on the commercial packaging.

5.8.2 Storage Requirements For The Patient

Bottles of abiraterone acetate should be stored at room temperature between 20°C to 25°C (68°F to 77°F) with the cap on tightly and should not be refrigerated. Patients should be advised to keep all medications out of the reach and out of sight of children. Based on its mechanism of action, abiraterone acetate may harm a developing fetus. Therefore, women who are pregnant or women who may become pregnant should not handle abiraterone acetate without protection, e.g. gloves.

Patients should store prednisone according to manufacturer instructions as indicated on the commercial packaging.

5.9 Handling abiraterone acetate tablets

This medicine may cause harm to the unborn child if taken by women who are pregnant. It should not be taken by women who are breast-feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets. Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

5.10 Investigational Product Retention and Accountability at Study Site

At the time of delivery of study treatment to the site, the investigator, designee, or Pharmacist (where appropriate) will sign a drug receipt form to confirm that the supplies for the study have been received. This form will specify supply, lot numbers, quantities shipped/delivered, and date of receipt. The form will also contain statements confirming that the study treatment has been received in good condition.

Study treatment must be stored in a secure location. Accountability for study treatment is the responsibility of the investigator.

Study treatment must only be dispensed by a Pharmacist or medically qualified staff (research coordinator). Study treatment is to be dispensed only to patients enrolled in this study. Once the study treatment is prepared for a patient, it can only be administered to that patient.

The study site must maintain accurate records demonstrating dates and amount of study treatment (abiraterone acetate, Lupron, and prednisone) received, to whom dispensed (patient by patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed. No abiraterone acetate tablets or containers will be destroyed without prior written approval from Janssen. Study site staff should refer to information located in Investigator's Brochure for specific instructions on the handling, storage, and administration of the study drug.

6 STUDY PROCEDURES

6.1 Informed Consent

Written Informed Consent and Authorization must be obtained from the patient in accordance with local practice and regulations. The study will be discussed with the patient, and a patient wishing to participate must give written informed consent and Authorization for Use and Release of Health and Research Study Information prior to any study-related procedures or change in treatment.

A signed, Institutional Review Board/Ethics Committee (IRB) approved, informed consent must be obtained from patients before any study specific procedures can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record.

A copy of the fully signed informed consents will be given to the patient.

All patients who sign informed consent will be assigned a study number, in the order enrolled. Format will be the CC-IRB number (7639), patient number (001, 002, 003 …), patient initials: 7639-001-FML. Initials will be included in the case report forms, but will not be marked on blood or tissue samples.

6.2 Medical History

Medical history, such as previous treatments, procedures, and conditions will be collected during the screening period.

6.3 Physical Examination

Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the patient, then evaluations should overlap (i.e., examine the patient together and discuss findings) for at least one visit.

Physical examination includes HEENT (head, eyes, ears, nose, and throat), chest, cardiac, abdominal, extremities, neurologic, and lymph node examinations.

Vital signs include blood pressure, heart rate. Weight will be recorded at every visit. Height will be recorded at screening visit only.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Clinical laboratory tests will include the following:

Table 1. List of Laboratory Tests

Hematology:
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Platelet count with differential
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Additional laboratory tests:
- Prostate specific antigen (PSA)
- Serum drawn for hormone measurements

Serum Chemistry:
- Albumin (ALB)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Glucose
- Magnesium
- Potassium (K)
- Sodium (Na)

Liver Functions
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Alkaline phosphatase (ALK-P)
- Total bilirubin

6.4.2 Sample Collection, Storage, and Shipping

The institutional laboratories at Seattle Cancer Care Alliance and University of Washington will analyze all hematology, blood chemistry, and PSA samples collected for the study. Samples will be analyzed at a facility meeting Good Laboratory Practice (GLP) requirements and/or using methods documented in a methods validation report. Samples for hormones other than testosterone will be processed at University of Washington in the Mostaghel laboratory.

6.4.2.1 Biopsy acquisition and tissue handling

Please see the attached laboratory manual for detailed instructions regarding acquisition and handling of tissue specimens. In brief, CT guided biopsy of a bone or soft tissue lesion (pelvic nodes) or core needle aspirate of superficial nodal tissue (supraclavicular or cervical nodes) will be performed by an interventional radiologist or pain physician after evaluation of bone scan and CT scan.

On the day of biopsy, prior to the procedure, 20 ml of blood will be drawn for serum and plasma. Aspirin and other medications containing aspirin (e.g. Plavix, Aggrenox) should be discontinued 7 days prior to the biopsy. Patients requiring other anticoagulant therapy (coumadin, lovenox, pradaxa, etc.) are not eligible. Blood samples will be drawn as clinically indicated to document an acceptable coagulation profile (INR < 1.5, PTT < 45, platelets >50,000).

On the day of the biopsy, a short physical exam will be performed by the radiologist including assessing the patient's general ASA score and airway rating. Informed written consent will be obtained following discussion of the risks (bleeding, infection, adjacent tissue injury, and pain) and benefits of the procedure. Biopsies will be performed under CT- or ultrasound guidance without the administration of intravenous contrast.

RADI Bonopty 15 g needles [1.7 mm bore] (RADI Medical Systems, Uppsala, Sweden) are preferred for bone lesions with an intact cortex. Osticut or Jamshidi needles 14g may also be used.

Several bone specimens (up to 6) will be obtained. Samples will be given to a dedicated technician present during the procedure for sample processing.

Conscious sedation will be administered by a trained radiology nurse using small doses of Versed and fentanyl titrated to the patient's level of discomfort. Following the biopsy, patients will be observed following their last dose of conscious sedation for any complications (severe pain, hematoma, neurologic deficit). They will be discharged after fulfilling PACU discharge criteria prior to departing with a chaperone.

6.4.2.2 Sample Labeling

Samples will be marked with the assigned patient number, collection date and timepoint (e.g., BL, Wk 4, Wk 12, PD). Because collection date is included in the Limited Data Set defined by HIPAA, these samples cannot be considered de-identified. However, the link between patient number and patient identity are in a separate, locked room. Non-clinical staff will not have access to patient identifiers beyond the sample collection date.

6.4.2.3 Sample Storage

Unfixed samples will be stored on-site in a -80° freezer until processing. Fixed samples will be stored on-site in a temperature-controlled setting appropriate to the fixation medium.

Samples will be destroyed when the research described in this protocol is complete. Samples will be used for only the purposes delineated in this protocol.

6.5 Efficacy Assessments

6.5.1 The Primary Endpoint Measure

The primary efficacy endpoint (testosterone) will be assayed from the tumor biopsy procured at baseline, at approximately Week 4. Tumor testosterone will be analyzed from biopsies collected at baseline, and at week 4. Tissue androgen measurements will be performed by the Nelson and Mostaghel laboratories at Fred Hutchinson Cancer Research Center using previously published LC-MS/MS techniques.

6.5.2 Exploratory Endpoint Measures

The exploratory endpoint measures will address the exploratory objectives as described in Section 2.2.

1. Tissue and serum testosterone, DHT, androstenedione and DHEA will be analyzed from collection at baseline, at week 4, week 12 (± 2 weeks) and at progression (± 2 weeks) in the different cohorts of patients as described.
2. PSA response as defined as decline from the PSA at initiation of therapy and with dose escalation of abiraterone acetate will be evaluated per PCWG2 criteria. This will be determined by PSA's performed at monthly intervals. The subsequent response to dose escalation (if any) will be correlated with tumor androgens.
3. RECIST - participants with measurable disease will be assessed by RECIST (1.1), bone scan and PSA criteria. For the purposes of this study, participants should be re-evaluated every 4 weeks by PSA and every 12 week with CT and bone scan. PCWG2 recommendations for response and progression definitions will be followed for PSA progression and RECIST criteria for progression on imaging. Patients should not be taken off treatment for PSA progression alone but should remain on treatment until documented progression by imaging. Detailed discussion of progression and response is outlined in Appendix 5.
4. AR levels – tumor tissue will be evaluated by RT-PCR for wild type and splice variant (AResdel567 and ARv7) at initiation of therapy, 4 weeks, 12 weeks and progression.
5. Pharmacokinetics – plasma samples drawn at progression and after dose escalation will be analyzed by liquid chromatography followed by tandem mass spectrometry (LC-MS/MS) with subsequent calculation of Cmax, Tmax, and AUC(0-24)
6. MicroRNA - Plasma will be collected for miRNA analysis by the Tewari lab, Fred Hutchinson Cancer Research Center. In these analyses a panel of miRNA's will be assessed at baseline, 4 weeks, 12 weeks and progression in the cohorts undergoing biopsy at these time points. Plasma samples will be profiled for the relative abundance of 375 miRNAs by using miRNA Ready-to-Use PCR, Human Panel I, V2.M qRT-PCR arrays. Candidate miRNA strongly associated with response or progression will be quantitated in biopsy tissue as possible.
7. cDNA microarray – microdissected tumor from biopsies taken at progression will be processed and analyzed as previously described in order to identify signaling pathways relevant in progression (Risk, Clin Cancer Res. 2010 16:5414-23.)

6.6 Safety Assessments

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Safety assessments will be carried out as delineated in Section 7.7 and will include:

- Adverse events including laboratory adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
- Electrocardiograms (ECGs).
- Laboratory tests (CBC with differential, platelets, LFT's, chemistry, and serum lipids)
- Vital Signs (blood pressure, heart rate, respiratory rate and weight)
- Physical exam
- ECOG performance status

6.7 Safety Data Collection, Recording and Reporting

All observed or volunteered adverse events regardless of causal relationship to study drug will be recorded on the adverse event page(s) of the case report form (CRF).

Please refer to Appendix 4 for Janssen Services, LLC's "Adverse Event Reporting Requirements for Interventional Studies." Some of the information may overlap with the items below.

6.7.1 Definition of Adverse Event (AE)

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as "Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment" (ICH E6:1.2). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, diagnosis or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. For the purposes of this study, temporal association is defined as the time between the subject's informed consent signature through 28 days after the final dose of abiraterone acetate.

AEs further include worsening of a pre-existing medical condition (e.g., diabetes, migraine headaches, gout, hypertension, etc.) which has increased in severity, frequency or duration, or is associated with significantly worsened outcomes.

The investigator or a medically licensed designee must pursue and obtain information adequate to determine the following: Grade (CTCAE v4.0), Causality (relationship to abiraterone acetate) and Outcome. . The investigator's assessment of Grade, any Intervention (medication, procedure, etc.), Causality and Outcome will be indicated by signature of the PI or designated physician on the adverse event CRF. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, or his/her designated representative.

Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product cause the response. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Special Reporting Situations (SRS)

When a report contains a J&J product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- overdose of a Johnson & Johnson medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to medicinal product from breastfeeding
- suspected abuse/misuse of medicinal Johnson & Johnson product
- inadvertent or accidental exposure to medicinal Johnson & Johnson product
- any failure of expected pharmacological action (i.e., lack of effect) of medicinal Johnson & Johnson product
- unexpected therapeutic or clinical benefit from medicinal Johnson & Johnson product
- medication error involving medicinal Johnson & Johnson product with or without patient exposure to the medicinal Johnson & Johnson product (e.g., name confusion)
- suspected transmission of any infectious agent via a medicinal Johnson & Johnson product

Adverse events of special interest to Janssen Services, LLC include hypokalemia, abnormal liver function tests (AST, ALT, bilirubin), hypertension and edema. See Management of Study Drug-related Adverse Events, for clinical management of both special interest and general AEs.

If the investigator or designee determines that an AE meets the criteria for classification as a Serious Adverse Event (SAE) or Suspected Unexpected Adverse Event Reporting (SUSAR), s/he will immediately notify the UW/FHCRC Cancer Consortium IRB, Janssen Services and FDA. See Section 6.7.2 for definition of SAEs and SUSARs, and 6.7.4 for reporting guidelines.

Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

6.7.2 Definition of a Serious Adverse Event

An adverse event or suspected adverse reaction is considered ‘‘serious’’ if, in the view of the investigator or a medically licensed designee, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event,
    - *Life-threatening adverse event or life-threatening suspected adverse reaction*.
        - An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if its occurrence places the patient or subject at immediate risk of death. This definition does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization,

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- is a suspected transmission of infectious agents by a medicinal product

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A hospitalization meeting the definition for "serious" is any in-patient hospital admission that included a minimum of an overnight stay in a health care facility. Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered SAE/SUSARs for the purposes of this study. Inpatient admission does not include admissions to rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same day surgery (as outpatient/same day/ambulatory procedures) or social admission (e.g., subject has no place to sleep).

6.7.3 Suspected Unexpected Serious Adverse Events (SUSARS)

Suspected Unexpected Serious Adverse Reactions (SUSARS) are events which are serious as per the above criteria, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or Package Insert) and are judged by the investigator to be related to investigational product.

6.7.4 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all non-serious adverse events (as defined in Section 6.71 and as further specified below) observed by the investigator or reported by subjects are collected and recorded in the CRF. Source documents may include the subjects' medical records, patient diaries or study-specific worksheets. Recording for all events should be done in a concise manner using standard, acceptable medical terms. New AEs occurring between the patient's consent signature through 28 days after his last dose of abiraterone acetate will be captured.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event). Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring unplanned in-patient

hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE, as previously stated.

If, in the investigator's judgment, a clinically significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e.g., thrombocytopenia, peripheral edema, QT prolongation).

For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event (e.g., study drug, other illness, progressive malignancy, etc.). The relationship of the adverse event to the investigational product will be assessed by means of the question, "Is there a reasonable possibility that the event may have been caused by the investigational product?" The investigator should respond to this question with either Yes or No.

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 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:

1. test result is associated with accompanying symptoms, and/or
2. 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 a reportable AE), and/or
3. test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. test result leads to any of the outcomes included in the definition of a serious adverse event, and/or
5. test result is considered to be an adverse event by the investigator or sponsor, and/or
6. test result is CTCAE v4.0 grade 3 or above

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 deemed Related to IP must be recorded in the patient's CRF.

6.7.4.1 Serious Adverse Event Reporting Procedures (on-site SAEs)

New SAEs and SUSARS will be collected and recorded throughout the study period, from the signing of the informed consent through 28 days after the final dose of abiraterone acetate. Ongoing SAE/SUSARs with a causal relationship to the investigational product will be followed until the event or its sequelae resolve or stabilize at a level acceptable to the investigator or designee. Contact information, fax numbers and email addresses for FDA, CC-IRB and Janssen Services LLC are collated in Appendix 4.

Reporting to the FDA

The investigator is responsible for reporting SAE/SUSARs to the FDA **within 24 business hours** of discovery or notification of the event. The investigator or designee will complete Form FDA-3500A for submission to MedWatch. Form may be completed online via https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm (as of Jan2012), or printed and faxed as instructed online. All deaths within 28 days of final IP dose, whether SUSARs or not, will be reported in an expedited manner to the FDA.

Reporting to IRB

All serious adverse events that occur after the subject has signed the informed consent form or during the study at the University of Washington or Seattle Cancer Care Alliance must be reported to the Cancer Consortium IRB (CC-IRB, fax 206-667-6831). Report must be transmitted **within 24 business hours** of discovery or notification of the event and the event must meet institutional reporting guidelines. The Adverse Event Reporting Form is available online, http://extranet.fhcrc.org/EN/sections/iro/irb/forms/index.html#Reporting (as of Jan2012). SUSARs will be reported on the Expedited Reporting Form for Unanticipated Problems or Noncompliance. Special Reporting Situations (SRS) will be reported to CC-IRB either immediately or at annual renewal, upon consultation with IRB staff. The SAE, SUSAR or SRS should be recorded on the appropriate case report form (CRF).

Reporting to Janssen Services, LLC

The investigator or designee will transmit SAE/SUSAR on Form FDA-3500A. The form will be transmitted to Janssen Services LLC's designated fax number (or designated email address) **within 24 business hours** of becoming aware of the event(s). The form will be completed in English, and will include as much information as possible regarding the SAE/SUSAR.

All available clinical information relevant to the evaluation of an SAE, SUSAR, Adverse Events of Special Interest, and Special Reporting Situations including pregnancy reports (with or without an AE), including paternal exposure, are required.

- The investigator is responsible for ensuring that these cases from clinical studies are complete and if not are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented by the investigator and that follow-up

information is summarized (e.g. hospital records, coroner's reports, autopsy results) and recorded on the appropriate forms.

- A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. Reporting of follow-up information should follow the same timeline as initial reports.
- Janssen Services, LLC, requests copies of the study site's correspondence with regulatory authorities and ethics committees regarding all serious adverse events, regardless of causality. Janssen prefers to receive these copies by facsimile within 24 hours of transmission to or from the actual authorities.

Reports of SAEs should be signed and dated by the principal investigator. In the absence of the PI, reports should be signed and dated by the individual reporting the event. If s/he is not medically licensed, the report should also be signed by a licensed medical practitioner, preferably a sub-investigator for this protocol. The PI will review and sign the report at the next opportunity.

Each report should contain the following information:

- Protocol number
- Subject number
- Disease/histology, if applicable
- Date the event occurred
- Description of the SAE
- Relationship of the event to treatment (abiraterone acetate), or other causality
- Whether the event was "expected'
- Severity of the event
- Intervention
- Outcome of the event
- Detailed text that includes the following information:
  - An explanation of how the SAE was handled
  - A description of the patient's condition
  - Indication whether the subject remains on study
  - Recommendation whether an amendment will need to be made to the protocol and/or the consent form.

Relevant, redacted medical records should be provided as soon as they become available; autopsy reports should be provided for deaths if available. Determination of expectedness will be based on the contents of the current Investigator's Brochure or package insert.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the End of Study Case Report Form as well as all SAE/SUSAR reports.

6.7.4.2 Annual Safety Reports

In addition to the expedited reporting, sponsor shall submit, once a year throughout the clinical trial or on request a safety report to the competent authority and Institutional Review Board, taking into account all new available safety information received during the reporting period.

Cumulative logs of off-site SAEs, SUSARS and Special Reporting Situations will be forwarded to the IRB of record at least annually.

6.7.5 Management of Study Drug-Related Events

Based upon experience from Phase 1 and ongoing Phase 2 studies, abiraterone acetate is generally well tolerated. The most common adverse events related to abiraterone acetate monotherapy include fatigue due to reduced cortisol level as a result of CYP17 inhibition; and hypertension, fluid retention, and hypokalemia due to mineralocorticoid excess caused by compensatory ACTH drive. In this study, the concomitant administration of prednisone is expected to mitigate these side effects by supplementing cortisol and abrogating ACTH drive.

During study, corticosteroid treatment will be provided. It has been documented that following prolonged therapy with corticosteroids, patients may develop Cushing's 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.

For guidance on management of side effects of glucocorticoid usage, symptoms related to castration (androgen deprivation), severe and refractory headaches, fatigue, or other toxicities not listed below please contact the Principal Investigator at each institution.

Re-initiation of study treatment after resolution of adverse events must be discussed with and approved by the Principal Investigator.

6.7.5.1 Management of Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Use Abiraterone acetate with caution in patients with a history of cardiovascular disease. Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition [see Adverse Reactions (6) and Clinical Pharmacology (12.1)]. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of Abiraterone acetate

in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with Abiraterone acetate.

Table 2. Hypokalemia Management

Serum K+	Action	Further Action and/or Maintenance
Low K+ and/or history of Hypokalemia	Weekly (or more frequent) laboratory electrolyte evaluations	Titrate dose to maintain a Serum K+ ≥3.5mM ≤5.0mM (Maintenance of pts. at ≥ 4.0mM is recommended)
< 3.5mM - 3.0mM	Initiate oral K+ supplementation	Titrate dose to maintain a Serum K+ ≥3.5mM ≤5.0mM (Maintenance of pts at ≥ 4.0mM is recommended)
< 3.0mM	Withhold Abiraterone acetate (study) treatment and initiate IV K+ and cardiac monitoring	

6.7.5.2 Management of Adrenocortical Insufficiency

Adrenocortical insufficiency has been reported in clinical trials in patients receiving Abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with Abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

6.7.5.3 Management of Hepatotoxicity

All patients will undergo assessment of liver function prior to enrollment on study. For patients who develop hepatotoxicity during treatment with abiraterone at 1000 mg daily (ALT and/or AST greater than 5x ULN or total bilirubin greater than 3x ULN), interrupt treatment with abiraterone. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient'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. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient'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 hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with abiraterone. The safety of abiraterone re-treatment of patients who develop AST or ALT greater than or equal to 20x ULN and/or bilirubin greater than or equal to 10x ULN is unknown. Patients who develop hepatotoxicity (ALT and/or AST greater than 5x ULN or total bilirubin greater than 3x ULN) during treatment with dose escalated abiraterone at 1000 mg twice daily will be removed from study.

6.7.5.4 Management of Hepatic Impairment

Patients with Child-Pugh Class B or C hepatic impairment will not be treated on study.

6.8 DOSAGE FORMS AND Criteria for Discontinuation of Study

The development of ≥ 20% incidence of grade 3 or grade 4 toxicity (CTCAE v4.0) during administration of abiraterone acetate in the treatment of patients in cohort 3 will prompt review of toxicity and if appropriate, suspension of study.

6.9 Withdrawal from Study

The investigator may withdraw a patient from any phase of the study for any of the following reasons.

- Discontinuation of treatment criteria as defined in Section 6.8
- Dosing noncompliance: If a patient misses 14 or more doses within a 4 week period the patient should be discontinued from the study treatment period.
- Sustained Side Effects: Patients who have sustained toxicities, such as hyperglycemia or hypertension that do not return to NCI CTCAE (version 3) Grade 1 or less with appropriate medical management, should be discontinued from the study treatment.
- Administration of prohibited medications: The patient will be discontinued from the protocol treatment when prohibited drug is administered. Supportive care medications are permitted with their use following institutional guidelines. The concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists), or immunotherapy is prohibited during study treatment Phase. Use of other investigational drug therapy for any reason is prohibited.
- Patient withdraws consent. In this event, the reason(s) for withdrawal must be documented and clarification if withdrawal of consent includes follow-up phase for progression data collection. A patient's decision to take part in the study is voluntary and he may choose not to take part in the study or to stop taking part at any time. If he chooses not to take part or to stop at any time, it will not affect his future medical care or medical benefits.

If a subject terminates the study early, an Early Termination visit will be performed.

7 STUDY ACTIVITIES

7.1 Study Visit Overview

All protocol required therapy will be provided by prescription and taken by participant on an outpatient basis. A baseline biopsy of metastasis is performed prior to beginning therapy. Patients will be treated with abiraterone acetate 1000mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

Patients will then continue on combined therapy until progression or taken off study at the PI's discretion. Patients will be evaluated clinically and with laboratories on a monthly basis throughout protocol treatment. A metastasis biopsy will be done while still on abiraterone acetate at 4 weeks (cohort 1), or at 12 weeks (cohort 2) or at the time of progression (cohort 3). After progression, dose escalation to 1000 mg twice daily will be allowed. The tumor biopsy at designated time point (Baseline, 4 weeks, 12 weeks or progression) is mandatory and can be done +/- 30 days of initiation of therapy for baseline biopsy and at approximate timepoints for 4 and 12 week timepoints. Situations where the patient stops protocol therapy for reasons other than progression should be discussed with the PI if it is felt that the biopsy would not represent disease biology at the relevant time point.

Expected toxicities and potential risks as well as dose modifications for abiraterone acetate are described in Section 6.7.5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Screening Period

Patients for the study will be recruited from sites from within the Seattle Cancer Care Alliance (SCCA). Patients will be identified as eligible for the study and the study will be discussed with the patient by their provider. If patients are interested in participating, they will be counseled and informed consent will be obtained by one of the investigators.

Screening procedures to be completed within 30 days prior to the start of study treatment (Day 1):

- Informed consent
- Registration
- Medical history and demographics
- Physical examination, including weight and height
- Vital signs including blood pressure, heart rate, respiratory rate.
- Assessment of ECOG Performance Status
- 12 lead ECG
- Adverse event baseline
- Echocardiogram or MUGA
- Lab test:
  - CBC: WBC with differential count, RBC, hemoglobin, hematocrit, platelets.
  - Liver function tests (LFT's – AST, ALT, alkaline phosphatase, total bilirubin),
  - Serum chemistries (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, magnesium.
  - PSA (must be sampled prior to DRE)
  - Total testosterone optimally drawn before 10 AM
  - Research hormone levels optimally drawn before 10 AM
- Bone scan and CT or MRI of the abdomen/pelvis
- Chest film or chest CT

- miRNA collection
- Concomitant medications listing:

  Obtain a complete and thorough listing of all prescription and nonprescription (over the counter) medications currently taken including pain medications. This also includes any nutritional supplements and/or herbal preparations.

7.2 Pre-Treatment Biopsy

Patients will undergo pretreatment CT or ultrasound guided needle biopsies of a metastasis felt amenable to biopsy by the performing radiologist (6 cores) following registration.

7.3 Treatment Period

7.3.1 Visit 1 (Study Day 1)

- Patients will continue on Lupron throughout study
- Patients will start Abiraterone acetate 1000 mg PO daily.
- Patients will start prednisone 5 mg PO twice daily

The following procedures should be completed at this visit:

- Evaluation of patient compliance, adverse events and concomitant medications
- Physical exam
- Vital signs, including blood pressure, heart rate, respiratory rate, and weight.
- ECOG performance status
- CBC: WBC with differential count, RBC, hemoglobin, hematocrit, platelets.
- Liver function tests (LFT's - AST, ALT, alkaline phosphatase, total bilirubin),
- Serum chemistries (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, calcium, , magnesium, glucose)
- PSA
- Research hormone levels, optimally drawn before 10 AM.

7.3.2 Subsequent visits

During the first three months of therapy (Cycles 1-3) patients will undergo hepatic function testing (AST, ALT, alkaline phosphatase, total bilirubin) every 2 weeks (± 1 week). Patients who dose-increase to1,000 mg bid will resume hepatic function testing every two weeks (± 1 week) until end of treatment and follow-up.

Every 4 weeks after the initial dose of abiraterone acetate, all subjects will return every 4 weeks (± 4 days) where the following procedures will occur:

- Patients will be evaluated for compliance, adverse events, and concomitant medications
- Physical exam

- Vital signs, including blood pressure, heart rate, respiratory rate and weight.
- ECOG performance status
- CBC: WBC with differential count, RBC, hemoglobin, hematocrit, platelets.
- Liver function tests (LFT's - AST, ALT, alkaline phosphatase, total bilirubin) – to be performed monthly after the first three months of therapy,
- Serum chemistries (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, calcium, magnesium, glucose)
- PSA and research hormone levels
- Bone scan and CT or MRI of the abdomen/pelvis and Chest film or chest CT will be repeated every 12 weeks or as clinically indicated.

Patients will undergo planned repeat tumor biopsy at one of the following time points: 4 weeks (cohort 1), 12 weeks (cohort 2) or progression (cohort 3). Patients who progress prior to planned biopsy in cohorts 1 and 2 will undergo progression biopsy and additional patients will be enrolled in cohorts 1 or 2.

- Patients will undergo pretreatment CT or ultrasound guided needle biopsies of a metastasis felt amenable to biopsy by the performing radiologist (6 cores) following as per the Tissue Acquisition SOP listed in the Laboratory manual.
- Research hormone levels, optimally drawn before 10 AM
- miRNA levels drawn

7.3.3 Pharmacokinetics

All patients in all cohorts will be offered the option of participating in pharmacokinetic analysis at the time of progression while receiving 1000 mg daily and then after dose escalation to 1000 mg twice daily. The analysis of pharmacokinetics at progression will explore the potential that induction of abiraterone metabolism may result in suboptimal pharmacokinetics and subsequent pharmacodynamic effect on tumor as a mechanism of secondary resistance to abiraterone therapy. There is limited data available regarding abiraterone pharmacokinetics after prolonged dosing of abiraterone and there is evidence that ability of other, less effective CYP17 inhibitors such as ketoconazole, to suppress androgen levels wanes with time due either to incomplete CYP17 block or altered pharmacokinetics [31, 32]. The addition of formal pharmacokinetic evaluations before and after dose would provide important information about secondary resistance to abiraterone therapy. The proposed pharmacokinetic sampling would be as follows:

- At progression, dose = 1000 mg daily. Plasma samples will be drawn prior to daily dose and then at 1, 2, 3, 4, 6, 8, and 24 hours post dose (Note: patient will take the next daily dose AFTER the 24-hour post-dose sample is collected)

- 7-14 days after dose increase to 1000 mg twice daily. Plasma samples will be drawn prior to AM dose and 1, 2, 3, 4, 6, 8, and 12 hours post AM dose (Note: patient will take the evening dose AFTER the 12-hour post-dose sample is collected)

Special Instructions:

On the day of PK collection, patients MUST take abiraterone acetate (morning dose only) after an overnight fasting (~10 hours) and no food should be consumed until 1 hour after dosing.

Patients who are taking abiraterone acetate 1000 mg twice daily should take the morning dose and evening dose approximately 12 hours apart.

PK sample collection, processing, storage, and shipping instructions are presented in Appendix 6.

7.3.4 Dose escalation

All patients in all cohorts will be offered the option of dose escalation to 1000 mg twice daily. This dose escalation will explore whether subsequent response is associated with higher than anticipated tissue testosterone levels and/or CYP17 levels will explore the potential that resistance may be mediated by upregulation of the abiraterone acetate target CYP17 with subsequent tumor androgen maintenance, as seen in preclinical studies cited in section 1.1. As previously noted, in published phase I studies, there was no grade 3 or 4 toxicity in patients treated with 2000 mg daily abiraterone acetate achieved proportional increases in serum abiraterone acetate levels [26]. Those patients who go on to therapy with abiraterone acetate 1000 mg twice daily will be monitored for toxicity and progression exactly as those patients treated at 1000 mg daily except that liver function tests will be performed every 2 weeks indefinitely. At the time of subsequent progression, abiraterone acetate will be discontinued. There is no minimum or maximum number of patients who may dose escalate. Target enrollment for PK sampling is 20 patients.

The rationale for dose escalation to 1000 mg twice daily compared to 2000 mg once daily is that previous data indicated that there was minimal increase in abiraterone PK exposure when the dose increased from 1000 mg QD to 2000 mg QD. Given the poor solubility of abiraterone acetate, this less than dose proportional increase in PK exposure was most likely caused by solubility-limited absorption. Administering the total daily dose (2000 mg per day) in two divided doses (1000 mg BID) may help circumvent this issue by increasing the soluble fraction of abiraterone acetate thereby enhancing overall absorption.

If a subject terminates the study early or at progression, a Termination visit with procedures as per the Study Calendar, and as follows.

- Patients will be evaluated for compliance, adverse events, and concomitant medications
- Physical exam
- Vital signs, including blood pressure, heart rate, respiratory rate and weight.
- ECOG performance status
- CBC: WBC with differential count, RBC, hemoglobin, hematocrit, platelets.
- Liver function tests (LFT's - AST, ALT, alkaline phosphatase, total bilirubin),
- Serum chemistries (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, calcium, phosphorus, magnesium, glucose)
- PSA, miRNA and research hormone levels will be drawn
- Abiraterone acetate will be discontinued

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

The primary endpoint is evaluation of the decrease of tissue testosterone from baseline (the last value on or before the date of first study treatment) to the 4-week time point. Sample size calculations for this endpoint are based on xenograft studies of abiraterone acetate. Planned analysis of primary and exploratory endpoints involves numerical and graphical summaries and standard statistical hypothesis tests and linear-model-based inference.

8.2 Determination of Sample Size

Basal tissue testosterone and testosterone after abiraterone acetate treatment at response were derived from xenograft studies of abiraterone acetate effect in castrate male mice. Baseline tissue testosterone in untreated CRPC xenografts was 0.687 ± 0.364 (mean ± SD) pg/mg, approximating that seen in human CRPC metastases. Nadir tissue testosterone after 7–21 days was 0.027 ± 0.009 pg/mg, approximating 4-week levels. Using the SD of testosterone derived from untreated observations (0.364 pg/mg), 6 patients provide 94% power to detect the anticipated 0.660 pg/mg difference in tissue testosterone relative to baseline based on a 2-sided paired t-test with alpha 5%. However, in our experience only 75% of CT and ultrasound guided biopsies yield evaluable tissue; consequently 6/10 patients are expected to provide evaluable tissue measurements at both baseline and after 4 weeks.

Data Analysis: Tissue testosterone measurements will be summarized numerically and graphically using plots of patient- and cohort-specific longitudinal patterns and side-by-side boxplots at each time point. Other tissue androgen levels will be similarly graphed and examined.

As in the power calculation, we will test the primary endpoint—change in tissue testosterone after 4 weeks—using a 2-sided paired t-test and consider an attained significance level of 5% statistically significant. We will also test exploratory hypotheses—change in tissue testosterone after 12 weeks and at progression—using the same test and significance level. We anticipate power to detect change in tissue testosterone after 12 weeks to be similar to that after 4 weeks. Based on preliminary data from xenograft studies, post-nadir tissue testosterone rose to 0.222 ± 0.246 pg/mg at progression; we therefore anticipate that, using the SD of testosterone derived from untreated observations (0.364 pg/mg), 7 patients achieving progression will provide 80% power to detect the anticipated 0.465 pg/mg difference in tissue testosterone relative to baseline based on a 2-sided paired t-test with alpha 5%.

Analysis of microarray data will evaluate change in gene expression (expressed as log ratio relative to human gold standard) by fitting linear models for each gene to test for changes in each cohort relative to baseline while controlling for false discovery using *limma*, *qvalue*, and related Bioconductor statistical analysis software packages.

8.3 Analysis Populations

All patients who receive at least one dose of study drug will be included in the analysis of safety (Safety Population).

8.4 Demographics and Baseline Characteristics

Demographic variables will include age, race, ethnicity, height, and weight. Baseline disease characteristics will include PSA, Gleason Grade, and clinical stage.

8.5 Safety Evaluations

Treatment emergent adverse events (AEs) directly related to abiraterone acetate are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be coded using the MedDRA coding system and all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE). An acute adverse event will be defined as an adverse event occurring up to and including 90 days after initiation of RT. A late adverse event will be defined as an adverse event occurring more than 90 days after the initiation of RT. Unacceptable toxicity is defined as grade 3 or higher toxicity. Incidence of AEs will be summarized by system organ class (SOC) and preferred term (PT). Adverse events will be summarized by grade, according to the worst grade experienced. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term.

Clinical laboratory test results will be collected pretreatment and through 28 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of abiraterone acetate.

Mean change from baseline in laboratory test values at each visit will be provided. On-study clinical laboratory test abnormalities will be summarized. Shifts in laboratory test values will also be summarized.

Electrocardiograms data will be descriptively summarized for QTc, PR interval, and QRS at each assessment. Comparison between baseline and maximum on-study QTc will also be presented. Both Fredericia and Bazett corrections will be reported.

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10 APPENDICES

APPENDIX 1 - SCHEDULE OF EVENTS

	Screening Day -30 to -1	Day 1 of Every Cycle[1]	Every 14 days Cycles 1-3 (± 1 wk)[2, 3]	Tumor biopsy at 4 wks Cohort 1	Every 12 wks (+/- 1 wk)	Tumor biopsy at 12 wks Cohort 2	Tumor biopsy at progression Cohort 3	Termination visit
Informed Consent	X							
Registration/Randomization	X							
Medical History	X	X						
Physical exam	X	X						X
Vital Signs	X	X						X
ECOG performance status	X	X						X
12 Lead ECG	X							
MUGA/Echo	X							
CBC (w/ platelets & differentials)	X	X						X
Serum chemistry & electrolytes	X	X						X
Hepatic function	X	X	X					X
PSA	X	X						X
Total testosterone	X							
Research serum hormones	X	X		X		X	X	X
Bone scan, and CT or MRI of pelvis/abdomen	X				X			
Chest film or chest CT	X				X			
Dosing Compliance Check		X						X
Concomitant medications	X	X						X
Adverse Events	X	X						X
Tumor Biopsies	X			X		X	X	
miRNA collection	X			X		X	X	X
Pharmacokinetics							X[2]	
Dose escalation							X[3]	

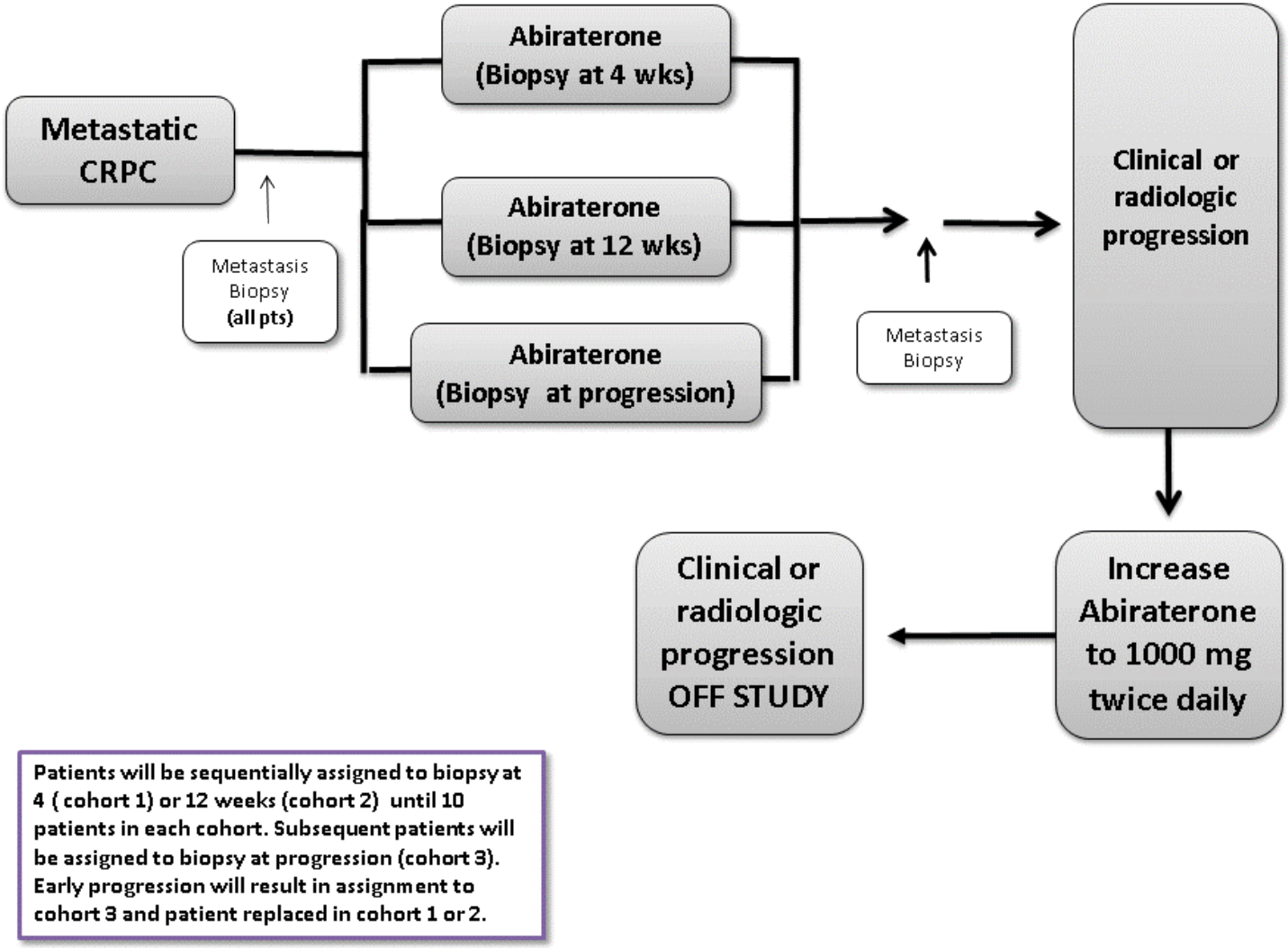
1 Screening procedures need not be repeated if performed within 7 days of Day 1.
2 Pharmacokinetic analysis will be performed at progression at 1000 mg daily and 7-14 days after dose escalation to 1000 mg twice daily. PK analysis is elective
3 Hepatic function monitoring every two weeks will resume after dose escalation.

- Baseline evaluations will be done within 30 days prior to start of therapy. All screening should be complete prior to registration. All study assessments and medications should be administered within 5 days of the protocol-specified date, unless otherwise noted.
- If chest imaging does not demonstrate metastatic prostate cancer, repeat imaging is not necessary.
- Tumor biopsy can be scheduled within 30 days before starting study medication. Patients will be registered before having biopsy. Preferred days of the week are Monday-Thursday to optimize processing.
- The tumor biopsies within each cohort are mandatory
- Physical Exam will include blood pressure, respiration, heart rate, and weight. Height will be measured at screening visit only.
- Androgen measurements should be drawn before 10:00AM if possible.
- Hepatic function includes AST, ALT, alkaline phosphatase and total bilirubin.
- Patients dose escalated to 1000 mg twice daily will continue to be followed as they were prior to progression except that hepatic function will be tested every 2 weeks until there is evidence of additional progression.

APPENDIX 2 - TISSUE ACQUISITION SOP

Laboratory manual
Tissue acquisition
Separate addendum

APPENDIX 3 - TREATMENT SCHEMATIC



APPENDIX 4 - ADVERSE EVENTS

JANSSEN SERVICES, LLC Adverse Event Reporting Requirements for "Interventional Studies"

I. Overview

As the sponsor of the Study, the University of Washington Medical Center (UWMC) and/or Bruce Montgomery, MD shall be solely responsible for complying, within the required timelines, with any safety reporting obligation towards the competent Health Authorities, the IRB/ECs and the participating (co- or sub-) investigators, as defined in the applicable laws and regulations. UWMC/Bruce Montgomery MD will be referred to as "the investigator" in the text below.

The investigator will submit safety information to the Janssen Services, LLC representative identified in the Research Funding Agreement section entitled "Regulatory Responsibilities of UWMC/Bruce Montgomery, MD and Adverse Event Reporting."

The investigator will provide safety reports to the Janssen Services, LLC representative on adverse events, pregnancies and product quality complaints as described below.

II. Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Events of Special Interest

Events that the Janssen Services, LLC representative is actively monitoring as a result of a previously identified signal (even if non-serious), and are described in Section 6.7, above.

Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product cause the response. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

J&J Medicinal Product

The specific J&J drug under study, abiraterone acetate (ZYTIGA™), and any other J&J medicinal product.

Product Quality Complaint (PQC)

Any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of a drug product.

A complaint may allege an injury or malfunction associated with the use of the drug product. It may also involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product.

Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered ‘‘serious’’ if, in the view of the investigator, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event,
    - *Life-threatening adverse event or life-threatening suspected adverse reaction*.
        - An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- is a suspected transmission of infectious agents by a medicinal product

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Special Reporting Situations

When a report contains a J&J product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- overdose of a Johnson & Johnson medicinal product (for this study, abiraterone acetate, specified below)
- pregnancy exposure (maternal and paternal)
- exposure to a medicinal product from breastfeeding
- suspected abuse/misuse of a Johnson & Johnson medicinal product, inadvertent or accidental exposure to a Johnson & Johnson medicinal product any failure of expected pharmacological action (i.e., lack of effect) of a Johnson & Johnson medicinal product unexpected therapeutic or clinical benefit from use of a Johnson & Johnson medicinal product medication error involving a Johnson & Johnson medicinal product with or without patient exposure to a Johnson & Johnson medicinal product e.g., name confusion)
- suspected transmission of any infectious agent via a Johnson & Johnson medicinal product

III. Management of Adverse Events, Serious Adverse Events and Special Reporting Situations

In general, the investigator must immediately report to the Janssen Services, LLC any serious adverse event and Special Reporting Situations, whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to the Janssen Services, LLC. The investigator must record non-serious adverse events and report them to the Janssen Services, LLC according to the timetable for reporting as specified either in the protocol or to fulfill regulatory reporting requirements.

For each subject, AEs, SAEs and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

A Serious Adverse event or Special Reporting Situation must be reported if it occurs during a subject's participation in the Study (whether receiving abiraterone acetate or not), from the consent signature date through 28 days of receiving the last dose of Study Product.

Any serious adverse event or Special Reporting Situations that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- -the event resolves or stabilizes;
- -the event returns to baseline condition or value (if a baseline value is available);
- -the event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

IV. Recording of Adverse Events, Serious Adverse Events and Special Reporting Situations

Recording should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e., a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

A: Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
B. Surgery or procedure planned prior to entry into the Study.

If, in the investigator's judgment, a clinically significant worsening from baseline is observed in any laboratory or other test parameter (e.g., electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate

medical terminology (e.g., thrombocytopenia, peripheral edema, QT prolongation).

V. Maintenance of Safety Information

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (= "last patient off treatment") as well as the end of the follow-up phase (= "last patient out") of the Study, the investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e.g., to fulfill a regulatory request. As such, the data shall be made available within a reasonable timeframe at Janssen Services, LLC's request.

VI. Reporting Timelines

All safety information covered in Exhibit B (SAEs, Adverse Events of Special Interest, Special Reporting Situations, and PQCs) should be reported within **24 business hours** of becoming aware of the event(s).

All non-serious AEs should be reported according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

VII. Transmission Methods:

The following methods are acceptable for transmission of safety information to the Janssen Services, LLC:

- Facsimile (fax), receipt of which is evidences in a successful fax transmission report,
- Electronically subject to strict compliance with the following condition: Reporting may be done electronically only upon written approval by Janssen Services, LLC, which approval must acknowledge that the electronic transmission is in an acceptable encrypted email format. Without such acknowledgement, the approval to use an electronic transmission shall not be valid. The Parties hereby acknowledge the importance of strict precautions with the use of electronic transmission for the security, protection and maintenance of confidentiality of patient health information contained in the reports, or
- Telephone (for business continuity purposes, if fax or authorized electronic system is nonfunctional).

Please use the contact information and process information provided by Janssen Services, LLC

VIII. Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Special Reporting Situation, and Product Quality Complaints (PQCs) to Janssen Services, LLC

A: Serious Adverse Events (SAE), Adverse Events of Special Interest, and Special Reporting Situations

In clinical trials (including reports unblinded as to treatment for blinded studies) involving the Study Product regardless of whether causality with the administration of the Study Product is suspected by the investigator.

The investigator will transmit these reports in a form to be provided (or a form substantially similar to the form provided and approved for use by Janssen Services, LLC in writing) in accordance with Section VII Transmission methods, in English **within 24 business hours** of becoming aware of the event(s) along with the investigator's determination of whether the event was caused by a J&J product.

All available clinical information relevant to the evaluation of an SAE, Adverse Events of Special Interest, and Special Reporting Situations including pregnancy reports (with or without an AE) including paternal exposure are required.

- The investigator is responsible for ensuring that these cases from clinical studies are complete and if not are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented by the investigator and that follow-up information is summarized, e.g., hospital records, coroner's reports, autopsy results and recorded on the appropriate forms.
- A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Study Drug in the course of the Study, by facsimile within 24 hours of such report or correspondence being sent to applicable health authorities.

B. Product Quality Complaints

Any PQC, with or without an AE, (including reports of suspicion of counterfeiting, diversion, or tampering, and suspected transmission of pathogens) will be transmitted by the investigator in the form provided by Janssen Services, LLC in accordance with Section VII Transmission methods, in English, within **24 business hours** of becoming aware of the event(s).

C. Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Services, LLC will provide to the investigator a listing of all SAEs reported to the Janssen Services, LLC. The investigator will review this listing and provide any discrepancies to Janssen Services, LLC.

Upon request, the investigator shall provide Janssen Services, LLC with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, within a reasonable timeline, for reconciliation purposes.

IX. Dissemination of Safety Information from Janssen Services, LLC to the Investigator(s)

Janssen Services, LLC will provide to the investigator IND safety reports for the Study Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

APPENDIX 5 – PROGRESSION AND RESPONSE CRITERIA

Antitumor Effect– Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee.

Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.

Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or ≥10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Reminder: A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by

imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted at each follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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 is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Tumor Markers.

Tumor markers alone cannot be used to assess response. Study Outcome Measures based on PSA Decline – The following parameters will be recorded on a monthly basis.

- PSA decline will be measured according to PSAWG-2 (2008) criteria.
- PSA changes will be recorded on all patients.
- Time to PSA progression (TTP) will be based on revised PSA Working Group-2 criteria [30].

Individual response measures.

- The maximal decline in PSA for each patient will be recorded for each patient.
- The date of the maximal PSA decline (nadir date) will be recorded for each patient, as will the duration from the start of therapy to the nadir PSA.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (new lesions must be > slice thickness).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing, an overall assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time by review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable or progressive disease status.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks confirmation
CR	NonCR/Non-PD	No	PR	≥4 wks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression.

Response Review

Central review of the radiology assessments will be performed via SCCA.

APPENDIX 6 - METHOD FOR PHARMACOKINETIC SAMPLE COLLECTION AND HANDLING

PK plasma samples for determination of Abiraterone:

1. Materials and Labeling

Blood must be collected in Na_2EDTA/NaF containing blood collection tubes. Resulting plasma samples must be stored in polypropylene storage tubes with polypropylene or polyethylene caps (see Ref.).

No tubes with separation gel should be used

All tubes and containers will be labeled with preprinted labels. The preprinted information will include the study number, CRF number, treatment or treatment period, scheduled sampling day and time as stipulated in the flow chart, and the analyte name (abiraterone). No other information will be written on the labels.

Labels should be applied to the sample tubes as follows:

- Apply labels to the sample tubes so that they do not overlap and obscure any information. If possible expose an area between the 2 ends of the label to allow viewing of the contents of the tube.
- Do not alter the orientation of the label on the sample tube.
- Apply labels to all tubes in the same manner.

2. Preparation of Plasma Pharmacokinetic Samples

At a timepoint where Abiraterone needs to be determined:

- Collect 2 mL of blood into the appropriate collection tube (e.g. Vacutainer) at each time point. It is important to collect full volume. Immediately invert collection tube end-over-end 5 to 10 times for mixing of the anticoagulant with the blood collected.
- Following blood collection immediately place the Vacutainer tube in an ice bath until centrifugation for collection of plasma.
- Record the exact date and time of sampling in the CRF, as appropriate.
- Centrifuge blood samples within 60 minutes of collection in a clinical centrifuge at 1300 g (about 2500-3000rpm) for 10 minutes at 4°C to yield approximately 0.7-1.0 mL of plasma from each 2 mL whole blood sample.
- Transfer all separated plasma immediately with a clean, disposable glass or polyethylene pipette (use a new pipette for each sample) to a pre-labeled polypropylene storage tube (See ref.).

- Store plasma samples in an upright position, at -20°C or lower until transfer to bioanalytical facility.
- The time between blood collection and freezing the plasma will not exceed 2 hours.
- Ship specimens according to the instructions provided.
- Questions regarding handling the plasma pharmacokinetic specimens should be addressed to the contact person for the sponsor.

References:

Blood collection tubes:
Blood tubes 2 ml plastic Na_2EDTA/NaF (Becton Dickinson BD 367587 (US) or BD368520 (EU))

Plasma tubes:
Clear PP plasma tube: 1.8-ml NUNC Cryotube (Nunc CryoTubes™, Internal thread, Polypropylene (PP) tube and screw stopper; cat no: 368632)

Shipment of Samples for Drug Measurement

All samples for Drug Measurement will be sent to the bioanalytical facility in a single shipment at the end of the study or in multiple shipments as agreed upon with the bioanalytical scientist. An inventory list must be included with each shipment. The sponsor-provided logs can be used as an inventory list. The inventory list must note each specimen drawn for each subject, and note any missing specimens.

The investigator must follow the instructions below:

- For all international shipments, World Courier will be used. For domestic shipments, a reliable domestic courier, such as Federal Express will be used.
- The sponsor contact will be notified by fax or email that a shipment of samples is imminent. This notification will be made before the shipping date. As soon as shipment day and air bill number(s) are available, the site will e-mail Alex Attema, PhD (see next page). The e-mail must specify the study number, the number of samples, the time of shipment pick-up and the AWB/tracking number and include an electronic sample inventory.
- Notify the bioanalytical scientist and the courier, at least 24 hours in advance of the planned shipment. Provide the courier with the appropriate account number to be used, if applicable.
- Unless agreements were made with the Bioanalysis Scientist, samples will be shipped via overnight delivery only on Monday through Wednesday, excluding holidays.

- Preferably the frozen samples will be shipped in boxes, sorted by subject and sampling time. Boxes will be packed in bags that can withstand dry ice conditions (e.g., cryogenic bags).
- Pack the frozen samples in sufficient quantity of dry ice in appropriate containers, to maintain a frozen state for at least 3 days.
- For all biological samples, follow the International Air Transport Association (IATA) regulations for shipment.
- Ensure that the total package weight does not exceed 27.2 kg (60 pounds).
- Label the package with the sponsor name and study number.
- Include a return address (which includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for the shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment, in the study files.
- Deviations from the above procedure will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Samples must be sent to:
PRA International
To the attention of:

Mr. Alex Attema, PhD.
PRA International – Early Development Services
Westerbrink 3
9405 BJ Assen
The Netherlands

E-mail: Attemaalex@PRAIntl.com

Please be advised, as soon as shipment day and air bill number(s) are available, to notify the shipment of the samples to PRA International (e-mail: Attemaalex@PRAIntl.com) and to J&J PRD, Hans Stieltjes (e-mail: hstieltj@its.jnj.com) preferably by e-mail before the shipment.

APPENDIX 7 – SUMMARY OF CHANGES

First Release: v1.4, dated 9/20/12

Amendment 1: v2.0, 12/7/2013
- Title page: version and date updated
- Table of Contents: added Appendix 6, Summary of Changes (q.v.)
- Section 6.4.2.1 (page 26): updates to bone biopsy procedure

Throughout: minor typographyAmendment 2: v3/0, 2/4/13
- Title page: version and date updated
- Section 4.3, Exclusion Criterion #13 (page 20): Patients requiring therapeutic anticoagulation are not eligible for this study.

Amendment 3: v3.1, 3/12/13
- Title page: version and date updated
- Section 5.9: inserted language required by the supporting drug company (Janssen Services LLC), regarding handling precautions for women of childbearing potential, pregnant, or lactating.
- Throughout: minor typography

Amendment 4: v4.0, 4/21/13
- Throughout: added Dose Escalation for all cohorts (formerly only cohort 3 pts) and Pharmacokinetic Analysis (not previously included)
- Title page: version and date updated
- Exploratory Objectives (throughout): response to dose escalation; mechanisms of resistance via pharmacokinetic analysis; pharmacokinetics of 1000mg b.i.d. dosing
- Section 6.4.2.1, Biopsy Procedure: removed extraneous reference to anticoagulant therapy
- Section 6.6, Adverse Events: Lab abnormalities will be captured as AEs if they are deemed clinically significant by the treating physician/clinician
- Section 7.3.3, Pharmacokinetics: added
- Appendix 1, Schedule of Events: Pharmacokinetics added at the Progression timepoint
- Throughout: minor typographic and/or formatting corrections

Amendment 5: v5.0, 04/13/2015
- Title page: version and date updated
- Section 5.5: updated drug interaction information for CYP2C8.
- Section 7: removed Phosphorus (PO) from Lab studies; protocol text now matches Labs table in Section 6.4.1.
- Clarified SAE Notification to IRB and Janssen to “within 24 **business** hours.”
- Throughout: minor typography

Amendment 6: v6.0, 09/10/2015
- 6.7.4.1 Updated SAE reporting guideline to match CC-IRB reporting guidelines.

Section 4.2 Inclusion criteria 13 changed to say 2 lines of chemotherapy.