Cover Page for Protocol

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Official title of Study	Abi Race: A Phase II open-label, parallel group study of Abiraterone Acetate plus Prednisone in African American and Caucasian men with metastatic castrate-resistant prostate cancer
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A Phase II open-label, parallel group study of Abiraterone Acetate plus Prednisone in African American and Caucasian men with metastatic castrate-resistant prostate cancer

An Investigator-initiated study, sponsored by Dr Daniel George, MD

and Duke University Health System

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LIST OF ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AE	Adverse Event
AKT	See PKB (protein Kinase B)
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK	Creatine Kinase
CK-MB	Creatine Kinase - Muscle and Brain isoenzyme
CR	Complete Response
CRF	Case report forms
CRD	Clinical Research and Development
CRPC	Castration resistant prostate cancer
CS	Cowden Syndrome
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
EGFR	Epidermal Growth Factor Receptor
18F-FDG	[18F]-Fluorodeoxyglucose
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
HDL	High density lipoprotein
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection fraction
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
PC	Prostate cancer
PD	Pharmacodynamic
PET	Positron Emission Tomography
PFS	Progression free survival
PI3K	Phosphatidylinositol 3'-kinase
PIN	Prostatic intraepithelial neoplasia
PK	Pharmacokinetic
PKB	Protein Kinase B (or AKT)
PR	Partial response
PT	Prothrombin Time
PTEN	Phosphatase and Tensin homolog
PTT	Partial Thromboplastin Time
QTc	QT interval (corrected)
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation In Solid Tumors
RP	Radical prostatectomy
S6K	Protein Kinase S6
SAE	Serious adverse event
SD	Stable disease
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SUV	Standardized Uptake Value
TdP	Torsades de Pointes
TTE	Transthoracic echocardiogram
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Count
WCBP	Women of Childbearing Potential
WHO	World Health Organization

1.0 SYNOPSIS

Study Title: A Phase II open-label, parallel group study of abiraterone acetate in African American and Caucasian men with metastatic castrate-resistant prostate cancer					
Protocol Number	Pro00046383	**Phase**	II	**Type**	Interventional
Condition/Disease: Castration resistant metastatic prostate cancer, chemo-naive					
Number of Subjects	100	**Duration of Subject Participation**			Up to 24 months on study drug
Number of Study Centers	5	**Duration of Study 3 years**			Anticipated 30 months accrual time, up to 24 month follow up

Rationale: African American men have a 60% greater incidence of being diagnosed with prostate cancer and nearly a 2.5 fold greater chance of mortality from the disease, yet the underlying cause for this increased mortality remains controversial [1]. Hormonal levels vary in men by race, with African American men having higher dihydrotestosterone (DHT), androstenedione (ASD) and sex hormone-binding globulin (SHBG) than Caucasian men with localized prostate cancer [2, 3]. Historically, African American men with prostate cancer have a worse overall survival than Caucasian men, however, this is confounded by the timing of androgen deprivation therapy (ADT) and access to other therapies [4, 5]. To what extent race affects response to therapy in prostate cancer is not clear.

Germline polymorphisms of genes involved in androgen signaling have been shown to vary significantly by race and may have important implications with regard to response to therapy targeted towards this pathway. Polymorphisms within the promoter region of the androgen receptor (AR) (specifically CAG repeats) have been well documented and vary significantly according to race, with African American men having significantly shorter CAG repeats resulting in greater AR activity [6]. These CAG repeats have been associated with more aggressive disease characteristics [6]. Recently, germline polymorphisms in androgen metabolism genes have been shown to have prognostic value in regards to the time to development of CRPC in men with prostate cancer on ADT. Ross et al tested 129 polymorphisms across 20 genes associated with androgen metabolism and identified three polymorphisms in separate genes (*CYP19A1*, *HSD3B1*, and *HSD17B4*) that were significantly associated with prolonged time to progression (TTP) on ADT [7]. Specifically, individuals carrying more than one of the polymorphisms were associated with *improved* time to CRPC than individuals carrying zero or one ($P < .0001$). More recently this group identified polymorphisms in two androgen transporter genes, *SLCO2B1* and *SLCO1B3* that were associated with a significantly *shorter* time to CRPC alone and in combination [8]. Incidences of these polymorphisms ranged from 15 to 81%; unfortunately, the cohort of patients used to identify these polymorphisms had limited numbers of African American patients or other racial and ethnic groups.

Recent studies have focused on discovering molecular mechanisms underlying prostate cancer disparities using DNA microarrays and bioinformatics. These studies have compared the gene expression profiles between African American and Caucasian American cancers and between prostate cancer and patient-matched normal prostate from African Americans and Caucasian Americans. By integrating gene expression profiling and pathway analyses, multiple components within the androgen receptor signaling pathway were revealed to be up-regulated in African American prostate cancer specimens along with the up-regulation of genes within other signaling pathways that converge on androgen receptor signaling, portending that androgen receptor pathway activation is a key component of prostate cancer health disparities. Overall the comparison of African American and Caucasian American prostate cancer specimens has led to the identification of a number of differentially expressed genes, including CYP19A1, AMFR, CXCR4, MMP9, SRD5A2, ADIPOQ, AKT1, ALOX12, ALOX15, ALOX15B, BMP2, CGA, ERG, FASN, IL1B, IL6, IL8, NFKB1, PIK3C3, PIK3CA, PI3K3R1, PLA2G2A, TGFB1, TIMP3, TNF, P38MAPK, STAT1, RHOA, ITGB5, MAPKAPK2, CSNK2A1, PIK3CB, ARA55, GNA01, GNB3, POLR2L, PRKCE, PRKD1, TBP, CALR, GNG2, GNG11, GNG12, CALM1, NFKB2, STAT2, RHOU, FGF13, EIF3B, and GIT1 [9-12]. Thus, germline polymorphisms of these differentially expressed genes also may have important implications with regard to response to therapy targeted towards the androgen signaling pathway.

To what extent racial differences affect response and time to progression on abiraterone acetate is unknown. Secondarily, to what extent differences in systemic hormonal levels as well as androgen transport gene polymorphisms affect response to abiraterone acetate is unknown. Understanding any potential differences in response to therapy by race and/or by

hormonal/genetic factors could impact on both our clinical use of abiraterone acetate as well as future clinical trial design. Finally, as other agents targeting the androgen/androgen receptor pathways become available, it will be important to differentiate their activity according to race, genetics and hormonal milieu.

We propose a pilot study to evaluate in a prospective, parallel group design, radiographic PFS in men with mCRPC treated with abiraterone acetate/prednisone by race. Secondary endpoints will describe the response to abiraterone acetate/prednisone, PSA kinetics, and safety and tolerability. Exploratory endpoints will describe the incidence and associations of key hormonal levels as well as germline polymorphisms in androgen signaling genes and genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers in both African American and Caucasian cohorts.

Primary Objective: The primary goal is to prospectively estimate the median radiographic PFS of African American and Caucasian men with mCRPC to abiraterone acetate and prednisone.

Secondary Objectives:

1) PSA kinetics: to determine the duration of PSA response, time to nadir, and percent of men who achieve a PSA < 0.1;

2) Radiographic assessments: to estimate the rate of objective response and incidence of bone flares

3) Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations

4) Overall survival

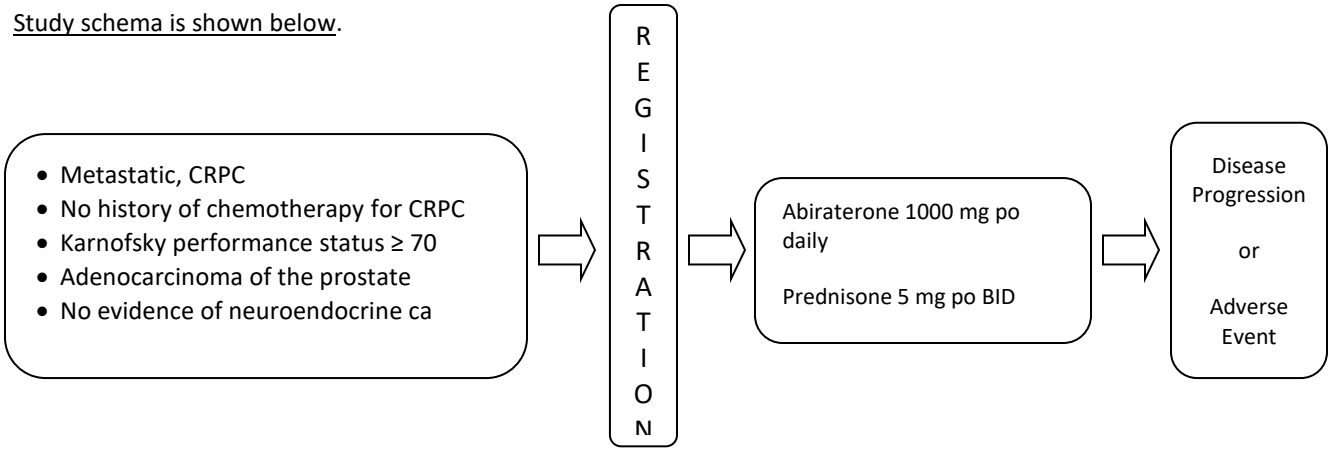
Exploratory Objectives:

1) Describe the baseline profile of serum hormone levels (including testosterone, DHT, DHEA, DHEAS, estradiol) and lipidomics, the change in levels with subsequent therapy (Cycle 4), and their correlation with response to abiraterone acetate.

2) Describe the germline SNP profiles of target genes involved in androgen signaling and target genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers as well as a genome wide analysis (GWAS) in both African American and Caucasian men with mCRPC and their associations with response to abiraterone acetate.

Design: This is a non-comparative pilot open-label, parallel arm, multicenter study of abiraterone acetate in African American and Caucasian men with mCRPC. The primary goal is to prospectively estimate the median radiographic PFS in African American and Caucasian men with mCRPC cancer treated with abiraterone acetate. Patients will self-report on race and 50 patients will be enrolled into each group. Patients will be treated on open-label treatment until evidence of disease progression as defined by Prostate Cancer Working Group Two (PCWG2) definition [13] or until two years at which point they will roll over to the standard of care at that time.

Study schema is shown below.



Study Population: This will be a Duke University Health System study conducted through the Duke Cancer Institute, composed of a large tertiary referral center and network sites, which treat a high volume of metastatic CRPC patients and who prioritize African American patient accrual to clinical trials. It is anticipated that the Duke Cancer Network and 6 satellite sites will be needed to accrue 100 subjects (50 African American and 50 Caucasian) over a 30 month accrual

period. Typically 20-30 African American subjects per year would be eligible for this protocol at Duke University Medical Center alone but this number would be substantially more by including the Duke Cancer Network and outreach sites. A parallel population of Caucasian patients will be accrued. All samples will be analyzed to determine the germline SNP profiles of target genes involved in androgen signaling and target genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers. In addition, for GWAS, all samples will be genotyped using Illumina's 2.5M beadchip.

Main Inclusion Criteria:

- Male, age ≥ 18 years
- Karnofsky performance status ≥ 70 (Appendix 1)
- Life expectancy of ≥ 12 months as determined by treating investigator
- Written Authorization for Use and Release of Health and Research Study Information (HIPAA authorization per institutional requirements)
- Willing/able to adhere to the prohibitions and restrictions specified in this protocol
- 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
- 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
- Adequate laboratory parameters
    - Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb>9 g/dL
    - Serum potassium > 3.5 mEq/L
    - AST/SGOT and ALT/SGPT ≤ 1.5 x Institutional Upper Limit of Normal (ULN)
    - Serum bilirubin ≤ 1.5 x Institutional ULN
    - Serum creatinine ≤ 1.5 x Institutional ULN or 24-hour clearance ≥ 50 mL/min
    - Serum albumin of > 3.0 g/dl
- Histologically confirmed diagnosis of adenocarcinoma of the prostate. Histologic variants of prostate cancer, including neuroendocrine features and small cell carcinoma of the prostate are excluded.
- Radiographic evidence of metastatic disease; evaluable non-target lesions and/or bone only metastasis are permitted.
- Ongoing ADT using an LHRH agonist (e.g. leuprolide, goserelin) or antagonist (e.g. degarelix) must continue on therapy unless prior bilateral orchiectomy has been performed. Screening serum testosterone must be ≤50 ng/dl.
- PSA ≥ 2.0 ng/mL
- Evidence of castration resistant disease on ADT as evidenced by one of the following:
    - Absolute rise in PSA of 2.0 ng/mL or greater, minimum 2 consecutive rising PSA levels with an interval of ≥ 1 week between each PSA level, **OR**
    - 2 consecutive PSA levels 50% or greater above the PSA nadir achieved on ADT and separated at least 1 week apart, **OR**
    - CT or MRI based evidence of disease progression (soft tissue, nodal or visceral disease progression) according to modified PCWG2 criteria or modified RECIST 1.1 criteria, or at least 1 new bone scan lesion as compared to the most immediate prior radiologic studies.
- A minimum of 2 weeks elapsed off of antiandrogen therapy prior to start of study drug (i.e. flutamide, nilutamide, bicalutamide)
- A minimum of 4 weeks elapsed off of sipuleucel-T prior to start of study drug
- A minimum of 4 weeks from any major surgery prior to start of study drug.
- Self-reported race of either African American or Caucasian.
- Ability to swallow, retain, and absorb oral medication.
- Ability to understand and the willingness to sign a written informed consent document. If the subject is unable to understand the consent due to comorbidity, such as Alzheimer's disease, consent by a legally authorized representative and assent by the subject will be obtained.

Main Exclusion Criteria:

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

1. Prior treatment with abiraterone acetate or enzalutamide
2. Active infection or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
3. Any chronic medical condition requiring a higher dose of corticosteroid than 5mg prednisone/prednisolone bid
4. Have known allergies, hypersensitivity, or intolerance to abiraterone acetate or prednisone or their excipients.
5. Pathological finding consistent with small cell carcinoma of the prostate
6. Symptomatic Liver or visceral organ metastasis
7. Have a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents
8. Known brain metastasis
9. Prior cytotoxic chemotherapy or biologic therapy for the treatment of CRPC
10. Previously treated with ketoconazole for prostate cancer for greater than 7 days
11. Prior systemic treatment with an azole drug (e.g. fluconazole, itraconazole) within 4 weeks of Cycle 1, Day 1.
12. 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
13. Poorly controlled diabetes
14. Active or symptomatic viral hepatitis or chronic liver disease
15. History of pituitary or adrenal dysfunction
16. 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
17. Atrial Fibrillation, or other cardiac arrhythmia requiring therapy
18. Other malignancy, except non-melanoma skin cancer, with a ≥ 30% probability of recurrence within 24 months
19. Administration of an investigational therapeutic within 30 days prior to Cycle 1, Day 1
20. Any condition which, in the opinion of the investigator, would preclude participation in this trial

Concomitant Treatment:

Prohibited:

- Chemotherapy, radiation therapy, or immunotherapy, or any anti-cancer therapy other than abiraterone acetate and prednisone and those described below.
- Immunosuppressive doses of systemic corticosteroids greater than prednisone 5mg twice daily or the equivalent.
- Agents known to significantly prolong the QTc interval (Appendix 2).
- Coumadin or other vitamin K antagonists.

Permitted:

- Standard therapies for preexisting conditions, medical/surgical complications including nausea and diarrhea, and palliation.
- Non-potent P450 CYPs isoenzyme inhibitors and/or inducers (Appendix 3).
- LHRH agonists or antagonists.
- Anti-hypertensive medications.
- Diabetic medications.
- Antidepressants or other medications for mood disorders.
- Analgesics including opioids.
- Bisphosphonates and/or denosumab.
- Erythropoietic agents.
- Systemic anticoagulation with low molecular weight heparin.
- Focal therapies for localized non-prostate cancers

Study Intervention and Administration: The study agent abiraterone acetate will be administered at a dose of 1000mg orally once daily with prednisone 5 mg BID in 4-week cycles throughout the treatment period. 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 acetate should be

taken with a glass of water and consumed over as short a time as possible. Patients should swallow the capsules whole and not chew them. Study drug will be provided by Janssen Scientific Affairs and distributed by DCI Investigational Chemotherapy Service. Patients will be instructed to take a 5-mg prednisone tablet, twice daily. It is not required for the prednisone to be taken at the same time as abiraterone acetate. The dose of prednisone will remain unchanged in the event that the study drug dose is changed. If a prednisone dose is missed, it should be omitted and will not be made up. Should a dose modification of the prednisone be needed due to toxicities, the site will need to discuss this with the medical monitor.

Study Assessments:

Vital signs, performance status, and physical exam will be assessed at each visit. The following laboratory studies will be obtained at intervals specified in the study flow chart to assess subject safety, specifically the risk of infection, hyperglycemia, and/or bone marrow, liver, and kidney abnormalities: complete blood count, blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, magnesium, phosphorus, glucose, albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT).

For efficacy assessment, standard-of-care biomarkers including PSA will be drawn prior to initiation and after each cycle of therapy. A CT scan with contrast of chest, abdomen, and pelvis, a bone scan and a circulating tumor cell count will be performed within 42 days prior to the intended cycle 1 day 1 visit and every 3 cycles (12 weeks).

Correlative Sciences:

Whole blood will be collected in purple top EDTA tubes at baseline for DNA isolation and characterization of SNPs for androgen metabolism genes as well as genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers and ancestral genotyping. Additionally, a genome wide analysis (GWAS) is planned in both African American and Caucasian men with mCRPC and their associations with response to abiraterone acetate, in line with the specified endpoints and biomarkers defined in the trial. In addition baseline assessments of lipidomics and hormonal levels including testosterone, DHT, DHEA, DHEAS, estradiol and their change after 12 weeks on therapy will be evaluated. Finally additional baseline and 4 week plasma samples will be drawn to explore additional biomarkers that may have prognostic or predictive value.

Safety Evaluation:

Subjects receiving at least one dose of abiraterone acetate will be evaluable for safety.

- Safety will be assessed by physical exam, laboratory assessments, review of concomitant medications, adverse event (AE) and serious adverse event (SAE) evaluations every cycle throughout the study.
- Electrocardiogram prior to initiation and subsequently at the discretion of the treating physician
- NCI Common Toxicity Criteria (v 4.0) will be used to record and monitor for adverse events (Appendix 3).

  Treatment will be held and/or dose reduced for certain specified grade 3 or 4 adverse events until resolution to grade 1 as specified in the protocol

Efficacy Evaluation:

The primary endpoint will be radiographic **progression free survival** (rPFS) based on PCWG2 criteria or based on the onset of a skeletal related event. Imaging will be obtained every 12 weeks.

Secondary endpoints will include:

1. RECIST 1.1 defined radiologic response rates and incidence of bone flares
2. PSA response, time to nadir, and percent of men who achieve a PSA < 0.1
3. Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations

Statistical Considerations: Based on Ryan et al. the median time to radiographic progression free survival (rPFS) is 16.5 months [14]. This trial is non-comparative. Fifty (50) patients will be enrolled in each group (AA and Caucasians). With an accrual rate of 50 patients/group over 30-month accrual period, 24-months follow-up, and assuming that rPFS follows an exponential distribution, based on 5000 simulations the average width of a two-sided 95% confidence interval for the median rPFS is 16.

Ethical Considerations:

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH GCP

and the ethical principles that have their origins in the Declaration of Helsinki. The IRB must review and approve the protocol and ICF before any subjects are enrolled. Before any procedures specified in the protocol are performed, the subject must sign and date the IRB-approved ICF.

2.0 STUDY FLOW CHART

Procedure	Screening/ Baseline Testing[a]	On-treatment visits (+/- 3 for first cycle then +/- 7 days)				End of Treatment & Follow-up Visits			
	Within 30 days of dosing	Intended/ Cycle 1 Day 1[p]	Cycle 1 Day 15 (+/- 5 days)	Cycle 2, 3 Day 1	Cycle 4 Day 1 & every 3rd cycle (Cycles 7, 10, 13, etc.)	End of Treat-ment[c]	Follow-up safety visit[d]	Follow-up visits (until disease progression or new treatment)[d]	Follow up - survival[d]
Informed consent	X								
Inclusion / exclusion criteria	X								
Demographic data	X								
Prior and concomitant medications	X	X	X	X	X	X	X		
Prior and concomitant non-pharmacologic treatments	X	X	X	X	X	X	X		
Medical history and AE assessment[e]	X	X	X	X	X	X	X		
Vital signs, height, and weight[f]	X	X	X	X	X	X	X		
Karnofsky performance status[g]	X	X	X	X	X	X			
Physical examination[e]	X	X	X	X	X	X	X		
Electrocardiogram[h]	X								
Tumor Site Assessments: CT scans (chest, abdomen, pelvis) and bone scans[i]	X[i]				X[i]		X[d]	X	
Abiraterone acetate dispensed[j]		X[p]		X	X				
Assess survival									X[d]
Standard-of-care laboratory assessments[k]									
CBC with differential	X	X[b]	X	X	X	X	X		
Serum chemistries[k]	X	X[b]	X	X	X	X	X		
PSA	X	X[b]		X[k]	X[k]	X		X[k]	
Testosterone	X				X[k]				
Circulating tumor cell count (optional) [k]	X				X[k]	X			
Lactate dehydrogenase (LDH)	X								
Correlative/research studies									
Serum Hormone Levels[l]	X				X[l]	X[l]			
Plasma and serum markers[m]	X			X[m]					
DNA isolation and characterization of SNPs[n]	X								
Archival tissue collection[o]	X								

New cancer therapies								X	

Footnotes to Study Flow Chart:

a. Screening/baseline evaluations must be completed within 30 days prior to the intended cycle 1 day 1 visit, with the exception of informed consent (42 days) and scans (42 days).
b. If the CBC with diff,Serum Chemistries, and PSA are performed within 7 days of intended Cycle 1 Day 1 visit, do not repeat these at the intended Cycle 1 Day 1 visit unless requested by the site's PI.
c. The end of treatment visit is to occur +/- 7 days after the last dose of study agent.
d. The follow-up safety visit is to occur 28 days (+/- 7 days) after the last dose of study agent. CT and bone scan will be done at the safety follow up visit if scans have not been done within the last 8 weeks of the visit. After the Day 28 safety follow up visit, patients will visit the clinic once every 3 months for up to 24 months (+/- 14 days) from the start of therapy. Subjects who discontinue treatment due to reasons other than radiographic progressive disease will be followed until a new treatment is started or disease progression. Abiraterone prescribed off-study is not be considered a new treatment. Disease progression will be obtained through Standard of Care scans. Subjects who discontinue due to progression will not be followed. Survival will be assessed by chart review or phone call.
e. Medical history, physical examination and AE assessments will be performed prior to study agent administration, on Day 1 and 15 of cycle 1 and on Day 1 only of each subsequent cycles 2, 3, 4 7, 10 and every 3 cycles. An end-of-study medical history, physical exam, and AE assessment will be performed at the end of treatment or at progression. In addition, one safety follow-up visit with medical history, physical exam, and AE assessment will occur 28 +/- 7 days of the last dose of study drug.
f. Vital signs (BP, pulse, respirations, temperature and weight) will be recorded at each visit. Height will be measured at screening only.
g. Karnofsky performance status (Appendix 1) will be evaluated and recorded on all clinic visits on study and at the end of treatment.
h. Electrocardiogram prior to initiation and subsequently at the discretion of the treating physician
i. As part of routine tumor assessment, CT and bone scans will be performed within 42 days prior to intended cycle 1 day1 visit and every 3 cycles (approximately every 12 weeks) thereafter (i.e., baseline, Day 1 of cycles 4, 7, 10 and every 3 cycles). The timing of the scans will be within 7 days of the next planned cycle initiation. A CT scan will be performed at the above described timepoints with contrast as per radiology protocol of chest, abdomen, and pelvis. If the chest CT at baseline is clear, chest x-rays may be used for subsequent assessments at the enrolling physician's discretion. These tumor assessments will be performed locally, in strict accordance with the RECIST 1.1 guidelines. A total body bone scan will be performed at the above described timepoints and interpreted according to PCWG2 guidelines (Appendix 4). CT and bone scan modalities per standard institutional practices may be used, but the same modality should be used throughout the study for each subject. Scans during follow-up will be performed according to standard clinical practice and interpreted as described above.
j. Abiraterone acetate will be dispensed directly from clinic.
k. Standard-of-care laboratory assessments at the times indicated include:

   Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit at baseline, Cycle 1 Day 15, Day 1 of cycles 2, 3, 4 7, 10 and every 3 cycles, at the end of treatment visit and at safety follow-up visit.

   Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, carbon dioxide or bicarbonate, calcium, magnesium, phosphorus, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase at baseline, Cycle 1 Day 15, Day 1 of cycles 2, 3, 4 7, 10 and every 3 cycles, at the end of treatment visit, and at the end of Safety Follow-up Visit.

   PSA: Drawn at baseline, Day 1 of Cycle 1 and cycles 2, 3, 4, 7, 10 and every 3 cycles, and at the end of treatment visit. During follow-up for subjects who discontinue treatment due to reasons other than radiographic progressive disease, PSA will be collected every 3 months (+/- 28 days) and additionally as clinically appropriate.

   Testosterone: Drawn at baseline and the end of cycle 3 (at Cycle 4 Day 1).

   Circulating tumor cell count (if available): Standard Cellsearch® CTC test is drawn at baseline, Day 1 of every 3 cycles (i.e. cycles 4, 7, 10, etc.), and at the end of treatment visit.

   Note: Intended Cycle 1 Day 1 CBC, Serum Chemistries, &PSA lab tests do not have to be repeated if screening lab tests are obtained within 7 days prior to the intended Cycle 1 Day 1 visit.
l. Serum hormone levels include Testosterone (ultrasensitive) DHT, DHEA, DHEAS, and estradiol: One 5ml gold top tube will be collected at baseline, the end of cycle 3 (at Cycle 4 Day 1), and at the end of treatment visit, end of treatment research labs may be drawn at safety follow up visit if needed. Lipidomics will also be assessed at baseline and cycle 4 day 1 and the samples should be collected after fasting. See lab manual for detailed instructions.
m. Plasma for blood-based biomarkers: One 6ml lavender top tube and one 4.5ml light blue top tube will be collected at baseline and end of cycle 1 (Cycle 2, Day 1).

n. DNA isolation and characterization of SNPs: One 4ml lavender top tube will be collected at baseline See lab manual for detailed instructions.
o. If available and consistent with local regulations, banked tumor tissue (unstained slides and/or a paraffin-embedded block) will be obtained and evaluated to assess somatic expression of target genes involved in androgen metabolism, target genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers, and AR splice variants, potentially predictive of abiraterone acetate antitumor activity. See lab manual for detailed instructions.
p. All assessments must be performed on the intended cycle 1 day 1 visit. However, Cycle 1 day 1 is the first day of treatment and must occur within 2 weeks of the intended cycle 1 day 1 visit.

Note: Screening/baseline correlative research studies may be drawn on screening/baseline or Intended Cycle 1 day 1 visit.

3.0 CURRENT TREATMENT FOR METASTATIC CRPC

3.1 Metastatic Castrate Resistant Prostate Cancer

Prostate cancer has become an increasingly important health issue globally. With 903,500 men diagnosed in 2008, prostate cancer is the second most diagnosed cancer worldwide [15]. It is estimated by the American Cancer Society that in 2012, prostate cancer will be diagnosed in 241,740 men in the United States alone and that 28,170 will die [1].

The most significant morbidity of prostate cancer is bone metastasis. It develops initially in the axial skeleton and later in the appendicular skeleton in advanced prostate cancer and metastasis to bone is present in > 90% of patients [16-18]. These lesions can cause pain, skeletal fractures, spinal cord compression, anemia and thrombocytopenia. Clinical sequelae can include pain, paralysis, diminished mobility, fatigue and increased risk of infections. Side effects such as constipation and delirium from analgesics required to palliate pain are also significant. They further compromise patient quality of life. In addition, soft tissue metastasis occurs in about 40% of advanced patients. Pelvic lymphadenopathy may lead to anatomic obstruction of the ureters, or fistula formation [16]. When tumor recurs in the prostate gland or bed, urethral obstruction may also ensue.

Prostate cancer is hormone sensitive at the time of initial diagnosis. Although most patients with advanced metastatic disease initially respond to conventional androgen deprivation with medical or surgical castration, the median duration of disease control has been 13-22 months and historically overall survival may be as short as 28-36 months from starting androgen deprivation therapy [19-21]. The clinical status of patients after failure of castration is commonly referred to as hormone-refractory prostate cancer (HRPC), or androgen-independent prostate cancer (AIPC). However, recent investigations have established that tumor progression often remains androgen-dependent albeit at much reduced systemic androgen levels after castration. Although used widely in clinical settings, the terms HRPC and AIPC do not reflect the biology of advanced prostate cancer where androgen receptor (AR) and its ligand remain pivotal in tumor growth. Prostate cancer progression after conventional medical or surgical castration should, therefore, be considered castration-resistant prostate cancer (CRPC). Patients with metastatic CRPC have a very limited life expectancy and most often die of their prostate cancer.

In the castrate state, remaining ligands to the AR have been thought to be derived primarily from the adrenal glands. Conventional androgen deprivation therapy removes 90% of circulating androgens produced in the gonads. As much as 10% of circulating testosterone remains, in part due to the peripheral conversion of adrenal steroids to testosterone. In addition, several recent studies suggest that androgen levels in the microenvironment of prostate cancer may be maintained in spite of reduced systemic levels [22, 23]. In patients with castrate levels of testosterone, the tissue levels of dehydroepiandrosterone, dihydrotestosterone, and androstenedione all remain sufficient to activate the AR. Furthermore, the ARs are predominately located in the nucleus in biopsy tissue, indicating

ligand-binding and the activation of androgen-dependent gene expression. Increased expression of the AR is common in advanced prostate cancer, and allows lower ligand levels to more strongly activate the AR [24]. A recent investigation made the observation that in high risk primary prostate tumors and in metastatic biopsies, CYP17A1 gene expression is highly upregulated, suggesting the possibility of in situ production of androgens as autocrine or paracrine growth factors despite castration.[25, 26] Similarly, investigators at MD Anderson Cancer Center also detected CYP17 expression by immunohistochemistry in bone marrow metastasis in CRPC [27]. Although these preliminary findings require further corroborating evidence, the need to suppress androgen production in adrenal glands and possibly at tissue levels persists in CRPC.

Complete androgen independence in CRPC is thought to be rare. A few patients (9%) have mutations in the AR; these changes could allow the AR to be activated by non-androgen ligands, or might allow ligand-independent AR association with coactivator molecules.[28]

Although gene fusions are well known to drive the development of blood cancers and sarcomas, only rarely have they been detected in the common solid cancers. Recent evidence indicates that a gene fusion may be important in the pathogenesis of prostate carcinoma.[29-33] Chromosomal translocations involving the androgen-responsive gene transmembrane protease serine 2 (TMPRSS2) and erythroblast transformation–specific (ETS)-related transcription factors ETV1, ETV4, and ETV5, have been identified in 50% to 70% of prostate cancer cases.[29, 30] Translocation of TMPRSS2 to the ERG gene, found in a high proportion of human prostate cancer, results in overexpression of the 3'-ERG sequences joined to the 5'-TMPRSS2 promoter. ERG and other ETS family members are transcription factors that are implicated in the control of cell growth and differentiation and the chimeric protein product of the gene translocation appears to retain hormoneresponsiveness.[31] Specific translocations in primary tumors have been associated with more aggressive natural clinical history, more advanced disease at diagnosis and greater lethality.[32-35] These gene rearrangements may be associated with tumor response to androgen deprivation therapy, including abiraterone acetate [36].

3.2 Asymptomatic or Mildly Symptomatic Patients with CRPC

Approximately 50% of patients with metastatic prostate cancer will have no noticeable symptoms related to the tumor.[37] The optimal management of these patients with asymptomatic or mildly symptomatic metastatic prostate cancer refractory to androgen deprivation therapy remains undefined.[38] There are no approved second-line hormonal therapies for this population, and cytotoxic chemotherapies (docetaxel, cabazitaxel, or mitoxantrone) are ordinarily reserved for patients with symptomatic or rapidly progressive cancer.[39] The American Society of Clinical Oncology / Cancer Care of Ontario and EAU guidelines for the cytotoxic treatment of CRPC emphasize the need to individualize the timing of nonhormonal therapy for prostate cancer and consider routine docetaxel questionable in men who have metastatic disease but lack symptoms.[40, 41] Similarly, the current ESMO guidelines for metastatic prostate cancer recommend that patients with castrate-resistant

disease should receive second and possibly third line hormonal therapies, while chemotherapy with docetaxel given every three weeks should be considered for patients with CRPC who are symptomatic.[42] Thus the non-cytotoxic treatment of patients with CRPC who are asymptomatic or mildly symptomatic remains a significant unmet medical need.

Patients with metastatic CRPC who are not good candidates for immediate chemotherapy may still benefit from alternate therapies since they develop symptomatic disease progression in a short period of time. This adverse natural history of patients with asymptomatic or mildly symptomatic CRPC was documented in two recent Phase III trials of novel agents in this population. A multinational, double-blind, placebo-controlled trial of the endothelin antagonist atrasentan in patients with meta
static CRPC who had not received chemotherapy and did not require opiates for cancer related pain enrolled 809 men.[43] Patients were randomized 1:1 to receive either atrasentan 10 mg per day or placebo. The primary endpoint was time to disease progression (TTP), which was determined according to radiographic and clinical measures. Analyses of overall survival and changes in biomarkers also were performed. Greater than 50% of patients on both the experimental and control arms developed protocol defined progression in less than 100 days, with 87% of the progressions by radiographic criteria. In addition more than half of patients on the control arm had a 50% worsening of the Pain Catastrophizing Scale (PCS) pain score within 12 months of study entry, primarily due to increasingly painful bone metastases.[44] The median survival was 20.5 months for atrasentan treated patients and 20.3 months for the control patients.

A second smaller Phase III study compared the investigational immunotherapy product Sipuleucel-T with placebo in patients with CRPC who had not received chemotherapy.[45] Patients with cancer-related bone pain, those requiring opioid analgesics for cancer pain, and those with visceral metastases were not eligible. Disease progression events included radiographic progression, cancer pain, and clinical events, with the great majority radiographic. The median for time to disease progression (TTP) for Sipuleucel-T was 11.7 weeks compared with 10.0 weeks for placebo. Median survival was 25.9 months for Sipuleucel-T and 21.4 months for placebo. These results demonstrate that patients with asymptomatic or mildly symptomatic CRPC have short times to disease progression and to the rapid appearance of painful metastases, with an approximate overall survival of two years or less. Therefore the development of an alternate non-cytotoxic therapy with an improved safety and toxicity profile, capable of delaying tumor progression, blocking onset or worsening of pain, and improving survival would be of significant clinical benefit to patients with CRPC.

3.3 Second line hormonal therapies for CRPC

Second line hormonal therapies in prostate cancer have limited efficacy, and none have received regulatory approval for this use. Historically, bilateral adrenalectomy was the first second line hormonal therapy to be evaluated.[46] Several of the adrenalectomized patients with widespread bone metastases had decreases in the bulkiness of their prostate tumor, reductions in prostatic acid phosphatase levels, increases in hemoglobin and red blood cell

levels, and strikingly, 5 of 7 patients had complete relief of their cancer pain within 48 hours of the surgery. However, patient and physician acceptance of adrenalectomy was low, due to the morbidity of major surgery in an advanced stage cancer patient population.

3.3.1 Adrenal Androgen Inhibitor

Historical attempts to obtain the benefits of total adrenalectomy medically without the side effects of surgery have met with limited success. Aminoglutethimide and ketoconazole both inhibit several adrenal enzymes involved with adrenal androgen synthesis. Modest therapeutic activities on prostate cancer were observed. However, the side effects were significant. For example, in combination with hydrocortisone, aminoglutethimide resulted in a PSA response proportion of 37% with the median duration for responders of nine months in a Phase 2 study at the expense of lethargy, skin rash, hypothyroidism, nausea and vomiting. Its use has been limited.[47, 48]

Ketoconazole inhibits several adrenal enzymes required for steroid biosynthesis. Its efficacy in prostate cancer in terms of PSA response is comparable to that of aminoglutethimide. Pilot studies in patients after failure of combined androgen blockade where ketoconazole was given simultaneously with anti-androgen withdrawal (AAWD) showed that 55% of patients achieved a 50% PSA decline.[49] When administered after AAWD, 36%-62.5% of patients had a 50% PSA decline.[50, 51] In a Phase 3 study conducted by Cancer and Leukemia Group B, PSA response rate was 27% with a median duration of response of 9 months in the group of patients randomized to the combination arm of AAWD and ketoconazole plus hydrocortisone versus the AAWD alone arm.[52] However, ketoconazole inhibits CYP3A4 with substantial risk of drug-drug interactions, such as warfarin and statins.[53] It is often poorly tolerated by patients, with commonly occurring side effects including diarrhea, nausea, vomiting, and depression.[50-52] Ketoconazole is not approved for the treatment of CRPC.

3.3.2 Glucocorticoids

Glucocorticoids appear to possess both hormonal and direct anti-tumor effects in prostate cancer. Patients with CRPC may still have hormone-sensitive disease that is stimulated by weak androgens of adrenal origin, and these androgens are suppressed by prednisone through its negative feedback on secretion of adrenocorticotrophic hormone (ACTH). Tannock et al have demonstrated that low-dose prednisone treatment (7.5 to 10 mg daily) led to a decrease in the concentration of serum testosterone in seven of nine patients where it was not initially suppressed below 2.0 nmol/mL, and caused a decrease in serum levels of androstenedione and dehydroepiandrosterone sulfate in more than 50% of patients.[54] These changes were associated with symptomatic and clinical improvement. Glucocorticoids may also have direct inhibitory effects on prostate cancer cells through enhanced growthinhibitory TGF-ß1 signaling and suppression of the transcriptional activities of NF–κB.[55, 56]

Prednisone, dexamethasone, and hydrocortisone have been frequently administered as standard of care in advanced prostate cancer because of their modest antitumor activity and

alliative effects on disease. Two prospective Phase 3 studies have documented the adverse event profile and palliative benefit of prednisone. Prednisone 7.5-10 mg daily was examined among 81 patients in one arm of a Phase 3 trial, with 22% of patients achieving a 50% PSA decline and a median time to progression of 4.0 months.[57] Likewise, in a randomized study control arm where 201 patients were treated with prednisone 5 mg twice daily, PSA decline of ≥ 50% was observed in 21% of patients.[58] Significant improvements in pain, quality of life and fatigue were also reported.

Other glucocorticoids have similar activity in advanced prostate cancer. Hydrocortisone has been evaluated as a control arm in prospective Phase 3 studies. In one study, 231 patients treated with hydrocortisone alone (control arm) showed that 16% of patients achieved a PSA decline of ≥50% with a median duration of response of 2.5 months.[59] Similarly, 14% of patients given hydrocortisone 40 mg daily achieved a PSA decline ≥ 50% lasting a median of 2.3 months in a Cancer and Leukemia Group B (CALGB) study.[60] The antitumor activity of hydrocortisone was slightly lower than prednisone in these Phase 3 studies (14%-16% PSA response rate for hydrocortisone versus 21%-22% PSA response rate for prednisone; median duration of response also favored prednisone). Likewise, dexamethasone has antitumor activity in prostate cancer.[61-63] No prostate cancer trials have directly compared 2 glucocorticoids.

3.3.3 Estrogens

Prostate cancer normally expresses estrogen receptors, and estrogenic compounds have been used for the treatment of CRPC. The most commonly used estrogen is diethylstilbestrol (DES), although DES-diphosphate, and the herbal phytoestrogenic supplement, PC-SPES, have also been investigated in clinical trials.

Recently, DES has been evaluated in two studies including 21 and 32 patients.[64, 65] A positive PSA response was achieved in 43% and 80%, respectively; the estimated survival at 2 years was 63%. However, even at low doses, 31% of the patients developed deep venous thrombosis and 7% experienced myocardial infarction. In another prospective randomized phase II trial, the clinical efficacy of the herbal supplement PC-SPES and DES were tested in a cohort of 90 patients, with PSA progression following initial androgen deprivation.[66] A PSA decline > 50% was noted in 40% with PC-SPES and in 24% with DES. Median time to progression was 5.5 months with PC-SPES and 2.9 months with DES; the differences were statistically not significant.

Although estrogens remain an option for the secondary hormonal treatment of CRPC, their use is limited by concerns regarding cardiovascular toxicity.[41]

3.4 Chemotherapy and Bisphosphonates for CRPC

Several agents have been approved as palliative therapy for prostate cancer. Estramustine was approved in the 1970s. However, in a randomized study where overall survival was compared, diethystilbesterol was found to be superior to estramustine.[67] In 1996, mitoxantrone and prednisone were approved in the United States for palliation of pain and improvement in

quality of life in a randomized study with prednisone as control.[57] However, there was no survival benefit. Recently, zoledronic acid was approved for reduction in skeletal morbidity in solid tumors, including prostate cancer.[68] None of these agents improved the overall or prostate cancer-specific survival of patients with CRPC.

Docetaxel is the only agent to date that has demonstrated a survival benefit in CRPC. A 3-weekly docetaxel regimen had a median overall survival of 18.9 months (95% confidence interval 17.0 – 21.2), compared with the mitoxantrone control arm of 16.5 months (95% confidence interval 14.4 – 18.6 months). The hazard ratio for death was 0.76 (95% confidence interval 0.62 – 0.94, p =0.009) in the docetaxel regimen as compared with control.[69]

Results from the SWOG Study 99-16 trial of 770 men (3-weekly docetaxel + estramustine + dexamethasone vs mitoxantrone + prednisone), median overall survival 17.5 months vs 15.6 months, respectively, p=0.02 were consistent with the TAX-327 data.[70]

Results from TAX-327 were updated at ASCO 2007. Overall survival results were maintained after the additional 2 years of follow-up and an additional 276 deaths [71]. The median survival in the docetaxel 3-weekly arm and mitoxantrone arms were the same as previously reported in 2004, 18.9 months (95% confidence interval 17.0-21.2) for docetaxel every 3 weeks plus prednisone, and 16.5 months (95% confidence interval 14.4-18.6) for mitoxantrone plus prednisone. In an exploratory subset analysis, benefit was seen in patients who were free of pain at the time therapy was initiated. However, this analysis confirmed only consistency of effect across subpopulations, and the study was not powered to demonstrate survival advantage in symptomatic patients. Also, the similar benefit produced by docetaxel treatment in patients with or without pain suggests that holding chemotherapy in reserve for asymptomatic patients is a reasonable option.

4.0 ABIRATERONE ACETATE (JNJ212082)

4.1 Abiraterone Acetate and Mechanism of Action

Abiraterone (JNJ589485) is [17-(3-pyridyl)androsta-5,16-dien-3β-ol] and is a steroidal inhibitor of CYP17 (17α hydroxylase/C17,20-lyase) that blocks two important enzymatic activities in the synthesis of testosterone (Figure 1), based on the observation that nonsteroidal 3 pyridyl esters improve selectivity for inhibition of 17α-hydroxylase/C17,20 lyase. Abiraterone acetate is a potent inhibitor with an apparent inhibition constant of 0.5 nM. 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 in Phase 1 and Phase 2 studies conducted to date.[72]

Abiraterone acetate (JNJ212082) is the 3-acetylated analog of abiraterone and thus a pro-drug of abiraterone. The chemical nomenclature of abiraterone acetate is 3β acetoxy-17-(3- pyridyl) androsta-5,16-diene; its empirical formula is C26H33NO2 and molecular weight is 391.55. Once

absorbed after oral administration, abiraterone acetate is rapidly converted to the active form, abiraterone (Figure 2). In initial research studies, abiraterone acetate was the predominant, if not the only, metabolite of abiraterone acetate detected in blood, both in preclinical studies and in previously conducted clinical studies.[73, 74]

Figure 1. The Enzyme Complexes Inhibited by Abiraterone acetate

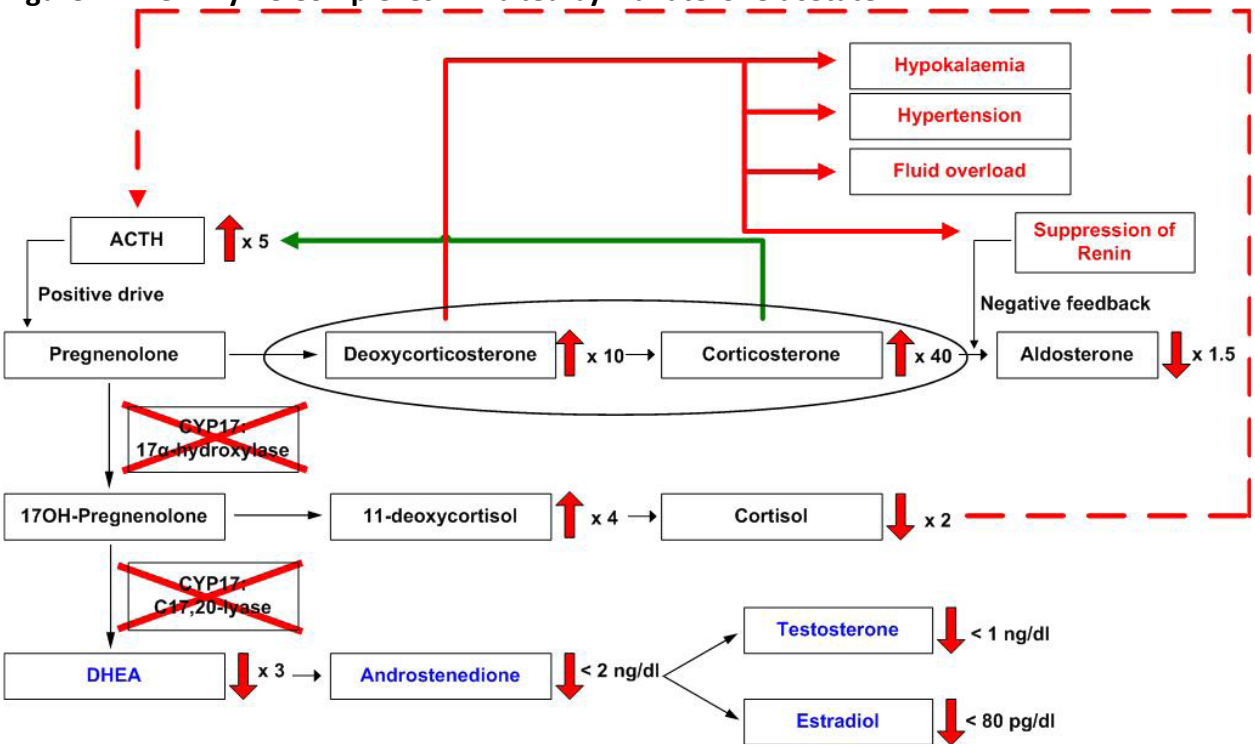
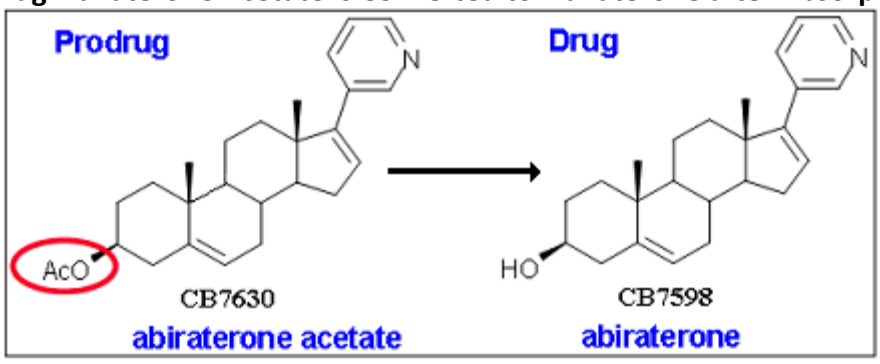


Figure 2. Prodrug Abiraterone Acetate is Converted to Abiraterone after Absorption



4.2 Clinical Trials with Abiraterone Acetate and Prednisone

COU-AA- 301 was a randomized, double-blind, International Phase III study comparing abiraterone acetate, given at 1000 mg once daily with prednisone 5 mg BID to placebo and prednisone 5 mg BID in men with mCRPC previously treated with docetaxel-based chemotherapy [75]. Overall survival was the primary endpoint and 1195 patients were enrolled. A planned interim analysis after 534 patients met the primary endpoint revealed a statistically significant difference in overall survival between the abiraterone acetate and

prednisone arm (median OS 14.8 months; 95% CI 14.1- 15.2) and the placebo and prednisone arm (median OS 10.9 months; 95% CI 10.2-12.0) with a hazard ratio of 0.646 and a $p < 0.0001$ [75]. Secondary endpoints were all statistically significant in favor of abiraterone acetate including time to PSA progression, radiographic progression, and PSA response. Subgroup analysis revealed all parameters in favor of abiraterone acetate. Side effects in this large phase III heavily pre-treated population were relatively low and balanced in both arms except for fluid retention, hypokalemia, hypertension and cardiac disorders; however, grade 3 or greater incidence of these toxicities were less than 5%. These results have led to the FDA-approval of abiraterone acetate with prednisone for patients with mCRPC who have failed doectaxel-based chemotherapy.

Early Phase II experience suggested that abiraterone acetate and prednisone was active and well tolerated in men with chemo-naïve mCRPC. A phase II study in 33 men revealed a 67% PSA response rate and a median time to PSA progression of 16.3 months [76]. These early results led to the COU-AA-302 study, a randomized, double blind, international phase III study comparing abiraterone acetate and prednisone to placebo and prednisone in men with mCRPC who were chemotherapy-naïve [77]. 1088 patients were randomized in a 1:1 ratio and treated until radiographic progression. Radiographic progression-free survival and overall survival were co-primary endpoint. Three interim analyses were pre-planned. At the time of the second interim analysis, following after 311 events (43% of events) the independent data safety monitoring committee recommended halting the study and unblinding the patients due to a statistically significant positive effect in favor of abiraterone acetate for radiographic progression-free survival (HR 0.43; 95% CI 0.35-0.52; $p < 0.0001$), a strong trend in favor of overall survival (HR: 0.75; 95% CI 0.61-0.93; $p = 0.0097$) and positive secondary endpoints as well [77]. These results led to the FDA-approval of abiraterone acetate with prednisone for patients with mCRPC in December 2012.

For the most comprehensive clinical information regarding the efficacy and safety of abiraterone acetate, refer to the latest version of the Package Insert for abiraterone acetate.

4.3 Rationale for the current study

African American men have a 60% greater incidence of being diagnosed with prostate cancer and nearly a 2.5 fold greater chance of mortality from the disease, yet the underlying cause for this increased mortality remains controversial [1]. Hormonal levels vary in men by race, with African American men having higher dihydrotestosterone (DHT), androstenedione (ASD) and sex hormone-binding globulin (SHBG) than Caucasian men with localized prostate cancer [2, 23]. Historically, African American men with prostate cancer have a worse overall survival than Caucasian men, however, this is confounded by the timing of androgen deprivation therapy (ADT) and access to other therapies [4, 5]. To what extent race affects response to therapy in prostate cancer is not clear.

Germline polymorphisms of genes involved in androgen signaling have been shown to vary significantly by race and may have important implications with regard to response to therapy

targeted towards this pathway. Polymorphisms within the promoter region of the androgen receptor (AR) (specifically CAG repeats) have been well documented and vary significantly according to race, with African American men having significantly shorter CAG repeats resulting in greater AR activity [6]. These CAG repeats have been associated with more aggressive disease characteristics [6]. Recently, germline polymorphisms in androgen metabolism genes have been shown to have prognostic value in regards to the time to development of CRPC in men with prostate cancer on ADT. Ross et al tested 129 polymorphisms across 20 genes associated with androgen metabolism and identified three polymorphisms in separate genes (*CYP19A1*, *HSD3B1*, and *HSD17B4*) that were significantly associated with prolonged time to progression (TTP) on ADT [7]. Specifically, individuals carrying more than one of the polymorphisms were associated with *improved* time to CRPC than individuals carrying zero or one ($P < .0001$). More recently this group identified polymorphisms in two androgen transporter genes, *SLCO2B1* and *SLCO1B3* that were associated with a significantly *shorter* time to CRPC alone and in combination [8]. Incidences of these polymorphisms ranged from 15 to 81%; unfortunately, the cohort of patients used to identify these polymorphisms had limited numbers of African American patients or other racial and ethnic groups.

Recent studies have focused on discovering molecular mechanisms underlying prostate cancer disparities using DNA microarrays and bioinformatics. These studies have compared the gene expression profiles between African American and Caucasian American cancers and between prostate cancer and patient-matched normal prostate from African Americans and Caucasian Americans. By integrating gene expression profiling and pathway analyses, multiple components within the androgen receptor signaling pathway were revealed to be up-regulated in African American prostate cancer specimens along with the up-regulation of genes within other signaling pathways that converge on androgen receptor signaling, portending that androgen receptor pathway activation is a key component of prostate cancer health disparities. Overall the comparison of African American and Caucasian American prostate cancer specimens has led to the identification of a number of differentially expressed genes, including CYP19A1, AMFR, CXCR4, MMP9, SRD5A2, ADIPOQ, AKT1, ALOX12, ALOX15, ALOX15B, BMP2, CGA, ERG, FASN, IL1B, IL6, IL8, NFKB1, PIK3C3, PIK3CA, PI3K3R1, PLA2G2A, TGFB1, TIMP3, TNF, P38MAPK, STAT1, RHOA, ITGB5, MAPKAPK2, CSNK2A1, PIK3CB, ARA55, GNA01, GNB3, POLR2L, PRKCE, PRKD1, TBP, CALR, GNG2, GNG11, GNG12, CALM1, NFKB2, STAT2, RHOU, FGF13, EIF3B, and GIT1 [9-12]. Thus, germline polymorphisms of these differentially expressed genes also may have important implications with regard to response to therapy targeted towards the androgen signaling pathway.

To what extent racial differences affect response and time to progression on abiraterone acetate is unknown. Secondarily, to what extent differences in systemic hormonal levels as well as androgen transport gene polymorphisms affect response to abiraterone acetate is unknown. Understanding any potential differences in response to therapy by race and/or by hormonal/genetic factors could impact on both our clinical use of abiraterone acetate as well as future clinical trial design. Finally, as other agents targeting the androgen/androgen receptor pathways become available, it will be important to differentiate their activity according to race, genetics and hormonal milieu.

We propose a pilot study to evaluate in a prospective, parallel group design, radiographic PFSin men with mCRPC treated with abiraterone acetate/prednisone by race. Secondary endpoints will describe the response to abiraterone acetate/prednisone, PSA kinetics and safety and tolerability. Exploratory endpoints will describe the incidence and associations of key hormonal levels as well as germline polymorphisms in androgen signaling genes and genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers in both African American and Caucasian cohorts.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study objectives

5.1.1 Primary objective

The primary goal is to prospectively estimate the median radiographic PFS of African American and Caucasian men with mCRPC to abiraterone acetate and prednisone.

5.1.2 Secondary objectives

1) PSA kinetics: to determine the duration of PSA response, time to nadir, and percent of men who achieve a PSA < 0.1;
2) Radiographic assessments: to estimate the rate of objective response and incidence of bone flares
3) Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations
4) Overall Survival

5.1.3 Exploratory objectives

1) Describe the baseline profile of serum hormone levels (including testosterone, DHT, DHEA, DHEAS, estradiol) and lipidomics, the change in levels with subsequent therapy (Cycle 4), and their correlation with response to abiraterone acetate.
2) Describe the germline SNP profiles of target genes involved in androgen signaling and target genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers as well as a genome wide analysis (GWAS) in both African American and Caucasian men with mCRPC and their associations with response to abiraterone acetate. The status of the aforementioned targets as well as AR splice variants will also be assessed in archival tumor tissue, if available, by sequencing, IHC and qRT-PCR.

5.2 Study endpoints

5.2.1 Primary endpoint

The primary endpoint will be radiographic **progression free survival** (rPFS) based on PCWG2 criteria or based on the onset of a skeletal related event. Imaging will be obtained every 12 weeks.

5.2.2 Secondary endpoints

Secondary endpoints will include:

1) RECIST 1.1 defined radiologic response rates and incidence of bone flares
2) PSA response, time to nadir, and percent of men who achieve a PSA < 0.1
3) Safety (NCI CTC v4.0) and tolerability, particularly incidence and grade of hypertension in the two populations
4) Overall survival

Exploratory correlative sciences endpoints:

Whole blood will be collected in purple top EDTA tubes at baseline for DNA isolation and characterization of SNPs for androgen metabolism genes (including *CYP19A1*, *HSD3B1*, *HSD17B4, SLCO2B1* and *SLCO1B3*), AR CAG repeats, as well as genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers (including, but not limited to, SLCO2B1, SLCO1B3, CYP19A1, HSD3B1, HSD17B4,AR CAG repeats, AMFR, CXCR4, MMP9, SRD5A2, ADIPOQ, AKT1, ALOX12, ALOX15, ALOX15B, BMP2, CGA, ERG, FASN, IL1B, IL6, IL8, NFKB1, PIK3C3, PIK3CA, PI3K3R1, PLA2G2A, TGFB1, TIMP3, TNF, P38MAPK, STAT1, RHOA, ITGB5, MAPKAPK2, CSNK2A1, PIK3CB, ARA55, GNA01, GNB3, POLR2L, PRKCE, PRKD1, TBP, CALR, GNG2, GNG11, GNG12, CALM1, NFKB2, STAT2, RHOU, FGF13, EIF3B, and GIT1) and ancestral genotyping. A genome wide analysis (GWAS) is planned in both African American and Caucasian men with mCRPC and their associations with response to abiraterone acetate, in addition to the aforementioned analyses of germline SNP profiles. In addition baseline assessments of hormonal levels including testosterone, DHT, DHEA, DHEAS, estradiol and their change after 12 weeks on therapy will be evaluated along with lipidomics analysis. Finally additional baseline and 4 week plasma samples will be drawn to explore additional biomarkers that may have prognostic or predictive value. The status of the target genes involved in androgen metabolism and the target genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers as well as AR splice variants will also be assessed in archival tumor tissue, if available, by sequencing, IHC and qRT-PCR.

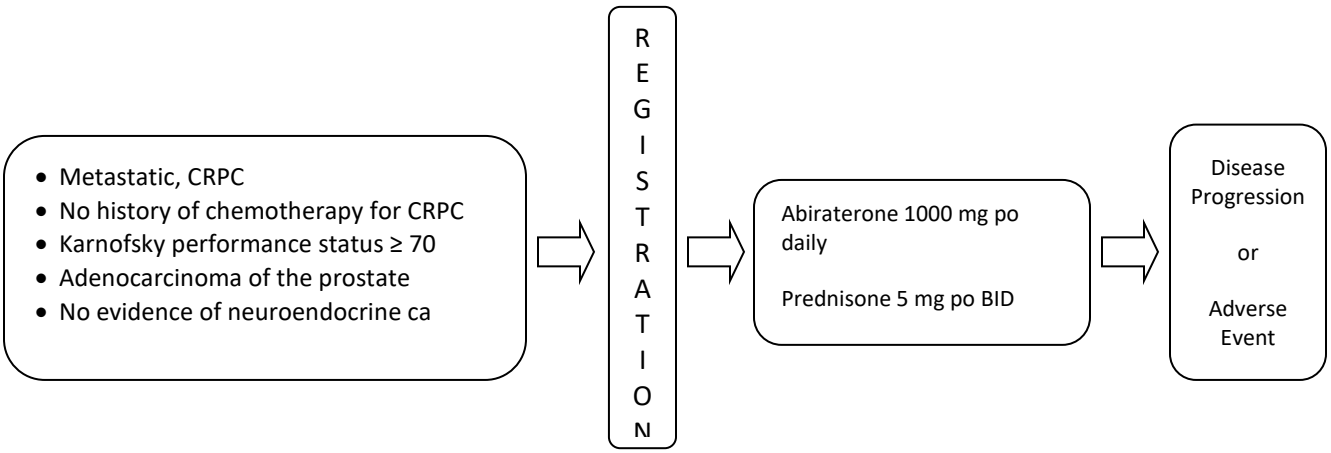
6.0 INVESTIGATIONAL PLAN

6.1 Overall study design

This is a non-comparative pilot open-label, parallel arm, multicenter study of abiraterone acetate in African American and Caucasian men with mCRPC. The primary goal is to

prospectively estimate the median radiographic PFS in African American and Caucasian men with mCRPC cancer treated with abiraterone acetate. Patients will self-report on race and 50 patients will be enrolled into each group. Patients will be treated on open-label treatment until evidence of disease progression as defined by Prostate Cancer Working Group Two (PCWG2) definition [13] or until two years at which point they will roll over to the standard of care at that time.

Study schema is shown below.



6.2 Study population

This will be a Duke University Health System study conducted through the Duke Cancer Institute, composed of a large tertiary referral center and network sites, which treat a high volume of metastatic CRPC patients and who prioritize African American patient accrual to clinical trials. It is anticipated that the Duke Cancer Network and 6 satellite sites will be needed to accrue 50 African American subjects over a 30 month accrual period. Typically 20-30 African American subjects per year would be eligible for this protocol at Duke University Medical Center alone but this number would be substantially more by including outreach sites. A parallel population of Caucasian patients will be accrued to this trial.

6.3 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of the baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator at Duke University, or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to any

screening procedures being performed. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria:

1. Male, age ≥ 18 years
2. Karnofsky performance status ≥ 70 (Appendix 1)
3. Life expectancy of ≥ 12 months as determined by treating investigator
4. Written Authorization for Use and Release of Health and Research Study Information (HIPAA Authorization per institutional requirements)
5. Willing/able to adhere to the prohibitions and restrictions specified in this protocol
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, and should be able to swallow tablets whole, without crushing/chewing tablets.
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. Adequate laboratory parameters

- Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb>9 g/dL
- Serum potassium $\geq$ 3.5 mEq/L
- AST/SGOT and ALT/SGPT ≤ 1.5 x Institutional Upper Limit of Normal (ULN)
- Serum bilirubin ≤ 1.5 x Institutional ULN
- Serum creatinine ≤ 1.5 x Institutional ULN or 24-hour clearance ≥ 50 mL/min
- Serum albumin of > 3.0 g/dl

9. Histologically confirmed diagnosis of adenocarcinoma of the prostate. Histologic variants of prostate cancer, including neuroendocrine features and small cell carcinoma of the prostate are excluded.

10. Radiographic evidence of metastatic disease; evaluable non-target lesions and/or bone only metastasis are permitted.
11. Ongoing ADT using an LHRH agonist (e.g. leuprolide, goserelin) or antagonist (e.g. degarelix) must continue on therapy unless prior bilateral orchiectomy has been performed. Screening serum testosterone must be $\leq$50 ng/dl.
12. PSA ≥ 2.0 ng/mL
13. Evidence of disease progression on ADT as evidenced by one of the following:

- Absolute rise in PSA of 2.0 ng/mL or greater, minimum 2 consecutive rising PSA levels with an interval of ≥ 1 week between each PSA level, **OR**
- 2 consecutive PSA levels 50% or greater above the PSA nadir achieved on ADT and separated at least 1 week apart, **OR**
- CT or MRI based evidence of disease progression (soft tissue, nodal or visceral disease progression) according to modified PCWG2 criteria or modified RECIST 1.1 criteria, or at least 1 new bone scan lesion as compared to the most immediate prior radiologic studies.

14. A minimum of 2 weeks elapsed off of antiandrogen therapy prior to start of study drug (i.e. flutamide, nilutamide, bicalutamide) .
15. A minimum of 4 weeks elapsed off of sipuleucel-T prior to start of study drug.
16. A minimum of 4 weeks from any major surgery prior to start of study drug.
17. Self-reported race of either African American or Caucasian.
18. Ability to swallow, retain, and absorb oral medication.
19. Ability to understand and the willingness to sign a written informed consent document. If the subject is unable to understand the consent due to comorbidity, such as Alzheimer's disease, consent by a legally authorized representative and assent by the subject will be obtained.

Exclusion criteria:

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

1. Prior treatment with abiraterone acetate or enzalutamide

2. Active infection or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated.
3. Any chronic medical condition requiring a higher dose of corticosteroid than 5mg prednisone/prednisolone bid.
4. Have known allergies, hypersensitivity, or intolerance to abiraterone acetate or prednisone or their excipients.
5. Pathological finding consistent with small cell carcinoma of the prostate.
6. Symptomatic Liver or visceral organ metastasis.
7. Have a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents.
8. Known brain metastasis.
9. Prior cytotoxic chemotherapy or biologic therapy for the treatment of CRPC.
10. Previously treated with ketoconazole for prostate cancer for greater than 7 days.
11. Prior systemic treatment with an azole drug (e.g. fluconazole, itraconazole) within 4 weeks of Cycle 1, Day 1.
12. 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.
13. Poorly controlled diabetes
14. Active or symptomatic viral hepatitis or chronic liver disease.
15. History of pituitary or adrenal dysfunction.
16. 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.
17. Atrial Fibrillation or other cardiac arrhythmia requiring therapy.
18. Other malignancy, except non-melanoma skin cancer, with a ≥ 30% probability of recurrence within 24 months.
19. Administration of an investigational therapeutic within 30 days of Cycle 1, Day 1.

20. Any condition which, in the opinion of the investigator, would preclude participation in this trial.

7.0 PATIENT REGISTRATION

After signing informed consent and completing eligibility screening, patients who are selected to participate will be registered with the lead site (Duke) and with their study site/institution. A record of patients who fail to meet entry criteria (i.e., screen failures) will be maintained. Patients who are registered and do not start study drug within 2 weeks of intended Cycle 1 Day 1 will be replaced. Patient registration must be complete before beginning any treatment.

7.1 Informed Consent

Authorized study personnel should fully explain the scope of the study to each patient before obtaining informed consent. If the patient is not able to fully understand the informed consent due to a known comorbidity, such as Alzheimer's disease, a legally authorized representative will be included in the consent process. Patients, and a legally authorized representative if appropriate, should be advised of any known risks inherent in the planned procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy. If a legally authorized representative signs the consent, the patients' assent will also be documented.

When obtaining informed consent, study personnel should:

First: Confirm that the patient is a potential candidate for study participation.
Next: Obtain dated and signed informed consent.
Finally: Confirm that the patient is eligible as defined in Section 6.3 (Inclusion/Exclusion Criteria). A record of patients who fail to meet entry criteria (i.e., screening failures) will be maintained.

For patients consented at the lead site ONLY, registration in the Duke clinical trial subject registry must be completed within 1 business day of the patient providing informed consent.

7.2 Lead Site Registration

Patient registration for all patients signing informed consent will be completed by Duke University Medical Center Genitourinary Oncology Group. Following consent and completion of the Eligibility Checklist, documents will be submitted for review and registration of subject. All subjects will be assigned a unique study ID.

Refer to Subject Registration Instructions for details.

Patients will be enrolled only after all pre-treatment screening evaluations are completed and all eligibility criteria are met. Once the patient has signed consent and been found to meet all eligibility criteria, the subject will be registered. The patient will be considered enrolled on the

day of first treatment. A unique patient study identification number will be assigned upon consenting. Treatment must not commence until the patient has received his approved documentation from the lead site. Treatment will commence according to the guidelines in the protocol.

7.3 Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form. Patients must be registered with their local site/institution and with the lead site before beginning any treatment or study activities.

8.0 TREATMENTS

8.1 Abiraterone acetate formulation

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 tabletting).

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**.** You should notify any caregivers and staff personnel of this information, to ensure the appropriate precautions are taken.

8.2 Abiraterone acetate administration

The study agent abiraterone acetate will be administered by the patient at a dose of 1000mg orally once daily with prednisone 5 mg BID in 4-week cycles throughout the treatment period. 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 acetate should be taken with a glass of water and consumed over as short a time as possible. Patients should swallow the capsules whole and not chew them. Study drug will be provided by Janssen Scientific Affairs and distributed by DCI Investigational Chemotherapy Service, which will be distributing drug to the satellite sites.

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 acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed.

Patients will be instructed to take a 5-mg prednisone tablet, twice daily with food. It is not required for the prednisone to be taken at the same time as abiraterone acetate. The dose of prednisone will remain unchanged in the event that the study drug dose is changed. If a prednisone dose is missed, it should be omitted and will not be made up. Should a dose modification of the prednisone be needed due to toxicities, the site will need to discuss this with the medical monitor.

Each treatment cycle consists of 28 consecutive days. No cycle will be delayed. If doses of study drug are held or missed, they will not be made up. The subject could complete a maximum of 26 cycles during the 24 month duration of the study. During the study period, starting with cycle 4, the patient will return to clinic every 3 cycles. The patient will be given enough study drug to last for 12 weeks. Patients may take abiraterone acetate plus prednisone until radiographic disease progression and/or unequivocal clinical progression (as defined in Section 12.5), at which time study treatment will be discontinued. The dose of prednisone may be gradually reduced if clinically indicated.

If vomiting occurs during the course of treatment, no redosing of the patient is allowed before the next scheduled dose. If the patient forgets to take her/his dose before 12:00 noon, then the dose should be withheld that day and abiraterone acetate should be restarted the following day.

Effects of Abiraterone Acetate 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 1,000 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 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA.

Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. 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 abiraterone acetate 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.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. If a patient requires a abiraterone acetate dose delay of >21 days from the previous dose, the patient must be discontinued from treatment (unless unrelated to study drug and approved by the medical monitor), return for an end of treatment visit +/- 7 days of the last dose or the day of the decision to remove from the study, and return for a follow-up safety visit 28 days (+/- 7 days) from date of last dose.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

8.3 Concomitant therapy

All medications (excluding prior chemotherapy and biologic, immunologic or radiation therapy) taken within 4 weeks prior to the administration of abiraterone acetate and all concomitant therapy administration during the study with reasons for therapy should be recorded. Patients on chronic medications that can be given concomitantly with abiraterone acetate should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the patient to notify the study site about any new medications he takes after the start of the study drug. All new medications, changes in medication dosing, and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) administered after the patient starts treatment with study drug will be recorded.

The following concomitant medication/therapies are permitted if deemed necessary for the care of the patient:

- Standard therapies for preexisting conditions, medical/surgical complications including nausea and diarrhea, and palliation.
- Non-potent CYP3A4 isoenzyme inhibitors and/or inducers.
- LHRH agonists or antagonists.

- Anti-hypertensive medications.
- Diabetic medications.
- Antidepressants or other medications for mood disorders.
- Analgesics including opioids.
- Bisphosphonates and/or denosumab.
- Erythropoietic agents.
- Systemic anticoagulation with low molecular weight heparin.
- Provenge, after the first 3 cycles on treatment are completed.
- Focal therapies for localized non-prostate cancers

The following medications/therapies are prohibited while the patient is on study:

- Other investigational therapies must not be used while the patient is on the study.
- Chemotherapy, radiation therapy, or immunotherapy, or any anti-cancer therapy other than abiraterone acetate and prednisone and those described above and below.
- Coumadin or other vitamin K antagonists.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
- **In lieu of surgical castration, the use of an LHRH agonist or antagonist must continue while on this study. However, antiandrogens, ketoconazole, estrogens, and all other forms of hormonal manipulation are not permitted for the treatment of cancer.**
- Investigators should keep in mind the possibility that abiraterone acetate may interact with concomitant medications, particularly those that are metabolized or activated by P450 CYPs 2D6 and 1A2 (see Appendix 2 for prohibited medications). Please see comments above regarding interactions. If at any time an investigator suspects a drug-drug interaction due to abiraterone acetate therapy, an adverse event report should be completed and Duke University notified.

8.4 Treatment compliance

Participating sites will be provided with a medication diary for each patient to document his self-administration of Abiraterone Acetate per cycle. A current and accurate account of the number of study treatment tablets the investigator received from Duke University, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Duke University during and at the completion of the study must be maintained. A detailed inventory must be completed for the study treatment. Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

9.0 STUDY ASSESMENTS

9.1 Vital signs, performance status, and physical exam

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight per the visit schedule.

Performance status will be assessed at screening and per the visit schedule using the Karnofsky performance status scale (Appendix 1).

Physical examination will comprise a total body examination (general appearance, skin, including eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system). Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

9.2 Laboratory evaluations

The following laboratory studies will be obtained at specified intervals to assess subject safety, specifically the risk of infection, hyperglycemia, and/or bone marrow, liver, and kidney abnormalities. Abnormalities will be captured as AEs only if deemed clinically significant by the treating physician/provider/investigator. This does not include the labs designated as an adverse event of special interest in 11.1.

- **Hematology:** Complete blood count (CBC) consisting total white blood cell count (WBC) with differential (total neutrophil count, lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin, hematocrit, and platelet count.
- **Blood chemistry:** Blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, chloride, bicarbonate (CO_2), magnesium, phosphorus, glucose, albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT).
- PSA to be obtained at baseline, Day 1 of intended Cycle 1 and cycles 2, 3, 4, 7, 10 and every 3 cycles, and at the end of treatment visit. During follow-up for subjects who discontinue treatment due to reasons other than radiographic progressive disease, PSA will be collected every 3 months (+/- 28 days) and additionally as clinically appropriate. Testosterone to be obtained at baseline and the end of cycle 3 (at Cycle 4 Day 1).

9.3 ECG

A standard 12-lead ECG is to be performed at screening and significant findings must be recorded. Additional EKGs may be performed at the discretion of the treating physician.

9.4 Imaging

A CT scan with contrast of chest, abdomen, and pelvis will be performed within 42 days prior to the intended C1D1 visit, and every 3 cycles (approximately every 12 weeks) as part of routine tumor assessment. These scans are to be performed on day 1 of every 3 cycles (i.e. baseline, Day 1 of cycles 4, 7, 10, etc.) within 7 days prior to starting the next cycle. If the chest CT at baseline is clear, chest x-rays may be used for subsequent assessments at the enrolling

physician's discretion. The tumor assessments will be performed locally, in strict accordance with the RECIST 1.1 guidelines. A total body bone scan will be performed within 42 days of the intended C1D1 visit and every 3 cycles (approximately every 12 weeks) and interpreted according to PCWG2 guidelines. CT and bone scan modalities per standard institutional practices may be used, but the same modality should be used throughout the study for each subject.

Because the primary endpoint is progression free survival based upon radiographic disease progression, patients will continue to have CT scans and Bone Scans performed according to standard clinical practice even if study treatment is discontinued for reasons other than radiographic disease progression.

9.5 Exploratory correlative studies

9.5.1 SNP Analysis

Human whole blood will be collected in a 4mL lavender top K_2EDTA tube at baseline for DNA isolation and characterization of SNPs. Mix by gentle inversion 8-10 times. Do not centrifuge. Freeze tubes at -20^{o}C. Genomic DNA will be purified using the Qiagen QiaAmp DNA Blood Mini Kit or equivalent. Starting material used will be 200µl whole blood per column. Genomic DNA will be considered of appropriate quantity and quality if at least 300ng (preferably 1200ng) of A260nm/A280nm > 1.5 is obtained. Characterization of SNPs for androgen metabolism genes (including *CYP19A1*, *HSD3B1*, *HSD17B4, SLCO2B1* and *SLCO1B3*), AR CAG repeats, as well as genes that have been shown to be differentially expressed in African American and Caucasian American prostate cancers (including, but not limited to, SLCO2B1, SLCO1B3, CYP19A1, HSD3B1, HSD17B4,AR CAG repeats, AMFR, CXCR4, MMP9, SRD5A2, ADIPOQ, AKT1, ALOX12, ALOX15, ALOX15B, BMP2, CGA, ERG, FASN, IL1B, IL6, IL8, NFKB1, PIK3C3, PIK3CA, PI3K3R1, PLA2G2A, TGFB1, TIMP3, TNF, P38MAPK, STAT1, RHOA, ITGB5, MAPKAPK2, CSNK2A1, PIK3CB, ARA55, GNA01, GNB3, POLR2L, PRKCE, PRKD1, TBP, CALR, GNG2, GNG11, GNG12, CALM1, NFKB2, STAT2, RHOU, FGF13, EIF3B, and GIT1) and ancestral genotypingwill be performed. A genome wide analysis (GWAS) is planned in both African American and Caucasian men with mCRPC and their associations with response to abiraterone acetate. The GWAS will be done using Illumina's 2.5M beadchip. The local site will process these samples and prepare them for shipment to the lead site per shipping instructions below. The lead site will perform the laboratory analysis. Neither the local sites nor the patients will receive information regarding individual subjects' results.

An additional 4mL lavender top K_2EDTA tube may be collected from subjects whose tube collected at baseline yielded no usable sample after DNA isolation. This additional tube would be used for DNA isolation and characterization of SNPs as described above.

9.5.2 Hormonal Levels

Serum testosterone, DHT, DHEA, DHEAS, and estradiol will be collected at baseline, the end of cycle 3 (at Cycle 4 Day 1), and the end of treatment visit.

For hormone levels, collect blood into one 5mL gold top SST vacutainer tube. Invert 5 times. Allow blood to clot for 30 minutes. Centrifuge for 10 minutes at 1100-1300 x g. Aliquot the serum into 1.8mL cryovials. Label according to instructions below and freeze cryovials at -80°C. Samples should be frozen within 2 hours of collection. If a -80°C freezer is not available and samples are being stored at -20°C, then all samples will remain frozen and shipped within 48 business hours on dry ice following the directions below.

9.5.3 Plasma samples for blood-based biomarkers

Plasma samples will be collected at baseline and at the end of cycle 1 (at Cycle 2 Day 1) to explore additional biomarkers that may have prognostic or predictive value. These additional biomarker analyses will be in support of the specified endpoints in the protocol.

For plasma samples, collect blood into one 6mL lavender top (K_2EDTA coagulant vacutainer) **AND** one 4.5 mL light blue top (3.2% sodium citrate) vacutainer. Invert the tubes several times and centrifuge for 15 minutes at 2500 x g. Remove the plasma and transfer to a clean 5 mL glass test tube. Repeat centrifuge at 2500 x g for 15 minutes. Aliquot the plasma – 0.5 mL into the provided 1.8mL cryovials. Label according to instructions below and freeze cryovials at -80°C. If a -80°C freezer is not available and samples are being stored at -20°C, then all samples will remain frozen and shipped within 48 business hours on dry ice following the directions below.

Storage and Shipping Instructions

See Laboratory Manual for further details regarding sample collection and shipping.

Once complete, these samples will be analyzed for their appropriate endpoints as indicated in the study (i.e. SNP analysis, lipidomics, hormone or plasma biomarker levels). SNP analysis will be done in collaboration with the Duke University DNA Analysis Facility, [redacted] ancestral genotyping by Rick Kittles, PhD, City of Hope, Duarte, CA and lipidomics, hormone, and plasma biomarker levels will be done in collaboration with Andrew Nixon, PhD, Phase I Biomarker Laboratory, Duke University Medical Center, [redacted] Access to these samples will be limited to Drs George, Freedman, Nixon, Kittles and their proxy staff. These samples will be maintained indefinitely or until they are exhausted. Any future analyses not specified in this protocol will be agreed upon by prior approval from Janssen Scientific Affairs, LLC.

9.5.4 Collection of Archival Tumor Tissue for somatic SNP assessments

Formalin-fixed, paraffin-embedded archival tumor tissue will be collected from all patients whenever available. This tissue will come from diagnostic core biopsies and/or surgical specimens (prostatectomy or metastatic sampling). Tissue should be labeled and sent to the address in the lab manual. Up to five 10 micron thick sections from tumor blocks and/or 20 unstained slides should be de-identified except for protocol and subject number and sent at room temperature (see Laboratory Manual for further details regarding sample collection). Samples will be batched and evaluated collectively by sequencing, IHC, and qRT-PCR for the status of target genes involved in androgen metabolism and signaling, target genes that have been shown to be differentially expressed in African American versus Caucasian American prostate cancers, and AR splice variants. Sections of the FFPE tumor tissue will be utilized to assess the status of the aforementioned targets by IHC and DNA as well as RNA isolated from the FFPE tumor tissue will be utilized to assess the status of the aforementioned targets and AR splice variants by sequencing and qRT-PCR.

In patients without target SNP alterations, it will be important to confirm that there are not somatic tumor alterations within these genes. In order to evaluate for somatic tumor alterations within our target genes we will perform SNP analyses in available specimens. Discrepancies between germline and somatic mutations will be further evaluated by sequencing. Samples will be stored by Dr. Jennifer Freedman, PhD with access limited to key personnel. DUHS will maintain these samples indefinitely or until they are exhausted. Any future analyses not specified in this protocol will be agreed upon by prior approval from Janssen Scientific Affairs, LLC.

9.6 Follow-Up Period

During the Follow-up Period, subsequent therapy for prostate cancer should be assessed every 3 months for up to 24 months after the first dose of study drug. Since the primary endpoint is progression free survival based upon radiographic disease progression, patients will continue to have CT scans and Bone Scans performed according to standard clinical practice and their PSA measured every 3 months and additionally as clinically appropriate until they have radiographic progression or untill they have started another therapy. All subjects will be followed up for survival every 6 months +/- 1 month by phone or chart review.

10.0 MONITORING AND MANAGEMENT OF SUSPECTED ABIRATERONE TOXICITY

10.1 Management of Drug-Related Adverse Events

The most common adverse drug reactions (≥10%) reported in clinical studies were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, urinary tract infection, cough, hypertension, dyspnea, and contusion. The administration of prednisone is expected to mitigate these side effects by supplementing cortisol and abrogating ACTH drive.

Following prolonged therapy with corticosteroids, subjects 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 other 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 the Principal Investigator at Duke University should be contacted.

10.1.1 Management of hypokalemia

Subjects who experience hypokalemia are to be managed as presented in Table 1.

Table 10.1: Hypokalemia Management

Serum K+	Grade of Hypokalemia	Action	Further Action or Maintenance
Low K+ or history of hypokalemia		Weekly (or more frequent) laboratory electrolyte evaluations	Titrate dose to maintain a serum K+ >3.5 mM <5.0 mM (maintenance of subjects at >4.0 mM is recommended)
<3.5 mM – 3.0 mM	Grade 1	Initiate oral or i.v. K+ supplementation. Consider monitoring magnesium and replace if needed	Titrate dose to maintain a serum K+ >3.5 mM <5.0 mM (maintenance of subjects at >4.0 mM is recommended)
<3.5 mM – 3.0 mM Symptomatic	Grade 2	Initiate oral or i.v. K+ Supplementation Consider monitoring magnesium and replace if needed	Titrate dose to maintain a serum K+ >3.5 mM <5.0 mM (maintenance of subjects at >4.0 mM is recommended)
<3.0 mM – 2.5 mM	Grade 3	Withhold abiraterone acetate and initiate oral or i.v. K+ and cardiac monitoring. Consider monitoring magnesium and replace if needed	Call the Duke Principal Investigator or Project manager prior to re-initiating study treatment
<2.5 mM	Grade 4	Withhold abiraterone acetate and initiate oral or i.v. K+ and cardiac monitoring Consider monitoring magnesium and replacement if needed	Call the Duke Principal Investigator prior to re-initiating study treatment
i.v.=intravenous; K+=potassium; mM=millimole			

Correct hypokalemia before and during treatment with abiraterone acetate. Monitor serum potassium at least monthly until stable.

10.1.2 Management of hypertension

- If Grade 1 or 2 adverse events occur, management per investigator. No study medication dose reduction.
- If Grade 3 or 4 adverse events occur, hold study medication. Adjust or add medications to mitigate the toxicity or consider the specific mineralocorticoid receptor blocker, eplerenone. When hypertension improves to <140/90 (≤ Grade 1), resume study medication at full dose.
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When blood pressure improves to <140/90 (≤ Grade 1),, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When hypertension improves to <140/90 (≤ Grade 1), resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication). If blood pressure remains <140/90 (≤ Grade 1), for at least one month, the site investigator has the option of increasing the patient's dose by (1 tablet) 250mg to 750mg (3 tablets).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue study medication.

Control hypertension before and during treatment with abiraterone acetate. Monitor blood pressure at least monthly.

10.1.3 Management of edema, fluid retention

- If pedal edema occurs, supportive management per investigator. No study medication dose reduction.
- If anasarca or pulmonary edema requiring supplemental oxygen occurs, hold study medication. Adjust or add medications to mitigate the toxicity and consider the specific mineralocorticoid receptor blocker, eplerenone. When toxicity resolves to ≤Grade 1, resume study medication at full dose.
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue study medication

Monitor for symptoms of fluid retention at least monthly.

10.1.4 Monitoring and management of adrenocortical insufficiency

- Monitor for symptoms and signs of adrenocortical insufficiency.

- 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.

10.1.4 Management of abnormal liver function tests

Hepatic Impairment

- Baseline Moderate Hepatic Impairment (Child-Pugh Class B)
  - Reduce recommended abiraterone acetate dose to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised.
  - Monitor ALT, AST, and bilirubin
    - Prior to starting treatment with Abiraterone Acetate
    - Every week for the first month
    - Every two weeks for the following two months
    - Monthly after completing three months of treatment
    - If ALT and/or AST > 5 x ULN (upper limit of normal), discontinue abiraterone acetate and do not retreat
    - If total bilirubin > 3 x ULN, discontinue abiraterone acetate and do not retreat

- Baseline severe hepatic impairment (Child-Pugh Class C) – Avoid treating with Abiraterone Acetate.

Hepatotoxicity - For patients who develop hepatotoxicity during treatment with abiraterone acetate

- If Grade 3 hepatotoxicity occurs (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with abiraterone acetate. 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 acetate. The safety of abiraterone acetate 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.

10.1.5 Management of other non-mineralocorticoid based side effects

- If Grade 1-2 toxicities occur, give supportive care per institutional guidelines. No study medication dose reduction.
- If Grade 3 or higher toxicities occur, including headache (interferes with activities of daily living), nausea (total parenteral nutrition/intravenous fluids), vomiting (6 or more episodes in 24 hours, total parenteral nutrition/intravenous fluids), diarrhea (intravenous fluids, hospitalization, hemodynamic collapse), or any other toxicity judged related to study treatment is observed where the subjects safety is jeopardized, hold study medication. For unrelated Grade 3 adverse events, study medication can be held per PI discretion.
- When toxicity resolves to ≤Grade 1, the patient may resume study medication at full dose or with a dose level reduction.
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).
- If toxicity recurs despite aggressive medical management and 2 dose-level reductions, discontinue study medication.

10.2 Interruption or discontinuation of treatment

All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded.

Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

i. Disease progression by PCWG2 criteria
ii. Clinical progression by the discretion of the treating physician

iii. Need for radiation or new systemic therapy for prostate cancer
iv. Unacceptable toxicity requiring cessation of therapy, including adverse event(s), abnormal laboratory value(s), or abnormal test/procedure result(s): Patients who have sustained toxicities that do not return to NCI CTCAE (version 4.0) Grade 1 or less with appropriate medical management, should be discontinued from the study treatment.
v. Protocol violation
vi. Patient withdrawal of consent - the reason(s) for withdrawal must be documented and clarification requested whether withdrawal of consent applies only to the Treatment Phase (i.e. patient has not withdrawn consent for data collection during the post-treatment Follow-Up Phase) or to both the Treatment and Follow-Up Phases. 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.
vii. Death

Patients whose treatment is interrupted or permanently discontinued due to an adverse event must be followed in clinic at 4-week intervals or closer until resolution to Grade I or less. For clinically significant laboratory changes resulting in treatment interruption or discontinuation, patients must have their values monitored at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution to < Grade II or stabilization of the event, whichever comes first. If a patient requires a dose delay of >21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study (unless unrelated to study drug and approved by the medical monitor). If the patient requires more than 2 dose reductions, the patient should be discontinued from the study. All patients must be followed for adverse events and serious adverse events for 30 days following the last dose of Abiraterone acetate. All SAEs must be reported to Duke University as detailed in section 11.2-3.

An investigator may withdraw a patient from the study Treatment Phase at any time based on clinical judgment or for any of the following reasons listed above.

11.0 SAFETY ASSESSMENTS AND REPORTING

Safety assessments will consist of monitoring and recording all adverse and serious adverse events, the regular monitoring of hematology and blood chemistry values, regular measurement of vital signs and the performance of physical examinations.

These assessments should be performed within ±3 days of the scheduled day of assessment for the first cycle and +/- 7 days thereafter except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTCAE v. 4.0.

11.1 Definitions

Definition of 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. Lab abnormalities will be captured as AEs only if deemed clinically significant by the treating physician/provider/investigator. This does not include the labs designated as an adverse event of special interest.

Adverse Events of Special Interest

For Abiraterone acetate, the adverse events of special interest are:

- Mineralocorticoid excess (Hypertension, Hypokalemia, Fluid retention)
- Hepatotoxicity
- Cardiac disorders
- Osteoporosis including osteoporosis-related fractures
- Increased exposure with food
- Rhabdomyolysis/myopathy
- Acute liver failure/hepatitis which might be fatal
- Drug-drug interaction (CYP2D6)
- Allergic alveolitis

Note: Hypertension will be reported as an adverse event of special interest if there is a one grade increase from a baseline grade of ≥ grade 1. See 11.5 Reporting Timelines

Definition of 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 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 either the treating physician or PI, 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 either the treating physician or PI, 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.

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
- pregnancy exposure (maternal and paternal)
- suspected abuse/misuse of a medicinal Johnson and Johnson product
- inadvertent or accidental exposure to a medicinal Johnson and Johnson 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 product
- suspected transmission of any infectious agent via a medicinal product.

11.2 Management of Adverse Events, Serious Adverse Events and Special Reporting Situations

In general, the PI or designate must immediately report to JANSSEN SCIENTIFIC AFFAIRS 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 JANSSEN SCIENTIFIC AFFAIRS. The PI must record non-serious adverse events and report them to JANSSEN SCIENTIFIC AFFAIRS following completion of the accrual and follow up period 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 Situations must be reported if it occurs during a subject's participation in the Study (whether receiving Study Product or not) and within 30 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.

11.3 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 PRINCIPAL INVESTIGATOR's judgment, a clinical 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).

11.4 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 PI 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, and as such the data shall be made available within a reasonable timeframe at JANSSEN SCIENTIFIC AFFAIRS's request.

11.5. Reporting Timelines

Serious safety information (SAEs, Adverse Events of Special Interest, Special Reporting Situations, and PQCs), whether or not considered drug related, should be reported to the lead site/sponsor within **<u>24 hours</u>** of becoming aware of the event(s), using the provided Janssen SAE Report Form and the DCI SAE Review Form (Site Assessment). These documents should be sent to:

The DCI Safety Desk fax: [redacted]

If the safety desk cannot be reached within 24 hours, the Medical Director/Monitor should be contacted: Dr. Daniel George [redacted]

The initial report for each SAE or death should include at minimum the following information:

- protocol # and title
- patient initials, study identification number, sex, age
- date the event occurred

- description of the SAE
- dose level and cycle number at the time the SAE occurred
- description of the patient's condition
- indication whether the patient remains on study
- causality

Signature by physician

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible.

Upon receipt of the Serious Adverse Event Reporting form by DCI Safety Desk, the PI will be notified and be required to complete the PI assessment of the DCI Safety SAE Report Review Form. The DCI safety desk will, in turn, send the Janssen SAE Report Form to Janssen Scientific Affairs. Safety information will be sent to Janssen Scientific Affairs by encrypted email using Cisco Registered Envelope Service to [redacted] Delivery and read receipt of the secure email will serve as evidence of successful communication.

11.5.1 Reporting SAEs at Participating Institutions

Staff at participating sites are responsible for reporting all SAEs to the lead site/sponsor within 24 hours of becoming aware of the event. **The DCI Safety Desk at Duke University** [redacted] should be contacted when reporting an SAE or death. If this person cannot be reached within 24 hours, the Principal Investigator should be contacted: Dr. Daniel George [redacted]

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

11.5.2 FDA Reporting Requirements

The Sponsor/Investigator (Duke) is responsible for reporting serious adverse events to the FDA in accordance with applicable IND Safety Requirements (21 CFR 312.32).

11.6. Transmission Methods

The following methods are acceptable for transmission of safety information to JANSSEN SCIENTIFIC AFFAIRS:

- 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 SCIENTIFIC AFFAIRS, 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 non-functional).

Please use the contact information and process information provided by JANSSEN SCIENTIFIC AFFAIRS

11.7 Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Special Reporting Situation, and Product Quality Complaints (PQCs) to JANSSEN SCIENTIFIC AFFAIRS

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 PRINCIPAL INVESTIGATOR.

The INSTITUTION/PRINCIPAL 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 SCIENTIFIC AFFAIRS in writing) in accordance with Section VII Transmission methods, in English **within 24 hours** of becoming aware of the event(s) along with their 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 INSTITUTION and/ or PRINCIPAL 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 PRINCIPAL 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 INSTITUTION and the PRINCIPAL INVESTIGATOR in the form provided by JANSSEN SCIENTIFIC AFFAIRS in accordance with Section VII Transmission methods, in English, within **24 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 SCIENTIFIC AFFAIRS will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to JANSSEN SCIENTIFIC AFFAIRS. SPONSOR and/or PRINCIPAL INVESTIGATOR will review this listing and provide any discrepancies to the JANSSEN SCIENTIFIC AFFAIRS.

Upon request, INSTITUTION and PRINCIPAL INVESTIGATOR shall provide JANSSEN SCIENTIFIC AFFAIRS with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

11.8 Dissemination of Safety Information from JANSSEN SCIENTIFIC AFFAIRS to INSTITUTION/PRINCIPAL INVESTIGATORS

JANSSEN SCIENTIFIC AFFAIRS will provide to the INSTITUTION/PRINCIPAL INVESTIGATOR IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by the JANSSEN SCIENTIFIC AFFAIRS 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).

12.0 EFFICACY ASSESSMENTS

12.1 Baseline tumor evaluation

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [78]and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG2) [13].

Traditional measures of response reflect when a treatment is working and measures of progression indicate when a drug should be stopped. Because assessing response in bone (the most common site of prostate cancer spread) is uncertain and the clinical significance of PSA changes in response to therapy is not a reliable predictor of response, measures of response have been expanded in consortium trials to include measures of progression.
Patients will be reevaluated for response every cycle according to the guidelines below:

Measurable disease: According to RECIST 1.1, measurable disease is defined as at least 1 lesion ≥ 10 mm in its longest diameter as measured by CT scan with slice thickness ≤ 5 mm, ≥ 10 mm by clinical exam with caliper measurement, or ≥20 mm by CXR. A lymph node is measurable if it is ≥ 15 mm in the short axis when assessed by CT scan. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters.

Nonmeasurable disease: Following RECIST 1.1, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 10 mm) and any of the following:

1. Leptomeningeal disease
2. Ascites
3. Pleural or pericardial effusion
4. Lymphagitic involvement of the skin or lung
5. Abdominal mass or organomegaly identified by physical exam but not by imaging techniques
6. Bone lesions
7. Lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

Target (nodal and visceral) lesions: Following RECIST 1.1, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately. All measurable lesions (up to a maximum of 2 lesions per organ and 5 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements. Lymph nodes can be considered a target lesion if the short axis is ≥ 15 mm by CT. The sum of diameters (long-axis for non-nodal lesions and short-axis for nodal lesions) of all target lesions will be calculated and reported as the *baseline sum diameter*. The baseline sum diameter will be used as a reference by which to characterize the objective tumor response.

Non-target lesions: All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (2) or total of all involved organs (5), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

PSA: Because the rate of rise has known prognostic significance, estimate a pretreatment PSA doubling time (PSA-DT) if at least 3 values are available, but do not delay either treatment or enrollment onto a trial simply to estimate PSA-DT.

12.2 Response Criteria

12.2.1 Evaluation of target lesions:

Table 5 RECIST 1.1 response criteria for target lesions

Response	Evaluation of Target Lesions
Complete response (CR)	The disappearance of all target lesions. Any pathologic lymph nodes (target or non-target) must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum diameter of target lesions as compared to the baseline sum diameter.
Progressive disease (PD)	A ≥20% increase in the sum diameter of target lesions as compared to the smallest sum diameter on study. This must show an absolute increase of at least 5 mm. The appearance of one or more new lesions.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD based on the smallest sum diameter on study.

Target lesions that are too small to measure will be given a measurement of either 0 mm, if the radiologist believes the lesion has disappeared, or 5 mm, if the lesion is felt to be present. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, the residual lesion will be investigated with a fine needle aspirate or biopsy before confirming the complete response status.

If lymph nodes have been identified as target lesions, the short axis measurement will be recorded even if the nodes regress to < 10 mm. Therefore, the sum diameter may not be zero even if complete response criteria are met.

12.2.2 Evaluation of non-target lesions:

*Table 6 RECIST 1.1 response criteria for **non-target** lesions*

Response	Evaluation of Non-target Lesions
Complete response (CR)	The disappearance of all non-target lesions. All lymph nodes must be <10 mm by short axis.
Non-CR, Non-PD	The persistence of one or more non-target lesions.
Progressive disease (PD)	Unequivocal progression of existing non-target lesions and/or the appearance of one or more new lesions.

A clear progression of nontarget lesions only is exceptional. In such circumstances, the progression status, as assigned by the investigator, may be reviewed by a PCCTC panel.

New lesions: If unequivocal, the appearance of new lesions denotes disease progression. If a new lesion is equivocal, therapy will be continued and this lesion will be reevaluated on follow-up imaging as planned in the study flow chart. If repeat scans confirm the new lesion, progression will be documented using the date of the initial equivocal scan. New brain metastases identified while on study are considered new even if there was no baseline brain imaging.

12.2.3 Bone lesions

Record post-treatment changes as either "no new lesions" or "new lesions." When the bone scan is the sole indicator of progression, disease progression in bone is defined as 2 or more new lesions seen on bone scan compared with the baseline scan used for trial entry. In situations where scan findings suggest a flare reaction or where new lesion(s) may represent trauma, confirm these results with other imaging modalities. In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later.

12.2.4 PSA

To report PSA-based outcomes, PCWG2 recommends that the percent of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot. Because declines in serum PSA, if they occur, may not do so for several weeks, PSA measurements obtained during the first 12 weeks should not be used as the sole criterion for clinical decision making. As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

12.2.5 Symptoms

Transient increases in pain may occur before improvement, and those occurring in the first 12 weeks should not affect the course of treatment in the absence of other compelling evidence of disease progression. Changes in symptoms should be documented and confirmed as per other outcome measures.

12.2.6 Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until the end of treatment. The investigator's determination of best overall response will be based both on response criteria and on confirmation criteria. To be assigned a status of partial response or

complete response, changes in tumor measurements must be confirmed by repeat assessment performed 6-8 weeks after the criteria for response are first met. To confirm stable disease, follow-up measurements must meet SD criteria at a minimum interval of 6 weeks after SD was first documented. Table 7 will be used as an assessment tool.

Table7. Assessing Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Patients with global deterioration of health status who require treatment to be discontinued without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuing treatment.

Patients who do not have tumor response assessment due to rapid progression or toxicity will be considered nonresponders, will be included in the denominator for the response rate, and will be classified into one of the categories listed below:

- Death attributed to disease progression
- Early discontinuation attributed to disease progression
- Death attributed to drug toxicity
- Early discontinuation attributed to drug toxicity

Note: If a patient receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported. Reasons include clinical progression, drug toxicity, or secondary therapy for maintaining tumor response.

12.3 Confirming time-to-event outcomes

Any post treatment change in disease status, be it favorable or unfavorable, should be confirmed using a second assessment at a later time point, either 6 weeks later or at the next scheduled scan.

12.4 Duration of overall response

Duration of overall response is measured from the time when partial response or complete response is first noted until the date when recurrent or progressive disease is objectively documented. Duration of overall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

12.5 Progression-free survival

The primary endpoint is radiographic progression-free survival (rPFS), a composite endpoint using the time from study entry to disease progression.

Progression is defined as:

1) Radiologic progression by RECIST 1.1 [78] and/or bone scan progression by PCWG2 criteria [13](Appendix 4), or
2) Symptomatic progression, including clinical deterioration requiring new systemic therapy or a new a skeletal-related event (pathologic fracture, need for radiation to tumor site, malignant spinal cord compression).

A rise in PSA alone or CTC number alone, in the absence of radiologic or symptomatic indicators of disease progression, will not be considered disease progression. Increased pain alone, in the absence of changes in imaging or need for radiation therapy, will not be considered disease progression.

All assessments of disease should be collected at the same time interval. Post-treatment changes will be confirmed based on measurable target lesions, radionuclide bone scans, and symptoms as indicated below. Patients who withdraw from study treatment for reasons other than radiographic disease progression should continue to have results of their CT and Bone scans collected and recorded during the Follow-Up phase until demonstration of radiographic progression.

12.6 Secondary endpoint assessments

12.6.1 RECIST 1.1 defined radiologic response rates

Tumor assessments by CT chest/abdomen/pelvis and bone scan will be made at baseline and every 12 weeks while on therapy. If the chest CT at baseline is clear, chest x-rays may be used for subsequent assessments at the enrolling physician's discretion. Response rates will be calculated based on RECIST 1.1 criteria, as detailed in section 12.2 above centrally. Response rates will be analyzed using objective (defined as CR or PR) parameters. Response rates and

exact 95% confidence intervals based on the binomial distribution for the response rates will be computed.

12.6.2 Post-therapy changes in PSA

The proportion of patients achieving 30%, 50%, and 90% declines in PSA from baseline within 3 months on study and overall will be assessed. Response rates and exact 95% confidence intervals based on the binomial distribution for the response rates will be computed. Time to PSA progression as defined by the PCWG2 definition will also be captured.

12.6.3 Safety and toxicity monitoring

National Cancer Institute Common Toxicity Criteria (v 4.0) will be used to record and monitor for adverse events (Appendix 4). Data for safety and severe adverse events will be monitored on an ongoing basis through monthly investigator and staff meetings, including data from all centers involved.

12.7 Exploratory endpoints

i. Hormonal levels

We will describe the baseline profile of serum hormone levels (including testosterone, DHT, DHEA, DHEAS, estradiol), the change in levels with subsequent therapy (Cycle 4), and their association with response to abiraterone acetate as well as with race (self-reported and ancestral genotyping).

ii. SNP Analyses

We will describe the germline SNP profiles of target genes involved in androgen signaling as well as genes that have been shown to be differentially expressed in African American and Caucasian American prostate cancersas well as a genome wide analysis (GWAS) in both African American and Caucasian men with mCRPC and their associations with response to abiraterone acetate.

13.0 STATISTICAL METHODS

Sample Size Computation

This trial is non-comparative. Based on Ryan et al. the median time to radiographic progression free survival (rPFS) is 16.5 months [14]. Fifty (50) patients will be enrolled in each group (AA and Caucasians). With an accrual rate of 50 patients/group over 30-month accrual period, 24-months follow-up, and assuming that rPFS follows an exponential distribution, based on 5000 simulations the average width of a two-sided 95% confidence interval for the median rPFS is 16.

Because of the small sample size and short follow-up period, 26 radiographic PFS events/group are expected. Consequently, the radiographic PFS distribution by racial group will not be estimated with high precision.

Data Analysis
The proportion of patients who experience PSA decline of at least 30%, 50% and 90% at 3months from baseline and over the entire treatment period will be estimated with exact 95% confidence intervals based on the binomial distribution will be computed. In addition, post therapy changes in PSA will be explored as a continuous outcome. The Kaplan-Meier product limit method will be used to estimate the rPFS. Interim results at 3 months will not be reported, but will be used in the planning of larger trials.

The GWAS analysis will be mostly exploratory as the trial limited sample size will not permit definitive analyses. The SNP will be summarized using descriptive statistics.

14.0 DATA REPORTING AND REGULATORY REQUIREMENTS

14.1 Data Entry

Data collected during this study will be entered into a secure Oracle database. Staff at Duke University will be responsible for the initial study configuration and setup in the electronic database as well as for any future changes.

14.1.1 Case report forms

Electronic case report forms (CRFs) will be generated by Duke University for the collection of all study data. Site Investigators or designee will be responsible for ensuring that the CRFs are kept up-to-date. Each site will enter their own data into CRFs from source documents on site.

14.1.2 Source documents

Study documentation includes all paper case report forms, data correction forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approval, approved and signed subject consent forms, Statement of Investigator form, and clinical supplies receipts and distribution records).

The investigator will prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject participating in the study, promptly complete all original case report forms and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the Sponsor-Investigator.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to the Sponsor-Investigator/Regulatory Specialist by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of Sponsor-Investigator or responsible government agencies as required by law. The investigator agrees to promptly take any reasonable steps that are requested by Sponsor-Investigator as a result of an audit to cure deficiencies in the study documentation and case report forms.

14.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, each participating site's PI will maintain all source documents, study-related documents, and CRFs. Because the length of time required for retaining records depends upon a number of regulatory and legal factors, documents should be stored until the investigator is notified that the documents may be destroyed. In this study, records are to be retained and securely stored for a minimum of 6 years after the completion of all study activities.

14.2 Study monitoring and quality assurance

The Sponsor-Investigator is responsible for monitoring the protocol to ensure that the investigation is conducted in accordance with the general investigational plan and all applicable regulatory requirements. In addition, the protocol will be monitored independently via the Duke Cancer Center (DCI) Monitoring Team
The DCI Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the CPC, the Safety Oversight Committee (SOC), the Duke CTQA, the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, which may include but is not limited to the National Institute of Health, National

Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

14.3 Data Safety and Monitoring

Data for safety and severe adverse events will be monitored on an ongoing basis through monthly investigator and staff meetings, including data from all centers involved.

In addition a recruitment and withdrawal summary will be discussed at these meetings. Withdraws will be broken down into those due to AEs and what they were.

In terms of internal review, the Investigator will continuously monitor and tabulate adverse events. Appropriate reporting to the DUHS IRB will be made. If an unexpected frequency of Grade III or IV events occurs, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or closure of the study. The Investigator of this protocol will also continuously monitor the conduct, data, and safety of this protocol to ensure that:

- Risk/benefit ratio is not altered to the detriment of the subjects
- Appropriate internal monitoring of adverse events and outcomes is done
- Over-accrual does not occur
- Under-accrual is addressed with appropriate amendments or actions
- Data is being appropriately collected in a reasonably timely manner

This protocol is being conducted at additional sites external to Duke University Health Systems. The Sponsor-Investigator is responsible for monitoring these sites to assure the safety and protection of all subjects, and to assure that the study is conducted, recorded, and reported in accordance with the protocol and applicable regulations. To assure that the investigator obligations are fulfilled and all applicable regulations and guidelines are being followed, the Sponsor-Investigator will designate the DCI Monitoring Team to assure that the external site facilities are acceptable, the protocol and investigational plan are being followed, the IRB/IEC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor-Investigator and the IRB/IEC, study drug and study drug inventory are controlled and the Investigator is carrying out all agreed activities. Monitoring also includes review of regulatory and eligibility, conduct, data quality and adverse event reporting for select cases.

As pre-arranged by the Sponsor-Investigator, DCI Monitoring Team will monitor 1-3 subjects annually at external sites until closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk. Study teams will provide requested data for remote monitoring when possible. If feasible, the first visit will be conducted on site. Additional on-site visits will be completed as deemed necessary and as requested. Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits. Key variables (demographics, inclusion/exclusion criteria,

and safety) on the CRFs will be compared with select subject's source documents. Any discrepancies will be noted and resolved.

15.0 PROTOCOL AMENDMENTS OR CHANGES IN STUDY CONDUCT

Any change or addition to this protocol requires a written protocol amendment that must be reviewed by Duke University and Janssen Scientific Affairs before implementation.

16.0 PROCEDURES AND INSTRUCTIONS

16.1 Disclosure and confidentiality

The investigator agrees to keep all information provided by participating sites and by Janssen Scientific Affairs in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by participating sites and Janssen Scientific Affairs (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by participating sites and Janssen Scientific Affairs to the investigator may not be disclosed to others without direct written authorization from Janssen Scientific Affairs, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

16.2 Discontinuation of study

Duke University or Janssen Scientific Affairs reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

16.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations). The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

16.3.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Janssen before study initiation. Any amendments to the

protocol, other than administrative ones, must be reviewed by Janssen Scientific Affairs, and approved by this committee.

16.3.2 Informed consent

The investigator or designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

16.3.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects). Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

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APPENDIX 1: PERFORMANCE STATUS CRITERIA

Karnofsky Performance Scale	
%	**Description**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly
0	Dead

APPENDIX 2: CYP450 ISOENZYME INHIBITORS AND INDUCERS

PROHIBITED CYP450 ISOENZYME INHIBITORS AND INDUCERS

Strong CYP3A4,5,7 inhibitors	Moderate CYP3A 4,5,7 inhibitors	CYP3A4 inducers
Clarithromycin	Amprenavir	Avasimibe
Conivaptan	Aprepitant	Bosentan
grapefruit juice	Atazanavir	Carbamazepine
Indinavir	Cimetidine	Efavirenz
Itraconazole		Modafinil
Ketoconazole	Darunavir	Nafcillin
Lopinavir	Diltiazem	Oxcarbazepine
Mibefradil	Elvitegravir	Phenobarbital
Nefazodone	Erythromycin	Phenytoin
Nelfinavir	Fluconazole	pioglitazone
Posaconazole	Fosamprenavir	Rifabutin
Ritonavir	Tofisopam	Rifampin
Saquinavir	Tipranavir	St. John's wort
Telithromycin	Verapamil	Topiramate
Troleandomycin		
Voriconazole		

This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase Abiraterone acetate AUC > 5-fold, and moderate inhibitors are predicted to increase Abiraterone AUC ≥ 2-fold but < 5-fold.

This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche et al. 2008).

CYP450 SUBSTRATES TO BE USED WITH CAUTION

CYP2C8	CYP2C9	CYP2C19	CYP3A4,5,7**	
amodiaquine	celecoxib	amitriptyline	Adinazolam	fentanyl[2]
cerivastatin	diclofenac	citalopram	alfentanil[1,2]	flunitrazepam
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine[1]	fluticasone[1]
repaglinide	fluvastatin	clomipramine	alprazolam	lovastatin[1]
rosiglitazone	glibenclamide (glyburide)	clopidogrel	amlodipine	maraviroc[1]
torsemide	gliclazide	diazepam	aripiprazole	midazolam[1]
troglitazone	glimepiride	fluoxetine	atorvastatin	nifedipine
	glipizide	imipramine	brotizolam[1]	nisoldipine
	indomethacin	lansoprazole	budesonide[1]	nitrendipine
	irbesartan	moclobemide	buspirone[1]	perospirone[1]
	ketobemidone	omeprazole	cerivastatin	quinine
	lornoxicam	pantoprazole	chlorpheniramine	sildenafil[1]
	losartan	progesterone	cyclosporine[2]	simvastatin[1]
	meloxicam	propranolol	darifenacin[1]	sirolimus[1,2]
	naproxen	quazepam	Diazepam	tipranavir[1]
	nateglinide	rabeprazole	diergotamine[2]	trazodone
	piroxicam	sertraline	ebastine[1]	triazolam[1]
	S-ibuprofen	S-mephenytoin	eletriptan[1]	
	sulfamethoxazole		eplerenone[1]	
	tenoxicam		ergotamine[2]	
	tolbutamide		Estazolam	
	torsemide		everolimus[1]	
	valdecoxib			

* This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, and from (Zhou et al. 2009)

** CYP3A4,5,7 substrates were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; and supplemented by the FDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (*e.g.*, Torsades de Pointes).

APPENDIX 3: NCI COMMON TOXICITY CRITERIA

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 can be found here:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

APPENDIX 4: CRITERIA FOR DISEASE PROGRESSION

PROSTATE CANCER WORKING GROUP 2 (PCWG2) GUIDELINES [13]

Variable	Assessments	Progression
Soft-tissue lesions	Use RECIST 1.1 criteria, except: • Only report changes in lymph nodes that were ~2 cm in diameter at baseline • Record changes in nodal and visceral soft tissue sites separately • Record complete elimination of disease at any site separately • Confirm favorable change with next planned scan 8 weeks later	Use RECIST 1.1 criteria for progression, except: • Progression at first assessment must be confirmed by a second scan 6-8 weeks later (For some treatments, a lesion may increase in size before it decreases)
Bone	Record as either *new lesions* or *no new lesions* If no new lesions, continue therapy If new lesions: continue therapy but perform a confirmatory scan 6-8 weeks later. If confirmatory scan has no new lesions, continue therapy. If there are *additional* new lesions, this is progression.	The appearance of ≥ 2 new lesionsAND A confirmatory scan 6-8 weeks later showing at least 2 *additional* new lesions The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures One or more of the following criteria indicates disease progression: • Need for new systemic therapy • Need for palliative radiation therapy • Development of a new skeletal-related event	