Janssen Research & Development*

Clinical Protocol

A Multicenter, Open-label, Single-arm, Phase 2 Study of Abiraterone Acetate Plus Prednisone in Subjects with Advanced Prostate Cancer Without Radiographic Evidence of Metastatic Disease

IMAAGEN

Protocol 212082PCR2005; Phase 2
Amendment 6

Abiraterone acetate (CB7630)

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This study will be conducted under US Food & Drug Administration (FDA) Investigations New Drug (IND) regulations (21 CFR Part 312).

EudraCT NUMBER: Not applicable.

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Amendment 1	14 Apr 2011
Original Protocol:	08 Dec 2010

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

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SYNOPSIS

TITLE

A Multicenter, Open-label, Single-arm, Phase 2 Study of Abiraterone Acetate Plus Prednisone in Subjects with Advanced Prostate Cancer Without Radiographic Evidence of Metastatic Disease

STUDY NAME

IMAAGEN: **IM**pact of **A**biraterone **A**cetate in Prostate Specific Anti**GEN**

EudraCT NUMBER

Not applicable.

Abiraterone Acetate (CB7630)

Abiraterone acetate (CB7630) 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 $C_{26}H_{33}NO_2$ and molecular weight is 391.55. Once absorbed after oral administration, abiraterone acetate is rapidly converted to its active form, abiraterone. Abiraterone (CB7598), [17-(3-pyridyl) androsta-5,16-dien-3β-ol], is an oral selective and irreversible inhibitor of CYP17 with an apparent inhibition constant of 0.5 nM. Abiraterone blocks 2 important enzymes (17α hydroxylase/C17,20-lyase) in the androgen biosynthesis pathways based on the observation that nonsteroidal 3 pyridyl esters improve selectivity for inhibition of 17α-hydroxylase/C17,20 lyase.

OBJECTIVES

Primary Objective

To demonstrate that abiraterone acetate plus prednisone effectively decreases prostate-specific antigen (PSA) in subjects with non-metastatic castration-resistant prostate cancer (CRPC) who have a rising PSA despite castrate levels of testosterone.

Secondary Objectives

☐ To describe the time to radiographic progression of disease in subjects treated with abiraterone acetate in addition to the current standard of care.

☐ To describe the safety profile of abiraterone acetate when taken with prednisone 5 mg daily.

Exploratory Objectives

☐ To describe the duration and type of subsequent cancer therapy in subjects after radiographic disease progression.

☐ To evaluate exploratory biomarkers predictive of resistance to abiraterone acetate treatment. ☐

Optional Drug Holiday Phase

- To evaluate if patients who demonstrate no signs of disease progression (radiographic or PSA) after > 5 years of treatment for non-metastatic CRPC may no longer require medications that suppress the androgen signaling pathway.
- To evaluate PSA kinetics after withdrawal of abiraterone acetate plus prednisone and androgen deprivation therapy (ADT) in patients participating in this study phase.

Hypothesis

Abiraterone acetate plus prednisone, by decreasing testosterone levels, will further decrease PSA levels in this subject population.

Optional Drug Holiday Phase

Subjects who demonstrate no signs of disease progression after > 5 years of treatment may no longer require medications that suppress the androgen signaling pathway and may benefit by not being subjected to the side effects of these medications (abiraterone acetate, prednisone, and ADT.

OVERVIEW OF STUDY DESIGN

This is a Phase 2, prospective, multicenter, open-label, single-arm study of abiraterone acetate plus prednisone in subjects with non-metastatic CRPC with a rising PSA despite castrate levels of testosterone. Approximately 125 subjects will be enrolled at approximately 40 sites in the United States (US).

The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28-day cycles); a Pre-metastatic Disease Follow-up Phase, an Optional Drug Holiday Phase; and a 30-day Safety Follow-up Visit. A study treatment cycle is 28 days.

During the Core Study Treatment Phase, in Cycles 1, 2, and 3, subjects will be required to return to the study site twice per cycle (Days 1 and 15). In Cycles 4 through 6, subjects will be required to return to the study site on Day 1 of each cycle. Additional visits may occur as clinically indicated. The End of Core Study Treatment Visit is to occur as follows:

- ☐ On Day 1 of Cycle 7;
- ☐ At the time of discontinuation of abiraterone acetate if discontinuation occurs prior to completion of the Core Study Treatment Phase;
- ☐ If possible, at the time of withdrawal from the study if withdrawal occurs prior to completion of the Core Study Treatment Phase; or
- ☐ In the event of radiographic evidence of disease progression prior to completion of the Core Study Treatment Phase.

At the time of the current protocol, the Core Study Treatment Phase has been completed.

After the Core Study Treatment Phase, subjects may enter the Pre-metastatic Disease Follow-up Phase and continue to receive abiraterone acetate until metastatic disease progression is confirmed. During the Pre-metastatic Disease Follow-up Phase, subjects will be required to return to the study site at the start of each cycle to receive study agents. Assessments will be limited to blood sample collection for biomarker analysis, monitoring of study treatment compliance, safety reporting, and documentation of changes in prostate cancer disease status and therapy. Subjects may receive additional therapies at the investigator's discretion during this phase, with the exception of those noted in Section 8.2.2.1.

OPTIONAL DRUG HOLIDAY PHASE:

During the Pre-metastatic Disease Follow-up Phase, subjects who demonstrate no signs of radiographic or PSA disease progression after > 5 years of study treatment may choose to participate in this phase. During the Optional Drug Holiday Phase, subjects will discontinue abiraterone acetate plus prednisone and ADT. During the first year in this phase, subjects will be monitored closely for signs of PSA progression and will have the option to return to study medication if there is evidence of disease progression, confirmed as nonmetastatic by a negative conventional scan. Refer to the Time and Events Schedule for procedures to be performed and timing of assessments. If after one year, there are no signs of PSA progression, subjects will be followed for an additional year but will not have the option to return to study medication if progression is noted after 12 months off medication.

Note that prior to Protocol Amendment 4, subjects may have continued to receive abiraterone acetate in an Optional Post-metastatic Disease Follow-up Phase. While the option to enter the Post-metastatic Disease Follow-up Phase no longer exists, subjects who continue in the Post-metastatic Disease Follow-up Phase at the time of Protocol Amendment 6, may remain on study.

All subjects will be required to return to the study site 30 days after receiving their last dose of abiraterone acetate for safety follow-up.

A schedule of events showing the timing of procedures is provided in the Time and Events Schedule for Procedures to be Performed and a flow chart depicting subject participation in the study is provided in the Time and Events Schedule for Subject Participation in the Study and for the Optional Drug Holiday Phase.

Subjects may remain on abiraterone acetate until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, the subject elects to participate in the Optional Drug Holiday Phase as described in Protocol Amendment 6, or the sponsor determines it is necessary to stop the study.

The completion of the entire Core Study Treatment Phase is defined as the time at which the last subject completes the End of Core Study Treatment Visit. The end of the study is defined as the point at which all subjects have progressed to metastatic disease or for those participating in the Optional Drug Holiday Phase, the end of the 2-year period.

STUDY POPULATION

Below are the major inclusion and exclusion requirements for this study; refer to Section 4 for the full list of entry criteria.

Major Inclusion Criteria:

☐ Be a male ≥18 years of age

☐ Have adenocarcinoma of the prostate with histological or cytological confirmation without neuroendocrine differentiation or small cell histology

☐ Be currently receiving and have been receiving continuous therapy with GnRH monotherapy for at least 6 months before screening, with a serum testosterone of < 50 ng/dL (< 2.0 nM) or have undergone an orchiectomy with a serum testosterone level of < 50 ng/dL (< 2.0 nM)

☐ Have rising PSA defined as a PSA of ≥ 10 ng/mL obtained at screening or prostate-specific antigen doubling time (PSADT) of ≤ 10 months with the first of the 3 consecutive PSA values used to calculate PSADT ≥ 2.0 ng/mL.

☐ Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

Optional Drug Holiday Phase Inclusion:

☐ Patients on study who demonstrate no signs of disease progression (radiographic or PSA) after > 5 years of treatment

☐ Negative scan within the previous 3 months

☐ PSA values < 25% above nadir or < 10 ng/mL, within the previous 3 months

Major Exclusion Criteria

☐ Have prior or current evidence of local disease progression or metastatic disease as defined by modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria

☐ Have received chemotherapy for treatment of CRPC; however, if a patient received chemotherapy in an adjuvant setting, prior to having CRPC, for castrate-sensitive prostate cancer, the patient is still eligible.

☐ Are currently receiving any antiandrogen therapy (eg, bicalutamide, flutamide, or nilutamide).

- ☐ If previously treated with antiandrogen therapy, there must be documentation of at least 2 consecutive rising PSA values at least 2 weeks apart obtained prior to screening.
  - ☐ If previously treated with flutamide, at least 1 of the PSA values must be obtained 4 weeks or more after flutamide discontinuation.
  - ☐ If previously treated with bicalutamide or nilutamide, at least 1 of the PSA values must be obtained 6 weeks or more after antiandrogen discontinuation.

☐ Have previously received agents having any CYP17 inhibitory activity for the treatment of prostate cancer, such as ketoconazole

☐ Have previously received aminoglutethimide

☐ Have any health-related condition that would preclude participation in this trial as described in Section 4.

DOSAGE AND ADMINISTRATION

Study agents include abiraterone acetate and prednisone. Subjects are to receive the following:

- ☐ Abiraterone acetate 1000 mg (4 x 250 mg tablets by mouth [PO] once daily, taken on an empty stomach). The subject should not eat for at least 2 hours before and for at least 1 hour after taking abiraterone acetate.
- ☐ Prednisone 5 mg (2 x 2.5 mg tablets PO once daily, preferably with food).

Although not considered a study agent, subjects will also receive their regularly prescribed GnRH monotherapy (to be administered as prescribed). Subjects will begin taking study agents on Day 1 of Cycle 1.

Note that if prednisone and/or GnRH monotherapy are discontinued, a subject may continue to receive abiraterone acetate and continue on study as scheduled. If a subject needs to discontinue either of these therapies, the appropriate medical management of the subject needs to be discussed with the Medical Monitor. If abiraterone acetate is discontinued prednisone should also be discontinued as described in Section 10.2, and the subject should be discontinued from the study as described in Section 10.3.

EFFICACY EVALUATIONS/CRITERIA

During the Core Study Treatment Phase, efficacy will be measured by PSA levels, testosterone levels, and imaging studies (bone scans, and computed tomography [CT] or magnetic resonance imaging [MRI] of the chest, abdomen, and pelvis); a central laboratory will be used for PSA and testosterone evaluations. In addition, imaging studies will be read by both local readers and a central reader, and the results will be discussed in consultation with the sponsor, as described in further detail in Section 9.2.

During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, imaging studies for disease status will be done locally per standard of care. Note that while disease status will be evaluated locally per standard of care, disease progression is to be determined using RECIST criteria as described in Section 9.2.

BIOMARKER ANALYSIS

During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, a blood sample for biomarker analysis will be collected prior to and at the time of metastatic disease progression. For subjects currently enrolled in the study who have metastatic disease progression, a single sample will be obtained. A blood sample may also be collected at the 30-day Safety Follow-up Visit, if not previously obtained. Samples will be stored at a central laboratory and will be analyzed by a different contract research organization.

SAFETY EVALUATIONS

During the Core Study Treatment Phase, safety and tolerability will be assessed by complete physical examinations, vital signs, weight, examination for volume overload, 12-lead electrocardiograms (ECGs), laboratory tests (prothrombin time/partial thromboplastin time [international normalized ratio, INR], hematology, serum chemistry, fasting glucose, serum lipids, and liver function tests), compliance checks, and recording of adverse events and concomitant medications; laboratory evaluations will be conducted using a central laboratory.

During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, safety evaluations will be conducted per standard of care; laboratory evaluations will be conducted using a local laboratory.

STATISTICAL METHODS

Sample Size Justification

The sample size estimate for this study is based upon testing the primary endpoint of the proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment

Visit. Assuming a null hypothesis proportion equals 0.35 vs the alternative of 0.50; a 1-sided, alpha equal to 0.025; and 90% power, a sample size of 111 subjects will be required. Accounting for an approximate dropout rate of 10%, 125 subjects are planned for enrollment.

Primary Efficacy Endpoint and Analysis

The primary endpoint of the study is the proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit. This will be analyzed using a normal approximation to the binomial distribution comparing the observed proportion to a reference of 0.35; the 95% confidence interval (CI) interval will also be computed.

The primary analysis will be performed using an efficacy-evaluable population (defined as all subjects who completed at least one cycle of abiraterone acetate), and an additional sensitivity analysis will be performed on the per protocol population (defined as all subjects who did not have a major protocol violation during the Core Study Treatment Phase and completed at least 6 cycles of treatment).

Secondary Efficacy Endpoints and Analyses

Secondary efficacy endpoints include the following (for further details refer to Section 9.2):

- ☐ Time to radiographic evidence of disease progression
- ☐ Time to PSA progression
- ☐ The proportion of subjects with a ≥ 50% reduction in PSA after 3 cycles of treatment and absolute PSA reduction
- ☐ The proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit with and without local therapy
- ☐ PSA and testosterone over time as well as at nadirs

Time to radiographic evidence of disease progression and time to PSA progression will be summarized using the Kaplan-Meier method. The proportion of subjects with a ≥ 50% reduction in PSA levels after 3 cycles of treatment will be analyzed using a normal approximation to the binomial distribution comparing the observed proportion to a reference of 0.35; the 95% CI interval will also be computed. PSA and testosterone levels at each time point, as well as change from baseline, will be summarized descriptively. All secondary endpoints will be analyzed using the efficacy-evaluable population.

From the time of the End of the Core Study Treatment Phase until the end of the study, secondary endpoints collected during the Pre-metastatic Disease Follow-up Phase will be updated on an annual basis. After radiographic disease progression, the duration and type of subsequent cancer therapy will be summarized descriptively.

Biomarker Analyses

Blood samples collected at pre-metastatic, including at the time of the start of the Optional Drug Holiday Phase, and metastatic time points may be analyzed for a selective panel of molecular changes (androgen receptor anomalies such as mutation and splice variants etc.) and associations may be made with clinical endpoints.

The association biomarkers with clinical response or relevant survival endpoints may be assessed using appropriate statistical methods (eg, analysis of variance, categorical, or survival models), depending on the endpoints.

Safety Analyses

Safety will be assessed by summarizing and listing as appropriate the incidence and type of adverse events (overall and by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI CTCAE] Grade), deaths, serious adverse events, and adverse events resulting in discontinuation of study

agent. In addition, the proportion of subjects with mineralocorticoid excess (those with hypokalemia, hypertension and/or volume overload [edema, refractory edema, or pulmonary edema]) will be summarized combined and by each component, and the 95% CI interval will be computed. Laboratory data and vital signs will be summarized using descriptive statistics for each time point and for change from baseline. Safety data will be summarized for the Safety population (defined as all subjects exposed to study agents).

All safety endpoints will be reported through the end of the Core Study Treatment Phase and then in an Annual Addendum.

TIME AND EVENTS SCHEDULE FOR PROCEDURES TO BE PERFORMED

Procedures and Evaluations	Screening Phase (Days)	Core Study Treatment Phase: Cycle (Day)									End of Core Study Treatment Visit [b]	Pre-metastatic Disease Follow-up Phase [b]	30-day Safety Follow-up Visit [b]	Optional Drug Holiday Phase
		1		2		3		4	5	6				
	(-28 to -1)	(1)	(15)	(1)	(15)	(1)	(15)	(1)	(1)	(1)				
Informed consent	X													X
Dispense study card[c]	X													
Medical history, prior medications including prior prostate cancer therapies [d]	X													
Height	X													
ECOG status	X													
MUGA scan or Cardiac ECHO [e]	X													
Demography	X													
Complete physical exam [f]	X										X	per standard of care[o]		
Vital signs/weight/and examination for volume overload [g]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [o]	per standard of care [o]	per standard of care [o]
12 Lead ECG	X							X			X			per standard of care [o]
Coagulation factors PT/PTT (INR)	X		X										per standard of care [o]	
Biomarker sample												X[p]	X[p]	X[p]
Hematology	X	X	X	X	X	X		X	X	X	X	per standard of care [o]	per standard of care [o]	
Serum chemistry [h]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [o]	per standard of care [o]	
Fasting glucose	X	X	X	X	X	X		X	X	X	X	per standard of care [o]	per standard of care [o]	
Serum lipids	X					X			X		X	per standard of care [o]	per standard of care [o]	
Liver function tests [i]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [o]	per standard of care [o]	

Procedures and Evaluations	Core Study Treatment Phase												
	Screening Phase (Days)	Cycle (Day)									End of Core Study Treatment Visit [b]	Pre-metastatic Disease Follow-up Phase [b]	30-day Safety Follow-up Visit [b]	Optional Drug Holiday Phase
		1		2		3		4	5	6				
	(-28 to -1)	(1)	(15)	(1)	(15)	(1)	(15)	(1)	(1)	(1)				
Serum testosterone	X	X						X			X	per standard of care [o]	per standard of care [o]	X [q]
PSA [j]	X	X						X			X	per standard of care [o]	per standard of care [o]	X [r]
CT/MRI	X [k]							X [k]			X [k]	per standard of care [o]		X [o]
Bone scan	X [k]							X [k]			X [k]	every cycle per standard of care [k,o]		X [s]
Abiraterone acetate and prednisone distribution [l]		X		X		X		X	X	X	X	every cycle		
Study agents compliance assessment												every cycle		
Concomitant medications [d]	X	X	X	X	X	X	X	X	X	X	X	every cycle	X	X
Adverse events [m]	X	X	X	X	X	X	X	X	X	X	X	every cycle	X	X
Changes in prostate cancer therapy												every cycle[n]	X	X
Disease status												per standard of care [o]		per standard of care [o]

a. A cycle is defined as 28 days.

b. The End of Core Study Treatment Visit is to occur at the following times:
- On Day 1 of Cycle 7;
- At the time of discontinuation of abiraterone acetate if discontinuation occurs prior to completion of the Core Study Treatment Phase;
- If possible, at the time of withdrawal from the study if withdrawal occurs prior to completion of the Core Study Treatment Phase; or
- In the event of radiographic evidence of disease progression prior to completion of the Core Study Treatment Phase. At

the time of the current protocol, the Core Study Treatment Phase has been completed.

After the Core Study Treatment Phase, subjects may enter the Pre-metastatic Disease Follow-up Phase and continue to receive abiraterone acetate until metastatic disease progression is confirmed. At the time of metastatic disease progression, the subject is to be discontinued from abiraterone acetate.

Note that prior to Protocol Amendment 4, subjects may have continued to receive abiraterone acetate in an Optional Post-metastatic Disease Follow-up Phase. This Phase has been eliminated from the current protocol; however, those subjects who are currently in the Optional Post-Metastatic Follow-up Phase as of the date of this protocol may remain on study. For these subjects, procedures to be followed are listed under the Pre-metastatic Disease Follow-up Phase column.

All subjects will be required to return to the study site 30 days after receiving their last dose of abiraterone acetate for safety follow-up.

The duration of study participation was anticipated to be approximately 2 years. The completion of the entire Core Study Treatment Phase is defined as the time at which the last subject completes the End of Core Study Treatment Visit. The end of the study is defined as the point at which all subjects have progressed to metastatic disease or for those participating in the Optional Drug Holiday Phase, the end of the 2-year period.

c. Subjects must be provided with a study card indicating the name of the investigational study agents, the study number, the investigator's name, a 24-hour emergency contact number, and, excluded concomitant medications.

d. Refer to Section 8 for further details on reporting prior and concomitant medications.

e. MUGA or ECHO scan should be obtained at baseline (existing documented MUGA or ECHO scan up to 28 days prior to Cycle 1 Day 1 may be used for this screening assessment). A cardiac ECHO may be used if MUGA is not available, when ECHO is standard of care for the institution, or due to the time interval between the MUGA and bone scan that is required by the institution.

f. Complete physical examination includes head, eyes, ears, nose, and throat; chest; cardiac; abdominal; extremities; neurologic; and lymph node examinations.

g. Vital signs include upright blood pressure, heart rate, respiratory rate, and body temperature. Weight and an examination for volume overload will also be performed at these visits. If signs of volume overload are noted, and a diuretic is initiated, potassium will need to be monitored more frequently (refer to Section 6.2.3 for further details); similarly, if a subject is treated with a diuretic for hypertension, potassium will need to be monitored more frequently (refer to Section 6.2.2 for further details).

h. Subjects who enter the study on exogenous potassium supplementation or who experience low potassium may need more frequent monitoring for hypokalemia; refer to Section 6.2.1 for further details.

i. Liver function tests must include: alkaline phosphatase, ALT, AST, LDH, and direct and total bilirubin. Subjects who experience an abnormal liver function test result may need more frequent monitoring; refer to Section 6.2.4 for further details.

j. If a digital rectal examination is performed, PSA must be sampled prior to the examination.

k. Scans (existing documented bone scans, and CT or MRI of the chest, abdomen, and pelvis) performed up to 28 days prior to Cycle 1 Day 1 may be used for screening assessments. If disease progression is observed on a postbaseline scan, confirmatory scan is required within 6 to 8 weeks after the initial diagnosis (see Section 9.2 for further details). Study agents should continue in the interim.

l. Study agents include abiraterone acetate and prednisone. Subjects will also continue to receive their GnRH monotherapy as prescribed. Subjects will begin taking study agents on Day 1 of Cycle 1. If prednisone and/or GnRH monotherapy are discontinued, subjects may continue to receive abiraterone acetate and continue on study as scheduled. If a subject needs to discontinue either of these therapies, the appropriate medical management of the subject needs to be discussed with the Medical Monitor. If a subject prematurely discontinues abiraterone acetate, prednisone should also be discontinued. Refer to Sections 10.2 and 10.3 for reasons for permanently discontinuing study agents or withdrawal from the study, respectively.

   Subjects may remain on abiraterone acetate until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, or until the sponsor determines it is necessary to stop the study.

m. Adverse events should be collected from the date informed consent is signed until 30 days after the last dose of study agents. For the Optional Drug Holiday Phase, AEs will continue to be collected for the full duration. Refer to Section 6.2 for abiraterone acetate dose adjustment in the event of toxicity.

n. Prior to metastatic disease progression, new therapy for prostate cancer is prohibited as described in Section 8.2.2.1; for those currently on study who have metastatic disease progression, new therapy is prohibited as described in Section 8.2.2.2.

o. All imaging studies, laboratory tests, or other safety monitoring as noted in the column above for the Pre-metastatic Disease Follow-Up Phase, the Optional Drug Holiday Phase, and the 30-day Safety Follow-up Visit will be done locally per standard of care, except as noted in "p" below for analysis of biomarker data. Note that while bone scans to determine disease status will be performed locally per standard of care, disease progression is to be confirmed using RECIST criteria as described in Section 9.2.

p. For subjects who do not have metastatic disease progression, a blood sample for biomarker analysis will be collected prior to and at the time of metastatic disease progression. For subjects currently enrolled in the study who have metastatic disease progression, a single sample will be obtained. A blood sample may also be collected at the 30-day Safety Follow-up Visit, if not previously. For the Optional Drug Holiday Phase, samples will be collected at the time of study drug discontinuation, at confirmed PSA progression at any point during year 1, and at "off study" if no signs of disease progression.

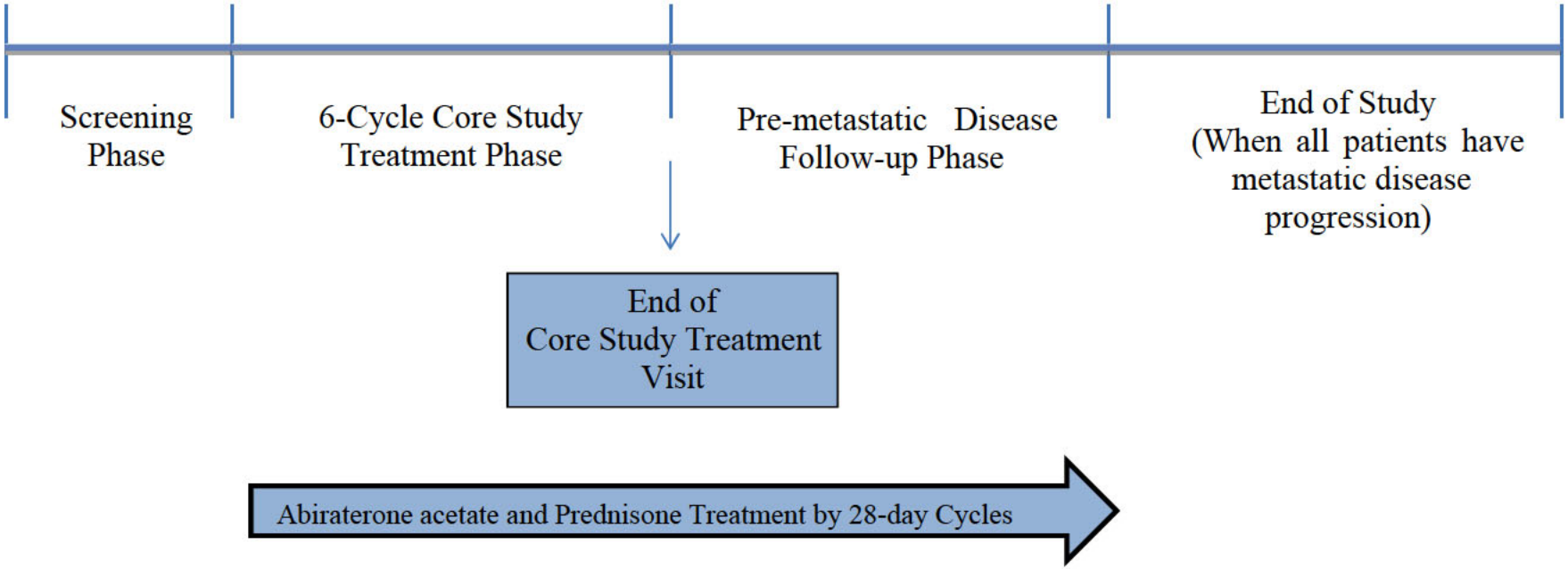
q. Serum testosterone will be monitored every 3 months until return to normal levels for up to 1 year.

r. PSA will be monitored monthly for 3 months and then once every 3 months thereafter for up to 1 year, and thereafter per standard of care.

s. Subjects with a negative bone scan within the previous 3 months and have been on study for > 5 years, are eligible to participate in the Optional Drug Holiday Phase, and thereafter per standard of care

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; GnRH = gonadotropin-releasing hormone; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PSA = prostate-specific antigen; PT/PTT (INR) = prothrombin time/partial thromboplastin time (international normalized ratio); RECIST = Response Evaluation Criteria in Solid Tumors

TIME AND EVENTS SCHEDULE FOR SUBJECT PARTICIPATION IN THE STUDY

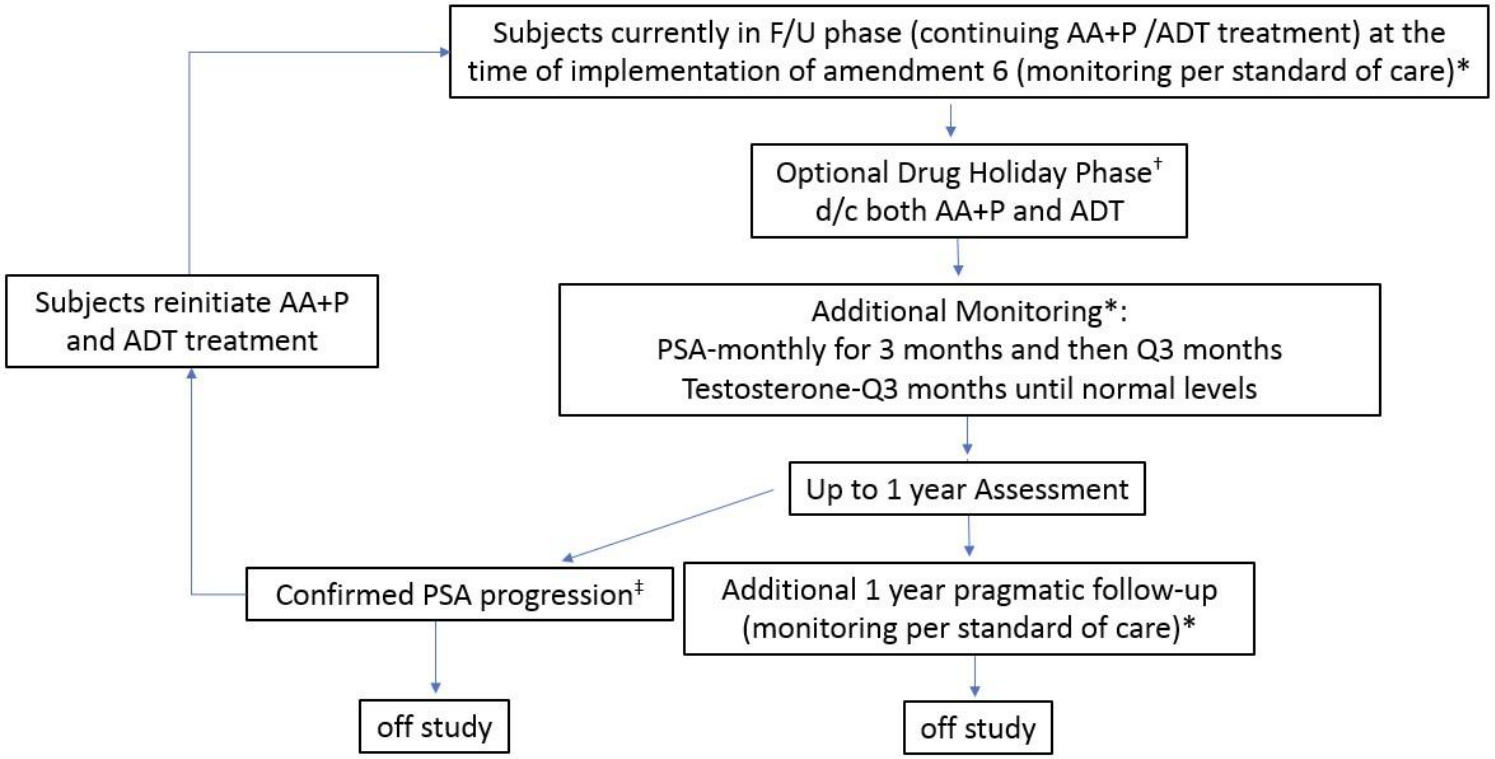


All subjects are required to return to the study site 30 days after their last dose of abiraterone acetate for safety follow-up.

Note: Prior to Protocol Amendment 4, subjects may have continued to receive abiraterone acetate in an Optional Post-metastatic Disease Follow-up Phase. This Phase has been eliminated from the current protocol; however, those subjects who are currently in the Optional Post-Metastatic Follow-up Phase as of the date of this protocol may remain on study.

Per Protocol Amendment 6, during the Pre-metastatic Disease Follow-up Phase, subjects who demonstrate no signs of radiographic or PSA disease progression after > 5 years of study treatment may choose to participate in the Optional Drug Holiday Phase. Refer to the study schematic for the Optional Drug Holiday Phase.

STUDY SCHEMATIC FOR THE OPTIONAL DRUG HOLIDAY PHASE



† Subjects eligible to participate in the Optional Drug Holiday Phase currently remain on study with stable disease and have had a negative (-) bone scan within the previous 3 months.
* Refer to Time and Events Schedule for detail.
‡ a ≥ 25% increase and an absolute increase of 2 ng/mL or more from the nadir, documented and confirmed by a second value obtained 3 or more weeks later. Also confirmed as nonmetastatic by a negative conventional scan.

F/U = follow-up
AA+P = abiraterone acetate plus prednisone
ADT = androgen deprivation therapy
PSA = prostate specific antigen
d/c = discontinue

ABBREVIATIONS AND DEFINITIONS

153Sm	Samarium
89Sr	Strontium
Abiraterone	CB7598
Abiraterone acetate	CB7630
ACTH	adrenocorticotropic hormone
ADL	activities of daily living
ADT	androgen-deprivation therapy
AIPC	androgen-independent prostate cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration curve
BCR	biochemical recurrence
BUN	blood urea nitrogen
CI	confidence interval
CFR	Code of Federal Regulations
Cmax	maximum concentration
CPK	creatine phosphokinase
CRF	case report form
CRPC	castration-resistant prostate cancer
CT	computed tomography
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
Fax	Facsimile
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GnRH	gonadotropin-releasing hormone
HCP	health care professional
HDL	High-density lipoprotein
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HRPC	hormone-refractory prostate cancer
ICF	informed consent form
ICH	International Conference on Harmonisation
IMAAGEN	**IM**pact of **A**biraterone **A**cetate in Prostate Specific Anti**GEN**
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IVF	intravenous fluids
JBI	Janssen Biotech, Inc.
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition scan
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events

PO	by mouth
PP	per protocol (population)
PQC	Product Quality Complaint
PR	partial response
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
TPN	total parenteral nutrition
TTPP	time to PSA progression
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. INTRODUCTION

For the most accurate and current information regarding the efficacy and safety of abiraterone acetate (CB7630), refer to the latest version of the Investigator's Brochure and the most recent product label.

The term sponsor used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Overall Rationale for the Study

Prostate cancer is the most commonly diagnosed cancer among men, and castration-resistant prostate cancer (CRPC) is the second most common cause of cancer-related death in men in the United States (US, Tang et al, 2010; Reid et al, 2010). In 2010, the American Cancer Society estimated that prostate cancer would be diagnosed in 217,730 men in the US and that 32,050 would die (Jemal et al, 2010). The widespread use of prostate-specific antigen (PSA) testing has resulted in most patients being diagnosed with asymptomatic, clinically localized cancer. Gleason score, PSA level, and stage assist to stratify patients into categories associated with different probabilities of cure. Life expectancy, comorbidities, potential side effects, and patient preference are also considered in the choice of initial therapy, which can consist of radical prostatectomy or radiation therapy/hormonal therapy as well the alternative of active surveillance.

Prostate cancer is hormone sensitive at the time of initial diagnosis. With progression of disease detected through a rising PSA, with or without radiographic evidence of metastases, androgen-deprivation therapy (ADT) is the standard of care in metastatic disease, and is being increasingly used in the treatment of men without evidence of metastatic disease (Smith et al, 2005; Ryan et al, 2010a).

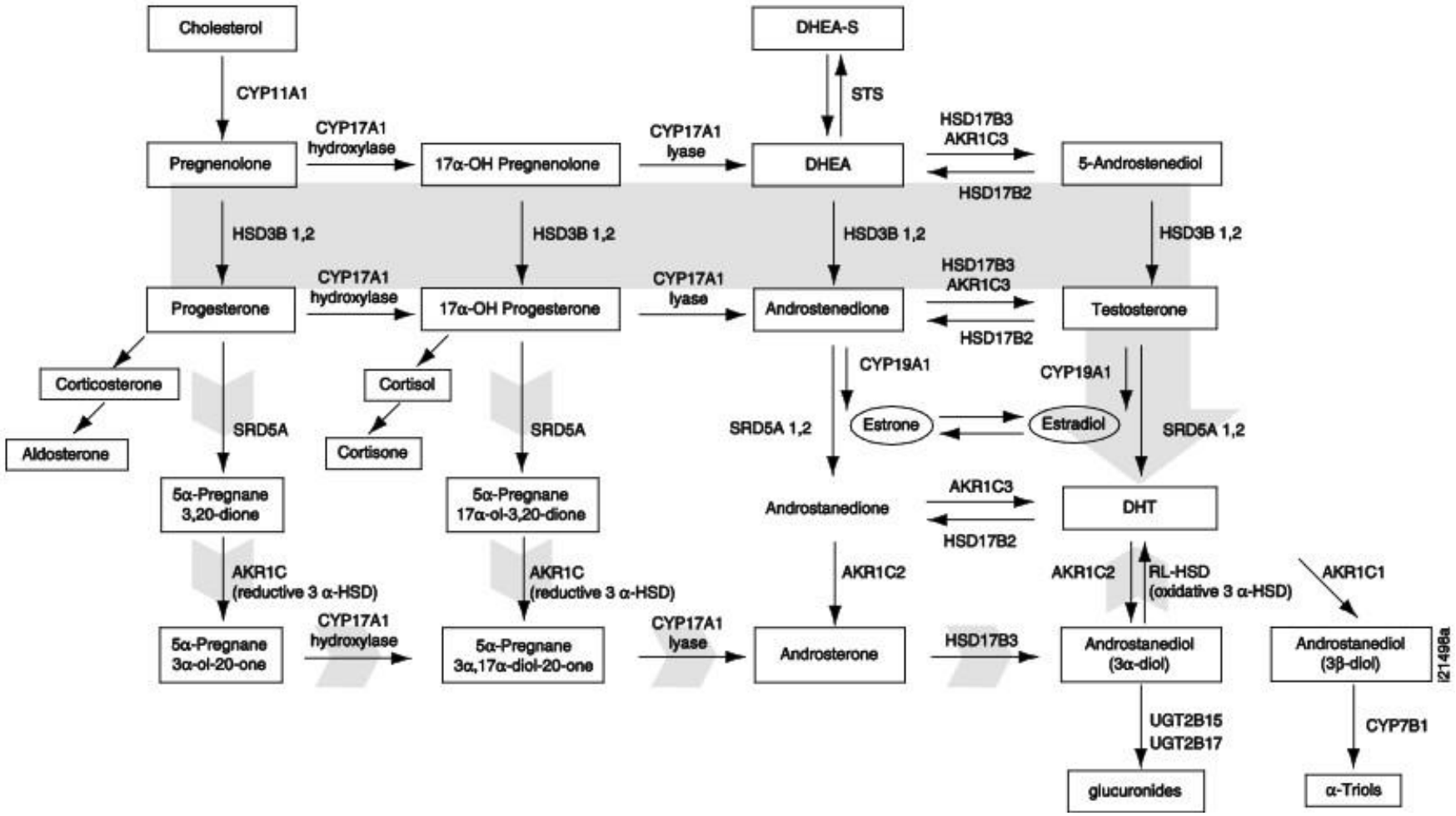
The clinical status of patients after failure of castration is commonly referred to as hormone-refractory prostate cancer (HRPC), or androgen-independent prostate cancer (AIPC). However, recent investigations have established that tumor progression often remains androgen-dependent, albeit at much reduced 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 the androgen receptor and its ligand remain pivotal in tumor growth. Prostate cancer progression after conventional medical or surgical castration should, therefore, be considered CRPC. Virtually all patients will develop CRPC despite ADT (Ryan et al, 2010b). While men with CRPC and metastatic disease have a median survival of 16 to 18 months, little is known about the natural history of CRPC without evidence of metastatic disease (Smith et al, 2005).

In the castrate state, ligands to the androgen receptor 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 patients with castrate levels of testosterone, the tissue levels of androgens remain sufficient to activate the androgen receptor. Furthermore, the androgen receptors are predominately located in the nucleus in biopsy tissue, indicating ligand-binding and the activation of androgen-dependent gene expression. Increased expression of the androgen receptor is common in advanced prostate cancer, and allows lower ligand levels to activate the androgen receptor more strongly (Chen et al, 2004). Complete androgen independence in CRPC is thought to be rare. A few patients (10%) have mutations in the androgen receptor (Taplin et al, 2003); these changes could allow the androgen receptor to be activated by non-androgen ligands, or might allow ligand-independent androgen receptor association with co-activator molecules.

There is recent evidence to support the existence of androgen biosynthesis at extratesticular sites. *In vitro* growth of a metastatic prostate cancer cell line, LNCaP cells, maintained physiologic levels of intracellular dihydrotestosterone (DHT; 10 nM) and proliferated despite castrate levels of testosterone in the media (Sedelaar et al, 2009). The xenograft cell line variant LuCaP35V was established from a recurring xenograft, LuCap35 cell line after castration, and it has been shown that the variant may also be androgen dependent as its growth was slowed when serum testosterone was suppressed to undetectable levels (Montgomery et al, 2009). In addition, androgen-regulated gene expression has been shown in prostatectomy specimens when the tumors were excised after as long as 9 months after neoadjuvant medical castration (Mostaghel et al, 2007).

There are 2 androgen biosynthesis pathways, classical and back-door. Two CYP17 enzymes (17 hydroxylyase and C17,20 lyase), play a crucial role in synthesizing key intermediates necessary for androgen synthesis. In the classical pathway, CYP17 enzymes are involved in the synthesis of testosterone from dehydroepiandrosterone (DHEA), androstenediol, and androstenedione observed in the testes, adrenal glands, and prostate. In the back-door pathway, DHT is synthesized from androstanediol without testosterone synthesis (Mostaghel and Nelson, 2008). Inhibition of testicular and extratesticular sources of androgens is considered to be a desirable therapeutic strategy, and CYP17 is considered a key therapeutic target (Figure 1).

Figure 1 Involvement of CYP17 in both classical and back-door pathways of androgen biosynthesis



Abiraterone is a selective and irreversible inhibitor of CYP17 and has demonstrated the ability to suppress testosterone levels below castrate levels (Mostaghel and Nelson, 2008). Rising PSA in non-metastatic prostate cancer occurs as a result of failure of initial local therapy, or in the setting of early hormone refractory prostate cancer prior to evidence of clinical metastases. PSA only recurrence or biochemical recurrence (BCR) occurs in up to 70,000 men each year after failed initial therapy (Moul et al, 2007). The incidence of rising PSA while on hormonal therapy without documented metastases is unknown, and evidence-based treatment options are limited.

Approximately 15-53% of patients undergoing primary curative therapy will develop BCR, which often precedes clinical detectable disease by years (Swindle et al, 2003). In a retrospective study, Pound et al (1999) demonstrated that only 34% of men with BCR developed metastatic disease following radical prostatectomy. The median time from development of BCR to identification of metastases was 8 years, and the median time from development of metastatic disease to death was 5 years. The risk of metastatic disease following BCR has been relatively well defined, and relates to prostate-specific antigen doubling time (PSADT). A PSADT of less than 6 to 12 months and a PSA recurrence of less than 12 months reflect a high risk of developing metastatic disease. The American Society of Therapeutic Radiology and Oncology has recommended the standard for BCR after radiation as a PSA rise by 2 ng/dL or increase above nadir, whether or not it is associated with endocrine therapy (Roach et al, 2006).

Local therapies such as salvage external beam radiotherapy to the prostate bed for patients having prior radical prostatectomy, and salvage radical prostatectomy or cryotherapy for patients with prior radiation therapy are commonly employed in men felt to have a low risk of distant metastases. Systemic therapies are focused primarily on ADT which consists of orchiectomy and gonadotropin-releasing hormone (GnRH) analog therapy which are the current mainstay of systemic treatment for BCR.

The decision to institute hormonal therapy has evolved into a risk-stratified approach in that PSA recurrence is generally a slow process, demonstrating that PSADT, Gleason sum, and timing of recurrence could be utilized to better assess for metastases and death (Pound et al, 1999). A follow-up study showed that for high risk PSA recurrence (PSADT < 12 months or Gleason 8-10), early hormones delayed clinical metastases (Moul et al, 2004).

In order to describe the natural history of CRPC without evidence of metastatic disease despite ADT, Smith et al (2005), reported on the outcomes of 201 placebo-treated patients from a study terminated before completion. At 2 years, 33% of the patients had developed bone metastases. Median bone metastasis-free survival was 30 months. Median time to first bone metastasis and overall survival were not met. Baseline PSA level greater than 10 ng/mL and PSA velocity independently predicted shorter time to first bone metastasis.

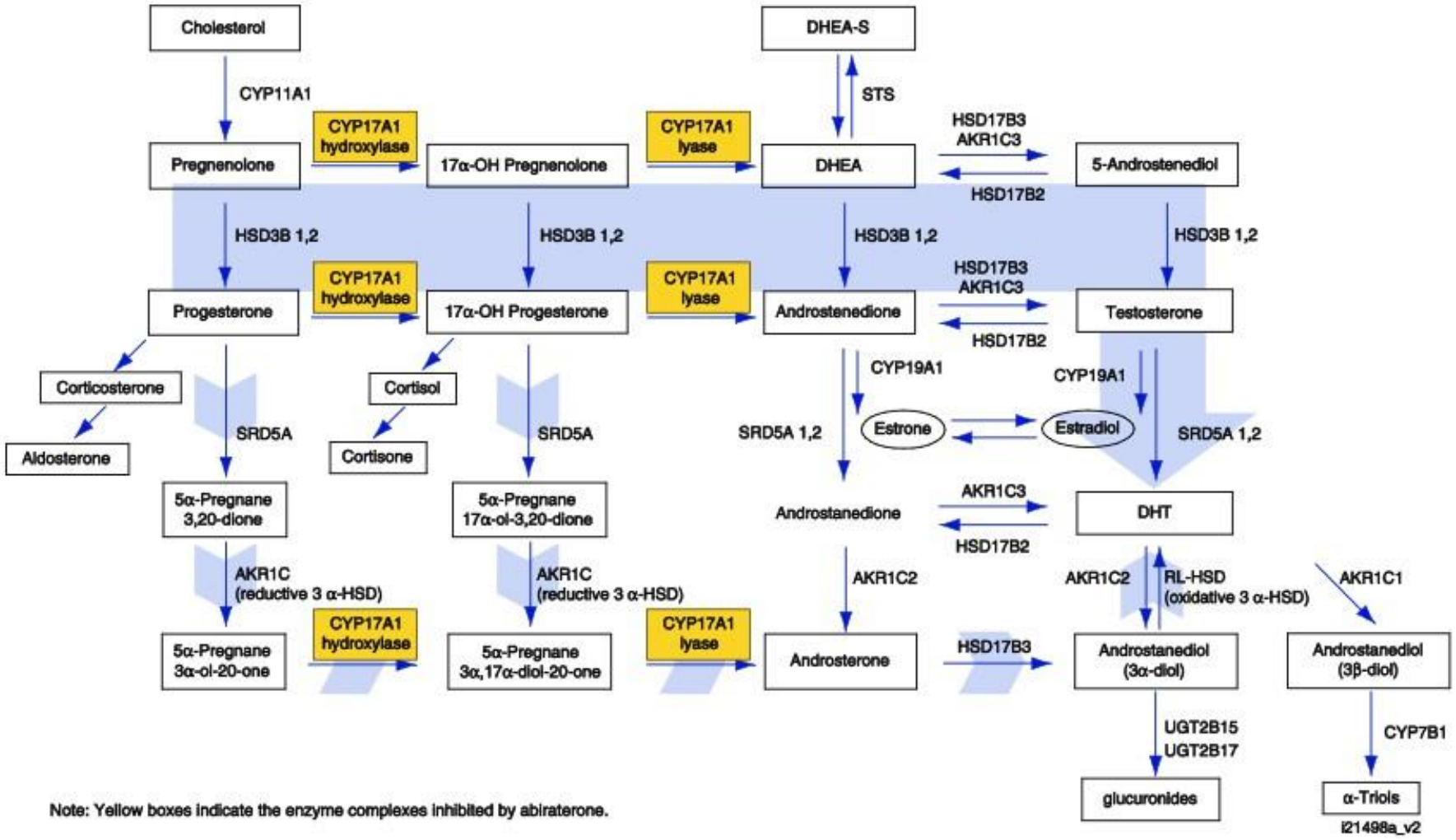
PSADT provides a dynamic picture of tumor behavior that may provide clues to the aggressiveness of underlying prostate cancer. It represents the relative rate of PSA change over time and is defined as the time needed for the PSA value to double. While Loberg et al, found no independent predictive value in the initial study of PSADT, the onset of CRPC significantly shortened PSADT, suggesting the emergence of more aggressive disease (Loberg et al, 2003). Ramirez et al (2008), reviewed the status of PSADT in various stages of prostate cancer, and found it to be an important prognostic factor in CRPC. Following ADT, PSADT maintains its value as a significant prognostic indicator and is now being included in nomograms. PSADT may also be a predictor for therapies in the CRPC population, as well a criterion in selecting patients for new therapeutic clinical trials.

In the setting of rising PSA in CRPC without metastases, the risk-stratified approach is recommended in the same manner as failure with initial therapy. The evidence-based treatment options are limited prompting the identification of a critical need for new pharmaceutical agents to treat this growing stage of prostate cancer (Moul et al, 2007).

1.2. Abiraterone and Abiraterone Acetate

Abiraterone (CB7598), [17-(3-pyridyl)androsta-5,16-dien-3β-ol], is an oral selective and irreversible inhibitor of CYP17. Abiraterone blocks 2 important enzymes (17α hydroxylase/C17,20-lyase) in the androgen biosynthesis pathways (Figure 2), based on the observation that nonsteroidal 3 pyridyl esters improve selectivity for inhibition of 17α-hydroxylase/C17,20 lyase.

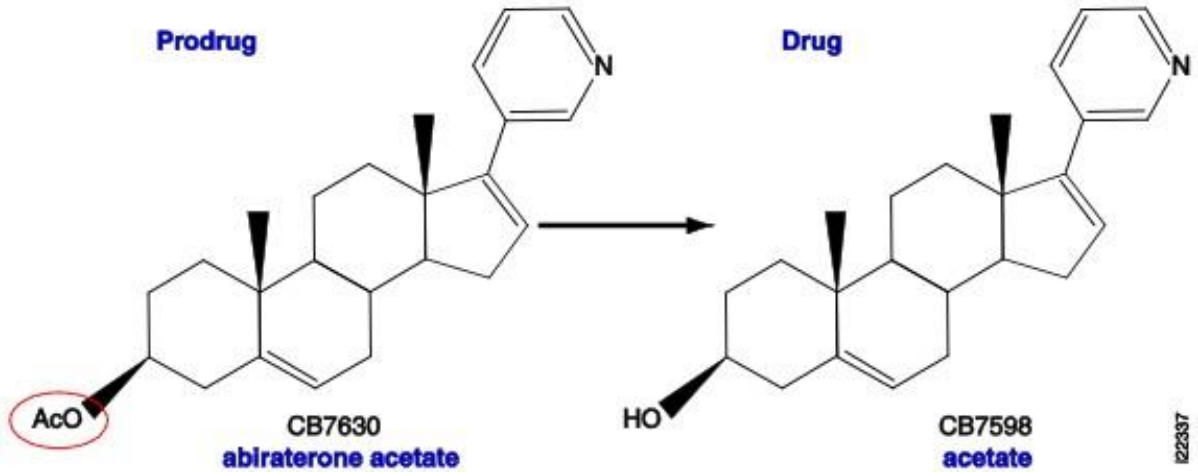
Figure 2 The enzyme complexes inhibited by abiraterone



Abiraterone is a potent inhibitor of CYP17 with an apparent inhibition constant of 0.5 nM. Pharmacodynamic studies have demonstrated that its effects on adrenal steroid synthesis are consistent with its mechanism of action. Antitumor effects were evidenced by PSA response as well as durable objective responses using Response Evaluation Criteria in Solid Tumors (RECIST) criteria in Phase 1 and Phase 2 studies conducted to date. Treatment with abiraterone acetate has led to undetectable testosterone levels < 1 ng/dL (Attard et al, 2008; Ryan et al, 2010a; see also the Investigator's Brochure).

Abiraterone acetate (CB7630) 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 $C_{26}H_{33}NO_2$ and molecular weight is 391.55. Once absorbed after oral administration, abiraterone acetate is rapidly converted to its active form, abiraterone (Figure 3).

Figure 3 Prodrug abiraterone acetate is converted to abiraterone after absorption



Abiraterone was the predominant, if not the only, metabolite of abiraterone acetate detected in blood, both in preclinical studies (Barrie et al, 1994) as well as in clinical studies (O'Donnell et al, 2004).

When this study was initiated, approximately 2,500 subjects had been treated with abiraterone acetate in Phase 1, 2, and 3 studies, with approximately 2,470 subjects at the 1000 mg dose level (data on file).

A Phase 1/2 study evaluated abiraterone acetate in 54 chemotherapy-naïve men with CRPC resistant to multiple hormonal therapies (n = 42 in Phase 2). Declines in PSA ≥ 30%, ≥ 50% and ≥ 90% were observed in 30 (71%), 28 (67%) and 8 (19%) of 42 subjects, respectively. By RECIST criteria, 24 subjects had measurable disease on CT scan with 9 subjects (37.5%) demonstrating a partial response (PR) and 16 (66%) subjects with no evidence of progression of

disease. Median time to PSA progression (TTPP) was 253 days for the subgroup of subjects with a ≥ 50% reduction in PSA (Attard et al, 2009).

Two Phase 2 studies in post-docetaxel CRPC subjects were also conducted. PSA declines of ≥ 50% occurred in 22 of 58 (36%) and 24 of 47 (51%) subjects, respectively, with the median TTPP of 169 days for both groups. PRs were seen in 4 of 22 (18%) subjects and 8 of 30 (27%) subjects with RECIST-evaluable target lesions, respectively. Abiraterone acetate has been shown to be well tolerated with encouraging antitumor activity in heavily pretreated CRPC subjects (Danila et al, 2010; Reid et al, 2010).

The most common adverse events related to abiraterone acetate monotherapy included fatigue due to reduced cortisol level as a result of CYP17 inhibition; and hypertension, fluid retention, and hypokalemia due to mineralocorticoid excess caused by compensatory adrenocorticotropic hormone (ACTH) drive. Co-administration of prednisone has been effective in mitigating symptoms of mineralocorticoid excess through negative feedback on ACTH production. In other studies, this was managed by treatment with eplerenone 50 to 200 mg daily (Attard et al, 2009).

The demonstrated effectiveness of abiraterone acetate in subjects with metastatic CRPC suggested that a similar benefit could be seen in earlier disease. Therefore, the current study was undertaken to evaluate abiraterone acetate plus prednisone in subjects diagnosed with non-metastatic CRPC who have a rising PSA despite crpcte levels of testosterone in order to investigate a novel androgen biosynthesis inhibitor in this area of a critical unmet need for this growing stage of prostate cancer with limited evidenced-based systemic therapies.

Originally, the study was designed such that subjects who had radiographic evidence of metastatic disease progression were to discontinue treatment with abiraterone acetate. After initiation of this study, abiraterone acetate in combination with prednisone was approved for use in patients with metastatic CRPC. The protocol was amended (Protocol Amendment 3) to provide those subjects having radiographic evidence of disease progression the option to continue to receive abiraterone acetate. This Optional Post-metastatic Disease Follow-up Phase was intended to provide descriptive information about longer term safety and subjects' response to abiraterone acetate plus prednisone after metastatic disease progression.

At this time, only a very limited number of subjects have taken advantage of this option, and as abiraterone acetate with prednisone is approved and available for metastatic CRPC, this option was eliminated from the protocol (Protocol Amendment 4). The few subjects (n=3) who continued into this Phase prior to Protocol Amendment 4 are permitted to continue on study; however, no further subjects were to be enrolled in this phase. Once a subject has documented metastatic disease progression, he is to be discontinued from abiraterone acetate.

In addition, following the sensitivity analysis for rPFS, the protocol (Protocol Amendment 4) was also modified to streamline procedures in the Pre-metastatic Disease Follow-up Phase such that imaging and safety evaluations are to be conducted locally per standard of care.

In addition, per Protocol Amendment 6, an Optional Drug Holiday Phase has been added to the protocol; further details on this phase of the study are provided in section 1.3. Rationale for Optional Drug Holiday Phase and the study schematic for the Optional Drug Holiday Phase.

As acquired genetic mutations in the androgen pathway may lead to resistance to drug treatment, biomarker evaluation may provide information on these changes that are associated with resistance to drug treatment and disease progression. Hence, blood sample collection was added to the protocol (Protocol Amendment 4) to evaluate gene expression from a panel of RNA and DNA biomarker candidates. Additional markers associated with the disease and treatment may be evaluated based on emerging evidence.

1.3. Rationale for Optional Drug Holiday Phase

As of July 2018, 16 subjects remain on study with a median duration of response of 69.3 months (60.4 - 86.3 months). This prolonged response may suggest that the subjects no longer require medication and may benefit from a period where they are not subject to the side effects of the medications (abiraterone acetate, prednisone, and ADT). The option for a "drug holiday" is consistent with other oncologic therapies and with a standard of care approach (Li et al, 2013; Petrioli et al, 2015).

If subjects choose to enroll in the Optional Drug Holiday Phase , they will have the option to return to study drug if a relapse (defined as PSA increase and confirmed as nonmetastatic by a negative conventional scan) occurs within the first year. In this first year, subjects will be closely monitored. In the second year of the Optional Drug Holiday Phase , they will follow standard of care disease management as directed by their physician. If no disease progression is detected within 2 years, patients will be considered as stable and at low risk of progression and will have completed this study. If patients later experience increases in PSA, there are now FDA approved treatment options (apalutamide [Erleada™] or enzalutamide [Xtandi®]) as well as clinical trials for patients with non-metastatic CRPC at their physician's discretion, whereas when the study was initiated, there were no options.

2. OBJECTIVES

Primary Objective

To demonstrate that abiraterone acetate plus prednisone effectively decreases PSA in subjects with non-metastatic CRPC who have a rising PSA despite castrate levels of testosterone.

Secondary Objectives

- ☐ To describe the time to radiographic progression of disease in subjects treated with abiraterone acetate in addition to the current standard of care.
- ☐ To describe the safety profile of abiraterone acetate when taken with prednisone 5 mg daily.

Exploratory Objectives

- ☐ To describe the duration and type of subsequent cancer therapy in subjects after radiographic disease progression.
- ☐ To evaluate exploratory biomarkers predictive of resistance to abiraterone acetate treatment.
- ☐ Optional Drug Holiday Phase:
  - To evaluate if patients who demonstrate no signs of disease progression (radiographic or PSA) after > 5 years of treatment for non-metastatic CRPC may no longer require medications that suppress the androgen signaling pathway.
  - To evaluate PSA kinetics after withdrawal of abiraterone acetate plus prednisone and androgen deprivation therapy (ADT) in patients participating in this study phase

Hypothesis: Abiraterone acetate plus prednisone, by decreasing testosterone levels, will further decrease PSA levels in this subject population.

Optional Drug Holiday Phase: Subjects who demonstrate no signs of disease progression after > 5 years of treatment may no longer require medications that suppress the androgen signaling pathway and may benefit by not being subjected to the side effects of these medications (abiraterone acetate, prednisone, and ADT.

3. OVERVIEW OF STUDY DESIGN

3.1. Study Design

This is a Phase 2, prospective, multicenter, open-label, single-arm study of abiraterone acetate plus prednisone in subjects with non-metastatic CRPC with a rising PSA despite castrate levels of testosterone. Approximately 125 subjects will be enrolled at approximately 40 sites in the US.

The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28-day cycles); a Pre-metastatic Disease Follow-up Phase, an Optional Drug Holiday Phase; and a 30-day Safety Follow-up Visit as described in further detail below. A study treatment cycle is 28 days.

Subjects eligible for this study include men ≥ 18 years of age with histologically- or cytologically-confirmed prostate cancer without evidence of neuroendocrine differentiation or small cell histology. The central reader must confirm that there is no metastasis on imaging scans before a subject is enrolled. Full details of inclusion and exclusion criteria are provided in Section 4.

After providing written informed consent, eligible subjects will receive abiraterone acetate 1000 mg once daily, prednisone 5 mg once daily, and their regularly prescribed GnRH monotherapy (see Section 6.1 for further details on treatments to be administered). Study agents (abiraterone acetate and prednisone) will be dispensed on Day 1 of each cycle. Note that if prednisone and/or GnRH monotherapy are discontinued, a subject may continue to receive abiraterone acetate and continue on study as scheduled. If a subject needs to discontinue either of these therapies, the appropriate medical management of the subject needs to be discussed with the Medical Monitor. If abiraterone acetate is discontinued, prednisone should also be discontinued as described in Section 10.2, and the subject should be discontinued from the study as described in Section 10.3 unless the subject has consented to the participate in the Optional Drug Holiday Phase as described below under "Optional Drug Holiday Phase.

During the Core Study Treatment Phase, in Cycles 1, 2, and 3, subjects will be required to return to the study site twice per cycle (Days 1 and 15). In Cycles 4 through 6, subjects will be required to return to the study site on Day 1 of each cycle. Additional visits may occur as clinically indicated. The End of Core Study Treatment Visit is to occur as follows:

- ☐ On Day 1 of Cycle 7;
- ☐ At the time of discontinuation of abiraterone acetate if discontinuation occurs prior to completion of the Core Study Treatment Phase;
- ☐ If possible, at the time of withdrawal from the study if withdrawal occurs prior to completion of the Core Study Treatment Phase; or
- ☐ In the event of radiographic evidence of disease progression prior to completion of the Core Study Treatment Phase.

During the Core Study Treatment Phase, efficacy will be measured by PSA levels, testosterone levels, and imaging studies (bone scans, and computed tomography [CT] or magnetic resonance imaging [MRI] of the chest, abdomen, and pelvis); a central laboratory will be used for PSA and testosterone evaluations. In addition, imaging studies will be read by both local readers and a central reader, and the results will be discussed in consultation with the sponsor, as described in further detail in Section 9.2.

Safety and tolerability will be assessed by complete physical examinations, vital signs, weight, examination for volume overload, 12-lead electrocardiograms (ECGs), laboratory tests (prothrombin time [PT]/partial thromboplastin time [PTT], international normalized ratio [INR], hematology, serum chemistry, fasting glucose, serum lipids, and liver function tests), compliance checks, and recording of adverse events and concomitant medications; laboratory evaluations will be conducted using a central laboratory.

Note that at the time of the current protocol, the Core Study Treatment Phase has been completed.

After the Core Study Treatment Phase, subjects may enter the Pre-metastatic Disease Follow-up Phase and continue to receive abiraterone acetate until metastatic disease progression is confirmed. If the subject elects to participate in the Optional Drug Holiday Phase subject will discontinue abiraterone acetate plus prednisone and ADT. During the Pre-metastatic Disease Follow-up Phase, subjects will be required to return to the study site at the start of each cycle to receive study agents. Assessments will be limited to blood sample collection for biomarker analysis, monitoring of study treatment compliance, safety reporting, and documentation of changes in prostate cancer disease status and therapy. All evaluations will be done locally per standard of care, with the exception of biomarker analysis, which will be done using a central laboratory. Note that while disease status is to be evaluated locally per standard of care, disease progression is to be determined using RECIST criteria as described in Section 9.2. Subjects may receive additional therapies at the investigator's discretion during this phase, with the exception of those noted in Section 8.2.2.1.

OPTIONAL DRUG HOLIDAY PHASE:

During the Pre-metastatic Disease Follow-up Phase subjects who demonstrate no signs of radiographic or PSA disease progression after > 5 years of study treatment may choose to participate in this phase. During the Optional Drug Holiday Phase, subjects will discontinue abiraterone acetate plus prednisone and ADT. During the first year in this phase, subjects will be monitored closely for signs of PSA progression and will have the option to return to study medication if there is evidence of disease progression, confirmed as nonmetastatic by a negative conventional scan. Refer to the Time and Events Schedule for procedures to be performed and timing of assessments. If after one year, there are no signs of PSA progression, subjects will be followed for an additional year but will not have the option to return to study medication if progression is noted after 12 months off medication.

Note that prior to Protocol Amendment 4, subjects may have continued to receive abiraterone acetate in an Optional Post-metastatic Disease Follow-up Phase. While the option to enter the Post-metastatic Disease Follow-up Phase no longer exists, subjects who continue in the Post-metastatic Disease Follow-up Phase at the time of Protocol Amendment 6, may remain on study. All subjects will be required to return to the study site 30 days after receiving their last dose of abiraterone acetate for safety follow-up.

Subjects may remain on abiraterone acetate until the subject elects to participate in the Optional Drug Holiday Phase or until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, or until the sponsor determines it is necessary to stop the study.

A schedule of events showing the timing of procedures is provided in the Time and Events Schedule for Procedures to be Performed, and a flow chart depicting subject participation in the study is provided in the Time and Events Schedule for Subject Participation in the Study and the Study schematic for the Optional Drug Holiday Phase.

The primary endpoint of the study is the proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit. Secondary efficacy endpoints and statistical analyses are described in further detail in Sections 9.2 and 11.2.

The duration of study participation was anticipated to be approximately 2 years. The completion of the entire Core Study Treatment Phase is defined as the time at which the last subject completes the End of Core Study Treatment Visit. The end of the study is defined as the point at which all subjects have progressed to metastatic disease.

3.2. Study Design Rationale

The trial objective endpoints are defined on the basis of preventing or delaying disease manifestations expected to occur in the non-metastatic, PSA rising group of prostate cancer subjects (Scher et al, 2008). In this Phase 2 study, subjects will have a rising PSA while demonstrating a serum testosterone level in the castrate range without evidence of metastatic disease. This study will include measures of response (PSA) as well as measures of testosterone and radiographic progression. Studies in subjects with metastatic disease treated with abiraterone acetate have demonstrated an impressive ability to suppress PSA at 12 weeks. In this study, PSA suppression will be measured after 3 cycles of treatment; however, the primary endpoint will be to show a sustained suppression after 6 cycles of treatment. After the primary endpoint, subjects may continue to receive abiraterone acetate and will be followed for the duration of their participation in the study.

The abiraterone acetate dose utilized in this study was selected based on results of 2 Phase 1 dose-finding studies. In the first Phase 1 study with capsule formulation (Attard et al, 2008), abiraterone acetate was evaluated for safety, pharmacokinetics, and its effects on adrenal steroid synthesis at dose levels ranging from 250 mg to 2000 mg. Preliminary analysis showed that abiraterone acetate had an acceptable safety profile at all dose levels. Subjects have received abiraterone acetate in that study and an extension protocol for up to 30 months. In the second Phase 1 study (refer to the Investigator's Brochure) that evaluated the safety and tolerability of abiraterone acetate tablet formulation at doses ranging from 250 to 1000 mg, a daily dose of 1000 mg was also found to have an acceptable safety profile for further clinical development.

Pharmacokinetic studies showed increased systemic drug exposure at higher doses. Adrenal metabolite analysis showed inhibition of CYP17 even at low doses of abiraterone acetate and a compensatory increase of corticosterone and deoxycorticosterone. Data from dose-finding studies indicated that when pharmacokinetic, adrenal CYP17 inhibition, and efficacy signals

were taken into consideration, the 1000 mg dose offered consistent pharmacological effects without additional side effects. Therefore, the 1000 mg dose has been chosen for further efficacy and safety evaluation in this Phase 2 study.

Data from early studies have contributed to the current understanding of the mechanism of abiraterone acetate action. These suggest that a state of mineralocorticoid excess can occur after pharmacologic inhibition of CYP17, with the resulting reduced cortisol levels leading to a compensatory ACTH surge and accompanying hypertension, hypokalemia, and fluid retention (Attard et al, 2009). These side effects have been readily managed with low-dose corticosteroids, potassium supplementation, antihypertensive agents, as well as eplerenone (selective mineralocorticoid antagonist). Grade 1-2 fatigue was observed in some subjects and was associated with discontinuation of corticosteroids as required per Phase 2 protocol entry criteria and extended duration of treatment with abiraterone acetate. Although there was no evidence of an abiraterone acetate dose-response relationship, administration of low dose corticosteroids improved symptoms of fatigue and tolerability of abiraterone acetate, including symptoms of mineralocorticosteroid excess. The improved tolerability of abiraterone acetate after concomitant administration of low-dose corticosteroids was associated with suppression of ACTH and upstream adrenal steroids, suggesting that this combination may be a better tolerated and safer regimen in this older and frail subject population. Prednisone was selected over other corticosteroids because it is commonly used as standard of care (Heidenreich et al, 2008) in combination with approved chemotherapy agents or as a monotherapy for palliation of symptoms.

The current study will be evaluating a dose of prednisone 5 mg once daily. Due to the potential longer duration of CYP17 inhibition with abiraterone acetate in the treatment of asymptomatic subjects with undetectable metastatic prostate cancer, it was felt that the lowest effective dose of prednisone would be most desirable. One of the secondary objectives will be to describe the safety of abiraterone acetate in combination with this lower dose of prednisone.

4. STUDY POPULATION

4.1. General Considerations

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria, the investigator should consult with the appropriate sponsor representative before enrolling the subject in the study.

4.2. Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study. Subjects ***must***:

1. Be a male ≥ 18 years of age.
2. Have adenocarcinoma of the prostate with histological or cytological confirmation without neuroendocrine differentiation or small cell histology.
3. Criterion modified per amendment.

   3.1. Subjects must currently be receiving and have been receiving continuous treatment with GnRH monotherapy for at least 6 months before screening with a serum testosterone level of < 50 ng/dL (< 2.0 nM) or have undergone an orchiectomy with a serum testosterone level of < 50 ng/dL (< 2.0 nM).
4. Criterion modified per amendment.

   4.1. Have rising PSA defined as a PSA of ≥ 10 ng/mL obtained at screening or PSADT of ≤ 10 months with the first of the 3 consecutive PSA values used to calculate PSADT ≥ 2.0 ng/mL. See Attachment 3 for a description of how to calculate PSADT.
5. Criterion modified per amendment.

   5.1. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. 6.

Criterion modified per amendment.

   6.1. Have a baseline serum potassium of ≥ 3.5 mEq/L. See Section 6.2.1.

7. Criterion modified per amendment.

   7.1. Have a hemoglobin of ≥ 9.0 g/dL.
8. Have an absolute neutrophil count of > 1500 cell/mm^3.
9. Have a platelet count of ≥ 100,000/µL.
10. Criterion modified per amendment.

    10.1. Have normal PT/PTT (INR). For patients not receiving anticoagulants, this means the patient is normal according to the lab values. In the case of patients receiving anticoagulants, the investigator will determine the appropriate therapeutic target for that patient and whether the INR obtained at screening is acceptable.
11. Have a serum albumin of ≥ 3.0 g/dL.
12. Criterion modified per amendment.

    12.1. Have a calculated creatinine clearance ≥ 60 mL/min.
13. Have aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels < 1.5 x ULN.
14. Be capable of swallowing study agents whole as a tablet.
15. Be willing/able to adhere to the prohibitions and restrictions specified in this protocol.
16. Have signed an informed consent document indicating that the subject understands the purpose of and procedures required for the study and are willing to participate in the study.

4.2.1. Optional Drug Holiday Phase Inclusion

1. Patients on study who demonstrate no signs of disease progression (radiographic or PSA) after >5 years of treatment.

2. Negative scan within the previous 3 months.

3. PSA values < 25% above nadir or < 10 ng/mL within the previous 3 months.

4. Have signed an informed consent document indicating that the subject understands the purpose of and procedures required for this phase of the study and are willing to participate in this phase of the study.

4.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study. Subjects ***must not***:

1. Have prior or current evidence of local disease progression or metastatic disease as defined by modified RECIST criteria.
2. Criterion modified per amendment.
   2.1. Have received chemotherapy for treatment of CRPC; however, if a patient received chemotherapy in an adjuvant setting, prior to having CRPC, for castrate-sensitive prostate cancer, the patient is still eligible.
3. Criterion deleted per amendment.
4. Criterion modified per amendment.
   4.1. Criterion modified per amendment.
   4.2. Are currently receiving any antiandrogen therapy (eg, bicalutamide, flutamide, or nilutamide).
      ☐ If previously treated with antiandrogen therapy, there must be documentation of at least 2 consecutive rising PSA values at least 2 weeks apart obtained prior to screening.
         ☐ If previously treated with flutamide, at least 1 of the PSA values must be obtained 4 weeks or more after flutamide discontinuation.
         ☐ If previously treated with bicalutamide or nilutamide, at least 1 of the PSA values must be obtained 6 weeks or more after antiandrogen discontinuation.
5. Have an active infection or other medical condition that would contraindicate prednisone use. 6.

Criterion deleted per amendment.

7. Have uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg); subjects with a history of hypertension are permitted in the study provided their blood pressure is controlled by anti-hypertensive therapy.
8. Have active hepatitis or chronic liver disease.
9. Have a history of pituitary or adrenal dysfunction.

10. Have clinically significant heart disease as evidenced by myocardial infarction or arterial thrombotic events in the past 6 months, severe or unstable angina, New York Heart Association Class III or IV heart disease, or left ventricular ejection fraction of < 50% at baseline.
11. Have poorly controlled diabetes.
12. Have a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents.
13. Have received an investigational therapeutic within 30 days of screening.
14. Have a pre-existing condition that warrants long-term corticosteroid use in doses in excess of prednisone 5 mg once daily.
15. Have known allergies, hypersensitivity, or intolerance to abiraterone acetate or prednisone or their excipients (refer to the Pharmacy Reference Manual for further description of the study agents).
16. Be taking or require the use of prohibited medications as listed in Section 8.2.2.
17. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements.
18. Criterion modified by amendment.

    18.1. Have partners of childbearing potential and are not 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.

19. Criterion modified by amendment.

    19.1. Individuals with a history of a non-prostate malignancy are ineligible for this study with the following exceptions. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 3 years: basal cell or squamous cell carcinoma of the skin.

20. Have previously received agents having any CYP17 inhibitory activity for the treatment of prostate cancer, such as ketoconazole.
21. Have previously received aminoglutethimide.

5. TREATMENT ALLOCATION

This is a single-arm, open-label study.

6. DOSAGE AND ADMINISTRATION

6.1. Description of Study Agents and Administration

Study agents include abiraterone acetate and prednisone. Subjects are to receive the following:

- ☐ Abiraterone acetate 1000 mg (4 x 250 mg tablets by mouth [PO] once daily, taken on an empty stomach). Subjects should not eat for at least 2 hours before and for at least 1 hour after taking abiraterone acetate.
- ☐ Prednisone 5 mg (2 x 2.5 mg tablets PO once daily, preferably with food).

Although not considered a study agent, subjects will also receive their regularly prescribed GnRH monotherapy (to be administered as prescribed).

Sufficient study medication for an entire 28-day cycle will be distributed on the first day of each cycle. Subjects will begin taking study agents on Day 1 of Cycle 1.

If prednisone and/or GnRH monotherapy are discontinued, a subject may continue to receive abiraterone acetate and continue on study as scheduled. If a subject needs to discontinue either of these therapies, the appropriate medical management of the subject needs to be discussed with the Medical Monitor. If abiraterone acetate is discontinued, prednisone should also be discontinued as described in Section 10.2, and the subject should be discontinued from the study as described in Section 10.3 unless the subject has elected to participate in the Optional Drug Holiday Phase as described in Section 3.1 Optional Drug Holiday Phase.

The dose of prednisone may be altered if clinically indicated in discussion with the sponsor. In the event that the abiraterone acetate dose is changed (but not discontinued) per protocol or in discussion with the sponsor, the dose of prednisone will remain unchanged. If an abiraterone acetate or prednisone dose is missed, dosing should not be made up that day; however, treatment with study agent(s) is to resume the following day.

6.2. Abiraterone Acetate Dose Adjustment in the Event of Toxicity

Based upon experience from Phase 1 through Phase 3 studies, abiraterone acetate is generally well tolerated. The most common adverse events related to abiraterone acetate monotherapy include fatigue due to reduced cortisol level as a result of CYP17 inhibition; and hypertension, fluid retention, and hypokalemia due to mineralocorticoid excess caused by compensatory ACTH drive. In this study, the concomitant administration of prednisone is expected to mitigate these side effects by supplementing cortisol and abrogating ACTH drive.

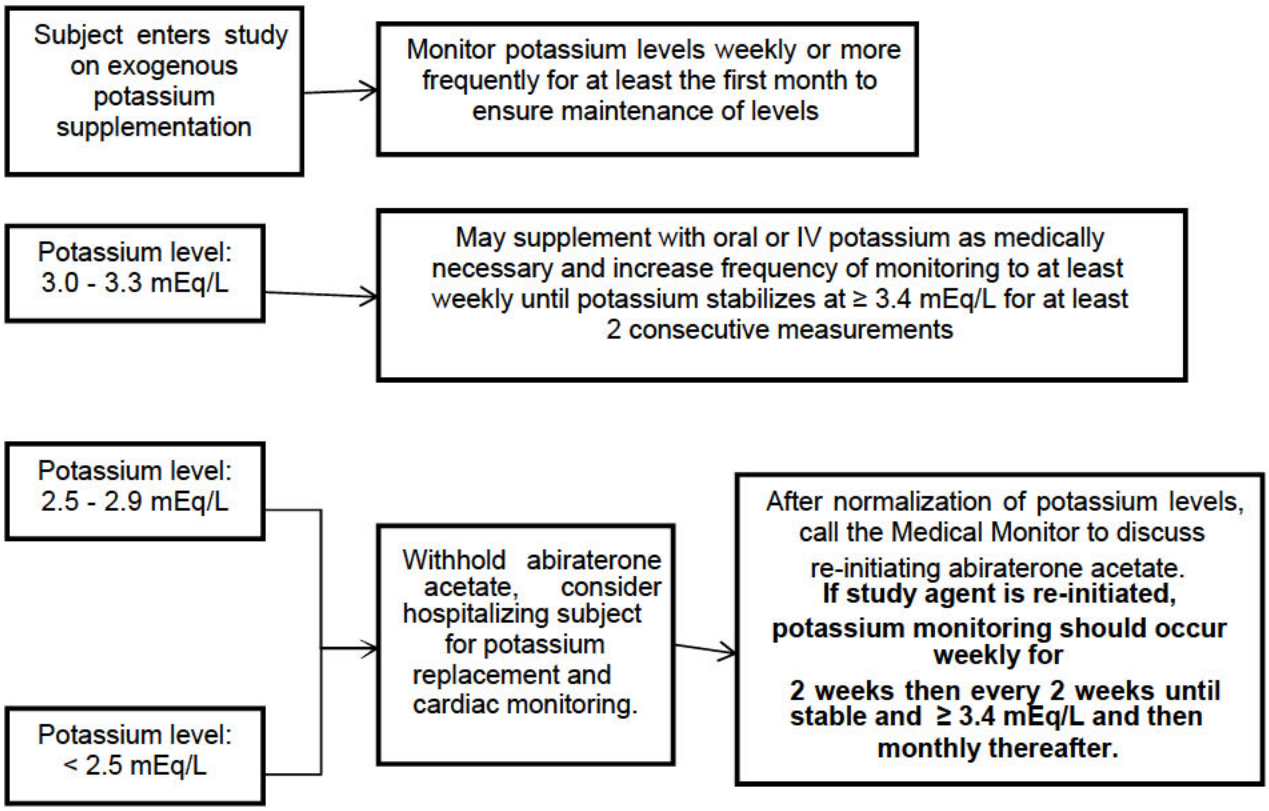
It has been documented that following prolonged therapy with corticosteroids, subjects may develop Cushing's syndrome characterized by central adiposity, thin skin, easy bruising, and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia,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

For guidance on management of side effects of prednisone usage, symptoms related to castration (androgen deprivation), severe and refractory headaches, fatigue, or other toxicities, please contact the medical monitor.

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

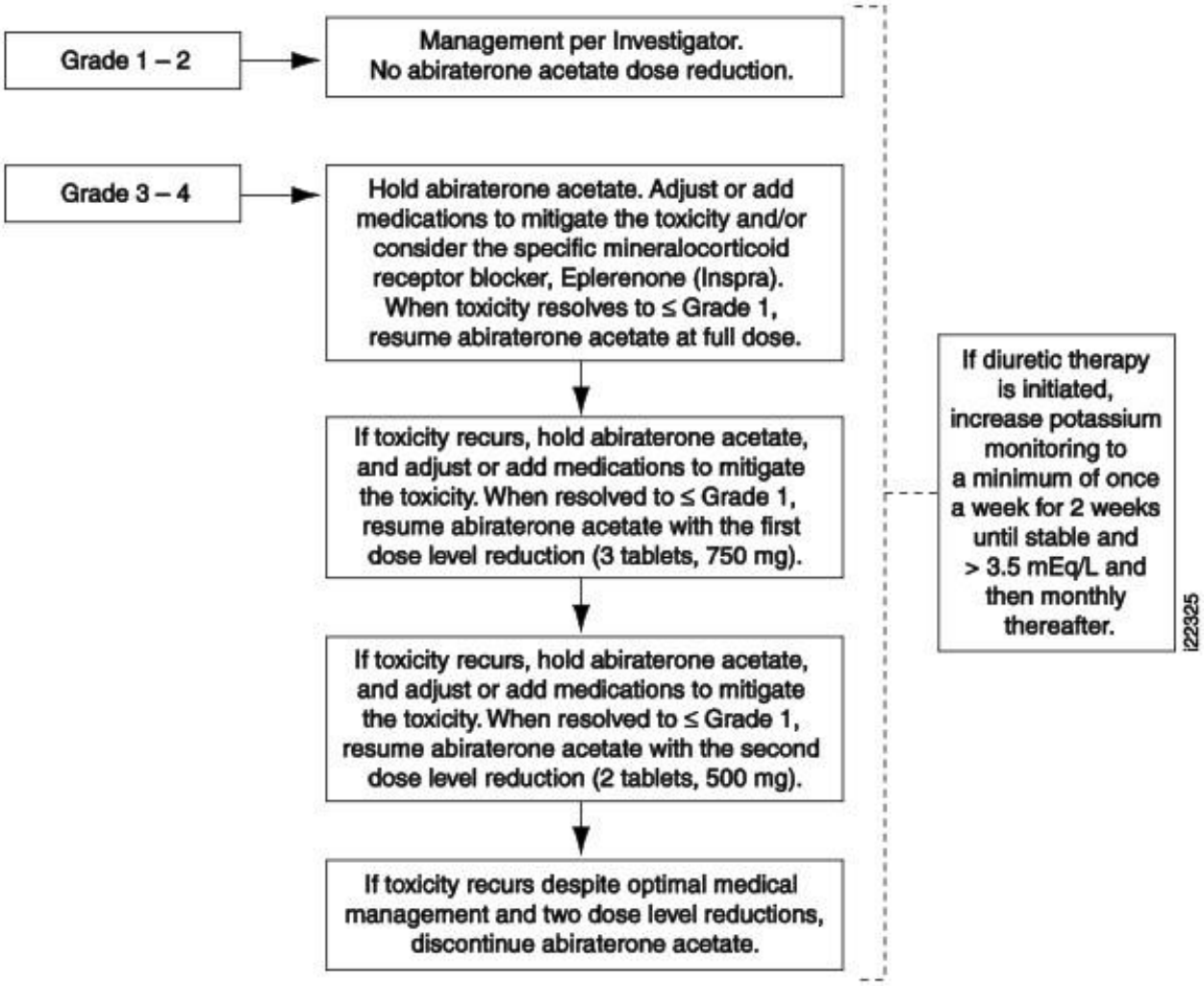
6.2.1. Management of Hypokalemia

Figure 4 Management of hypokalemia



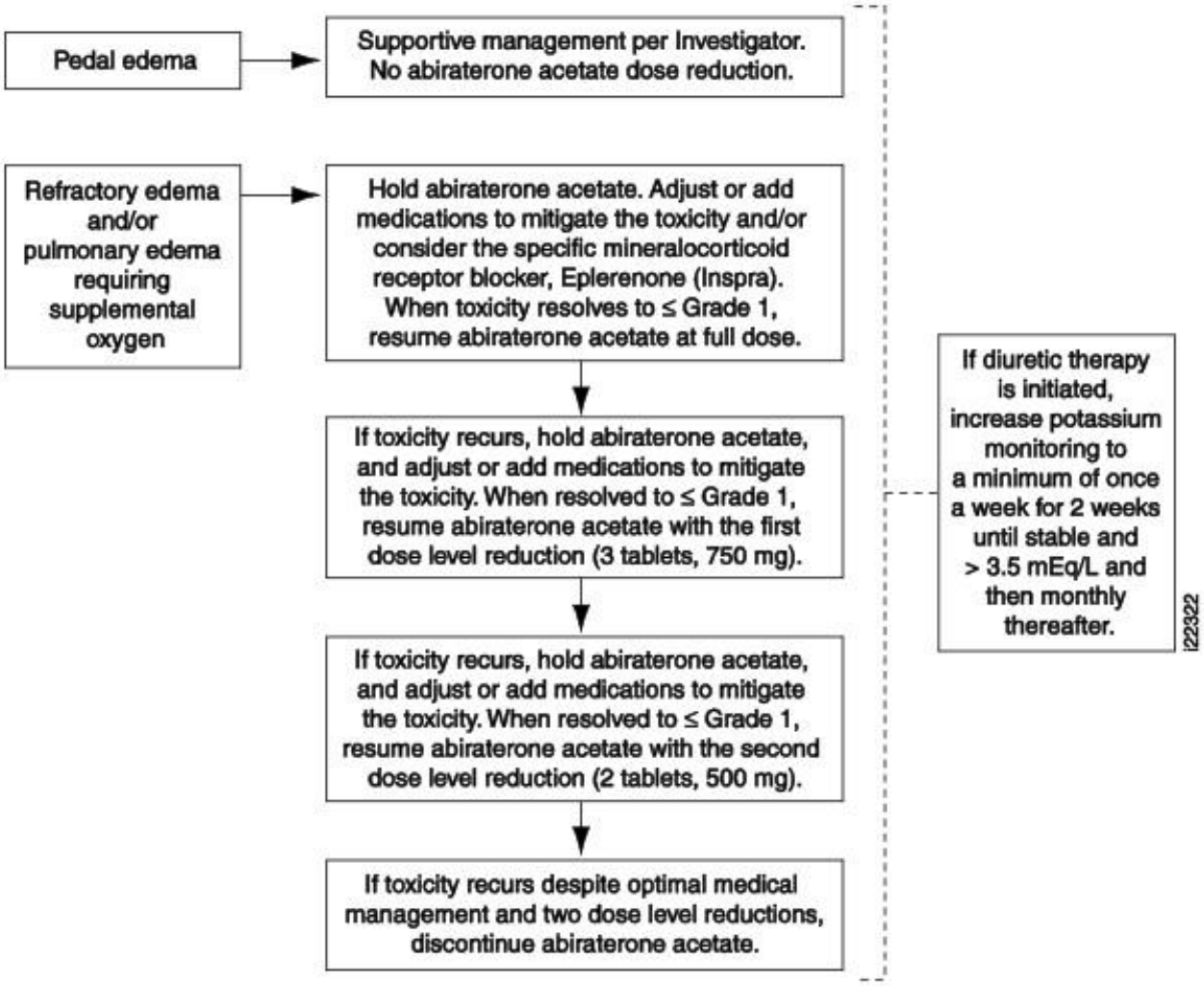
6.2.2. Management of Hypertension

Figure 5 Management of hypertension



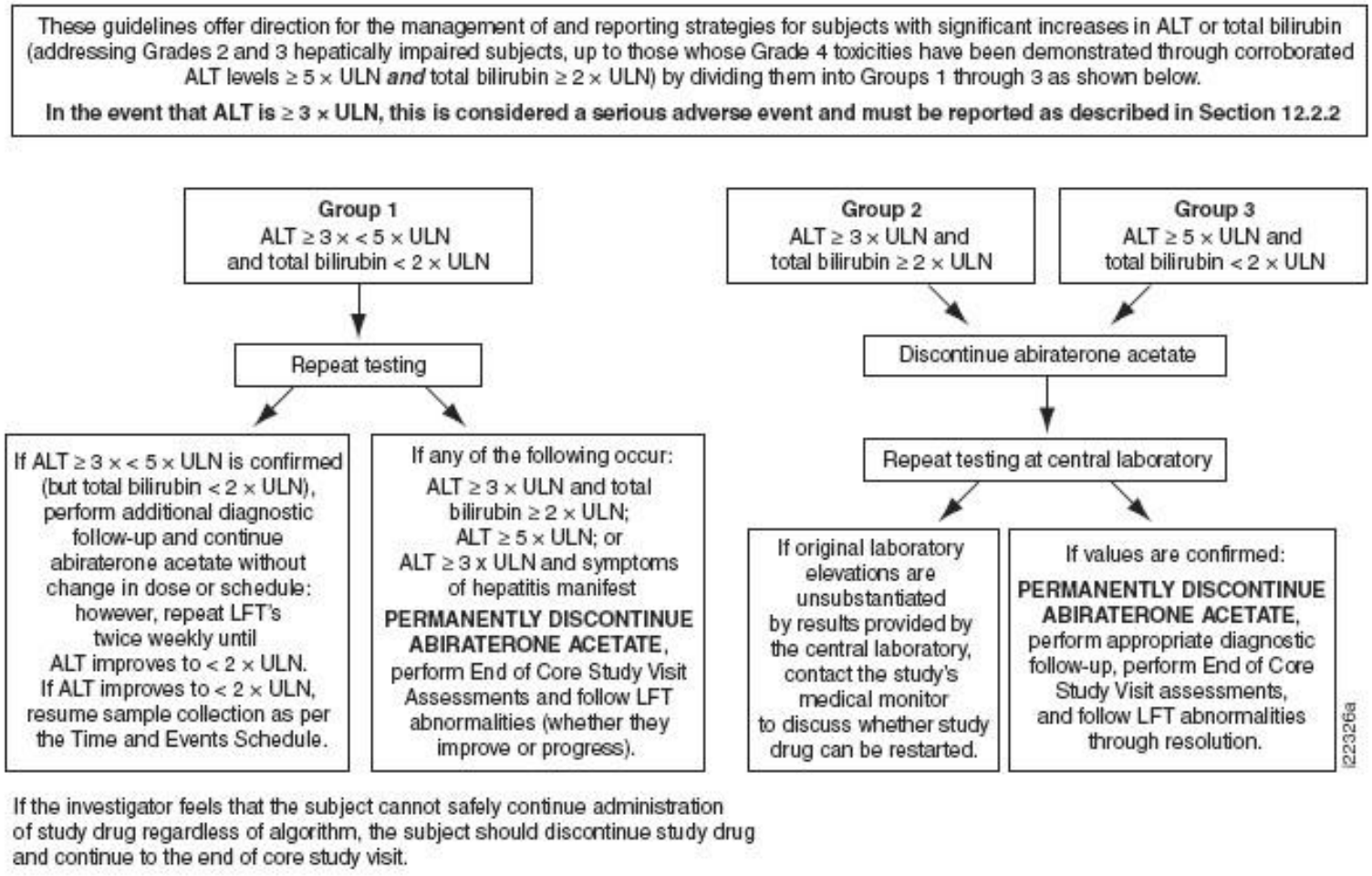
6.2.3. Management of Edema/Fluid Retention

Figure 6 Management of edema/fluid retention



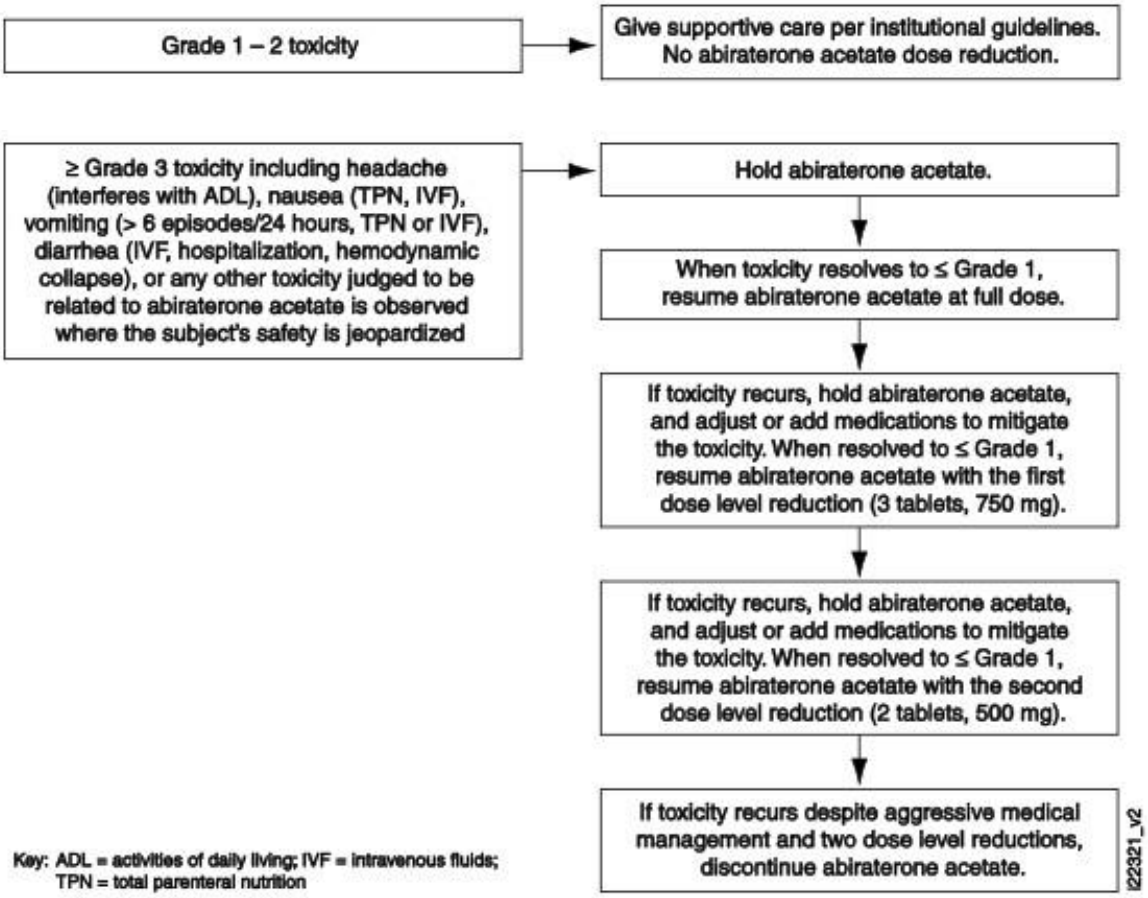
6.2.4. Management of Abnormal Liver Function Tests

Figure 7 Management of abnormal liver function tests



6.2.5. Management of Non-mineralocorticoid Based Side Effects

Figure 8 Management of non-mineralocorticoid based side effects



6.2.6. Abiraterone Acetate Dose-reduction Procedure for Adverse Event Management

In the event where dose-reduction is used for adverse event management, 2 dose reductions are allowed. At each dose reduction, one tablet of abiraterone acetate is to be removed, eg, 4 → 3 tablets, and 3 → 2 tablets. Any return to protocol dose level after dose reduction must follow documentation of resolution of the adverse event and a discussion with the medical monitor.

7. TREATMENT COMPLIANCE

Beginning in Cycle 2, compliance checks are to be performed on Day 1 of each cycle for information from the previous cycle. Study personnel will maintain a log of all study agents administered. Drug supplies for each subject will be inventoried and accounted for. Reasons for missed doses must be noted on the appropriate case report form (CRF) page.

8. PRE-STUDY AND CONCOMITANT THERAPY

All pre-study therapies administered up to 30 days prior to screening that are no longer being taken at the time of screening will be recorded at screening as prior medications.

Concomitant therapies to be recorded include those that are ongoing at the time of screening as well as therapies that are started up to 30 days after the last dose of abiraterone acetate.

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study agents must be recorded in the concomitant therapy section of the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

8.1. Pre-study Therapy

To be eligible for this study, subjects must be currently receiving and have received GnRH monotherapy for at least 6 months prior to screening unless the subject has undergone orchiectomy.

8.2. Concomitant Therapy

8.2.1. Permitted Therapy: Prior to or Following Metastatic Disease Progression

Note that the following permitted therapy applies to those who have not had metastatic disease progression and to the limited number of subjects currently enrolled in the Optional Post-metastatic Disease Follow-up Phase. Per Protocol Amendment 4, no further subjects were to continue on study after metastatic disease progression.

Supportive care medications are permitted with their use following institutional guidelines. Concurrent treatment with GnRH monotherapy is mandatory at screening and must be recorded unless the subject has undergone orchiectomy.

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

- ☐ Conventional multivitamins, selenium, and soy supplements
- ☐ Additional systemic glucocorticoid administration such as “stress dose” glucocorticoid is permitted if clinically indicated for a life-threatening medical condition, and in such cases, the use of steroids are to be documented as a concomitant drug
- ☐ Bisphosphonate and denosumab usage is allowed
- ☐ Transfusions and hematopoietic growth factors per institutional practice guidelines

If the permissibility of a specific drug/treatment is in question, please contact the study sponsor.

8.2.2. Restricted Therapy

8.2.2.1. Prior to Metastatic Disease Progression

The following are ***prohibited*** while a subject is receiving abiraterone acetate prior to confirmation of metastatic disease progression:

- Concurrent administration of other anticancer therapy, including cytotoxic or immunotherapy.
- Concomitant therapy with any of the following:
  - 5 α-reductase inhibitor
  - Chemotherapy
  - Immunotherapy
  - Androgen receptor antagonists (ie, bicalutamide, nilutamide, flutamide, enzalutamide)
  - Systemic ketoconazole (or other azole drugs such as fluconazole and itraconazole)
  - Diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
  - Radiopharmaceuticals such as strontium (89Sr) or samarium (153Sm)
  - Aldactone, Spironol (spironolactone)
  - Digoxin, digitoxin, and other digitalis drugs
  - Cyproterone acetate
  - Fludrocortisone acetate (Florinef)
  - Investigational agents other than abiraterone acetate or prednisone
- Concurrent enrollment in another clinical investigational drug or device study.

Initiation of a strong CYP3A4 inducer must be discussed with the sponsor's study responsible physician.

The decision to administer a prohibited drug/treatment should be made based on the consideration of the safety of the subject.

Prior to confirmation of metastatic disease progression, the sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Subjects who require the use of any of these prohibited agents will no longer be permitted to continue on study agents as described in Section 10.2.

8.2.2.2. After Metastatic Disease Progression

Concomitant therapy with any of the following is ***prohibited*** during treatment with abiraterone acetate following metastatic disease progression. Note that this only applies to the limited

number of subjects currently enrolled in the Optional Post-metastatic Disease Follow-up Phase. Per Protocol Amendment 4, no further subjects are to continue on study after metastatic disease progression.

- ☐ Systemic ketoconazole (or other azole drugs such as fluconazole and itraconazole)
- ☐ Diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
- ☐ Aldactone, Spironol (spironolactone)
- ☐ Digoxin, digitoxin, and other digitalis drugs
- ☐ Cyproterone acetate
- ☐ Fludrocortisone acetate (Florinef)

Subjects who require the use of any of these prohibited agents will no longer be permitted to continue on study agents as described in Section 10.2.

8.2.3. Potential for Drug-drug Interactions

8.2.3.1. Effects of Abiraterone on Drug Metabolizing Enzymes

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 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 (eg, thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

In vitro, abiraterone acetate inhibits CYP2C8. There are no clinical data on the use of abiraterone acetate with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate. Please refer to the Investigator Brochure for further details.

8.2.3.2. Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, abiraterone acetate is a substrate of CYP3A4. In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant use of strong CYP3A4 inducers during abiraterone acetate treatment (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital).

9. STUDY EVALUATIONS

9.1. Overview

All subjects must provide written informed consent prior to performing any study-specific procedures. The study consists of a 4-week Screening Phase; a Core Study Treatment Phase

(comprised of six, 28-day cycles); a Pre-metastatic Disease Follow-up Phase, an Optional Drug Holiday Phase; and a 30-day Safety Follow-up Visit, as described in further detail in Section 3.1. A study treatment cycle is 28 days. Refer to the Time and Events Schedule for Procedures to be Performed for the frequency and timing of procedures to be conducted during each phase of the study.

Scans (bone scans, and CT or MRI of the chest, abdomen, and pelvis) performed up to 28 days prior to Cycle 1 Day 1 can be used for screening assessments.

The total blood volume to be collected from each subject during the screening and the Core Study Treatment Phase will be approximately 60.9 mL. The total blood volume to be collected during the Pre-metastatic Disease Follow-up Phase is predicated upon standard of care, clinical need, and the duration of study participation. It is estimated that when a subject has sample(s) collected, the maximum blood volume collected at a visit, as applicable, should not exceed 9.7 mL. Up to two additional blood samples for biomarker analysis (12.5 mL each) may be collected. Sample collection times are shown in the Time and Events Schedule for Procedures to be Performed.

9.2. Efficacy

All screening imaging scans will be read by the local reader and sent to the central reader. The central reader will provide the results of the screening eligibility imaging scans to the sites through the sponsor. The central reader must confirm that there is no evidence of metastasis on screening imaging scans before a subject can be enrolled. If a disparity exists between the local and central reader in interpreting the imaging scans during the screening period, a blinded arbiter will be engaged at the central reading facility to make a final decision.

During the Core Study Treatment Phase, efficacy will be measured by PSA levels, testosterone levels, and imaging studies (bone scans, CT or MRI of the chest, abdomen, and pelvis). The timing for imaging studies as well as sample collection times for PSA and testosterone levels are shown in the Time and Events Schedule for Procedures to be Performed. Note that if a digital rectal exam is to be performed, sample collection for PSA levels must be obtained prior to the exam. A central laboratory will be used for PSA and testosterone evaluations and imaging studies will be read by both local readers and a central reader and the results will be discussed in consultation with the sponsor.

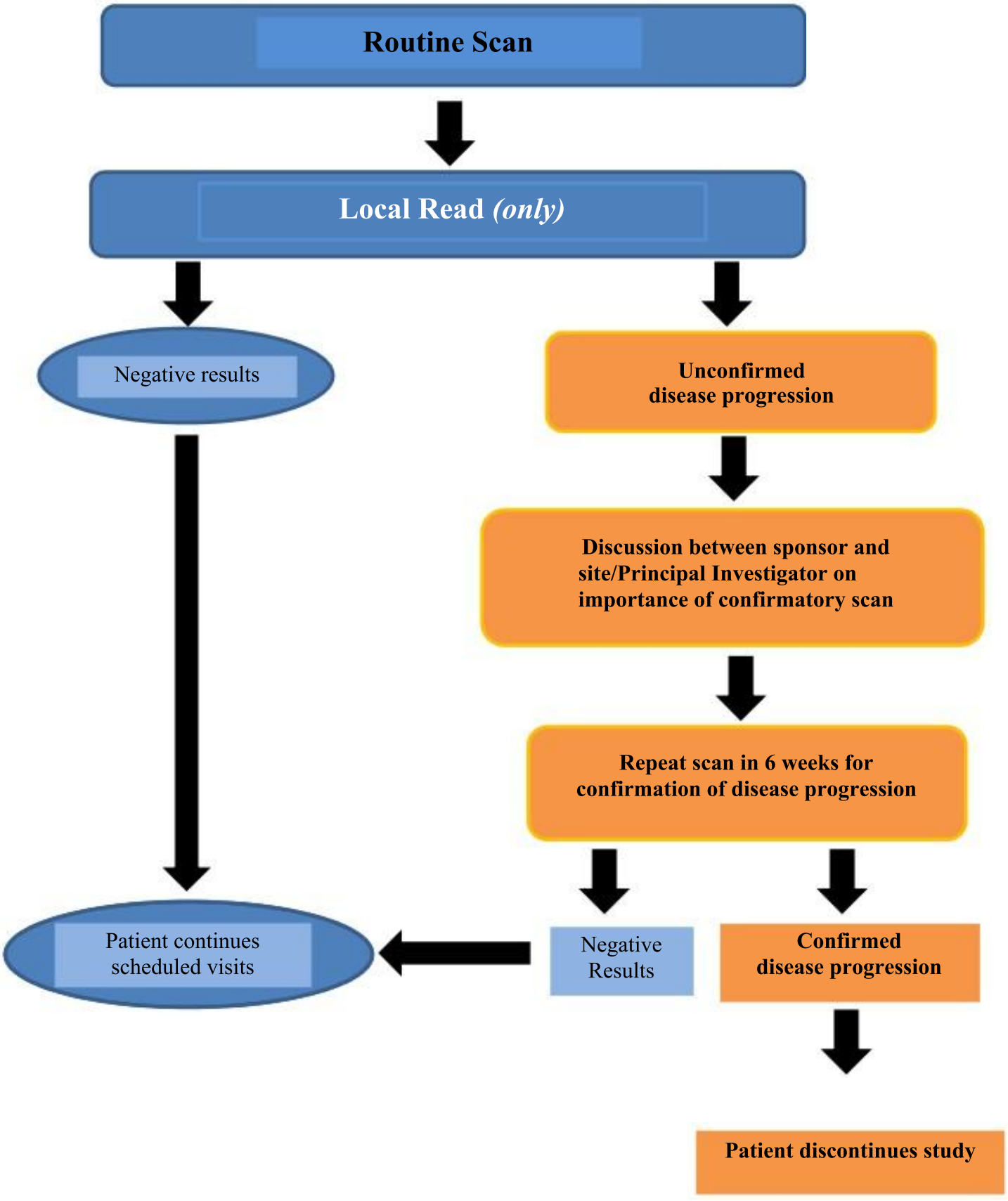
During the Pre-metastatic Disease Follow-up Phase, imaging studies will be used to evaluate disease progression and will be done locally per standard of care. Disease progression is to be determined using RECIST criteria as shown in Figure 9.

During the Optional Drug Holiday Phase, potential signs of disease progression (defined as a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir, documented and confirmed by a second value obtained 3 or more weeks later, and confirmed as nonmetastatic by a negative conventional scan) will be monitored by PSA levels monthly, for 3 months, and then once every 3 months thereafter, testosterone levels every 3 months until recovery (ie, within normal ranges), and imaging studies (bone scans, CT or MRI of the chest, abdomen, and pelvis) done locally per standard of care, for a period of 1 year.

Subjects who demonstrate no signs of disease progression may continue on study in the Optional Drug Holiday Phase for an additional 1-year period and will be monitored and have samples collected per standard of care, and will exit from study after completion of the additional 1 year follow up period.

Subjects that demonstrate signs of disease progression up to 1 year, may return to treatment with abiraterone plus prednisone and ADT or choose other treatments and discontinue from study. Blood samples will be collected at the time of clinical relapse or discontinuation from study.

Figure 9 Flow chart for routine imaging scans (per modified RECIST criteria)



The primary endpoint of this study is the proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit.

Secondary endpoints include:

- ☐ Time to radiographic evidence of disease progression
- ☐ Time to PSA progression defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained in 3 or more weeks (Scher et al, 2008)
- ☐ The proportion of subjects with a ≥ 50% reduction in PSA after 3 cycles of treatment and absolute PSA reduction
- ☐ The proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit with and without local therapy
- ☐ PSA and testosterone over time as well as at nadirs

Time to radiographic evidence of disease progression will be based on modified RECIST criteria as the time from the start of treatment to the occurrence of one of the following:

- ☐ A subject is considered to have progressed by bone scan if:
  1) The appearance of > 2 new lesions, and, for the first assessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions
  2) If > 2 new lesions are seen on scans following the first assessment, the confirmation is still required after 6 weeks; however, 2 additional lesions (eg, 2 + 2 = 4) are NOT required to confirm progression
  3) The date of progression is the date of the first scan that shows the changes
- ☐ Progression of soft tissue lesions measured by CT or MRI as defined in modified RECIST criteria (see Attachment 2)

Use RECIST criteria for progression, with the additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. Note that lymph nodes ≥ 2 cm in diameter should be used to assess for a change in size.

If disease progression is observed on a postbaseline scan, study agents should be continued until disease progression is confirmed on the second scan.

If disease progression is suspected on an image that was ordered outside of the study, contact the medical monitor to discuss.

9.3. Sample Collection for Biomarker Analysis

For subjects who do not have metastatic disease progression, blood samples will be collected for biomarker analysis prior to and at the time of metastatic disease progression. For subjects currently enrolled in the study who have metastatic disease progression, a single sample may be

obtained. A blood sample may also be collected at the 30-day Safety Follow-up Visit, if not previously obtained.

Blood samples may also be collected during the Optional Drug Holiday Phase. Samples will be collected at the time of study drug discontinuation, at confirmed PSA progression at any point during year 1, and at "off study" if no signs of disease progression.

Whole blood samples will be used to assess genetic changes from RNA (eg, androgen receptor splice variants) and plasma samples for detecting DNA changes (mutations, gene deletions, etc). Results will help us understand the biology of the disease at progression and in stable responders.

9.4. Safety

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the times shown in the Time and Events Schedule for Procedures to be Performed: adverse events, clinical laboratory tests, 12-lead ECGs, vital signs, weight, examination for volume overload, and complete physical examinations. In addition, compliance checks and monitoring and recording of concomitant medication use, which also comprise safety, are described in Section 7 and Section 8.2, respectively.

Adverse Events

Adverse events will be reported by the subject or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative for 30 days after the last dose of study agents. Adverse events will be followed by the investigator as specified in Section 12.2.1. Abiraterone acetate dose reduction in the event of toxicity is described in Section 6.2.

Clinical Laboratory Tests

During the Core Study Treatment Phase, blood samples for serum chemistry, hematology, and coagulation will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The following tests will be performed by the central laboratory:

☐ **Hematology Panel**

-hemoglobin
-hematocrit
-red blood cell (RBC) count
-white blood cell (WBC) count with differential
-platelet count

- **Serum Chemistry Panel**

-sodium
-potassium
-chloride
-bicarbonate
-blood urea nitrogen (BUN)
-creatinine
-fasting glucose
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-gamma-glutamyltransferase (GGT)
-direct and total bilirubin
-alkaline phosphatase
-creatine phosphokinase (CPK)
-lactic acid dehydrogenase (LDH)
-uric acid
-calcium
- phosphate
-albumin
-total protein
-serum lipids: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides
-magnesium

- **Prostate Panel**

-testosterone
-PSA

- **Coagulation Panel**

-PT/PTT (INR) During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, laboratory evaluations will be conducted locally per the Time and Events Schedule.

12-Lead ECG

During the Core Study Treatment Phase, standard 12-lead ECGs are to be obtained at the times shown in the Time and Events Schedule for Procedures to be Performed or at any time clinically indicated. After the start of study agents, clinically relevant abnormalities noted in ECG results are to be reported as an adverse event.

Scans

During the Core Study Treatment Phase, the Pre-metastatic Disease Follow-up Phase, and the Optional Drug Holiday Phase, scans (bone scans, and CT or MRI of the chest, abdomen, and pelvis) will be performed as shown in the Time and Events Schedule for Procedures to be Performed or at any time clinically indicated.

Vital Signs, Weight, and Examination for Volume Overload

Vital signs include upright blood pressure, heart rate, respiratory rate, and body temperature. Vital signs, weight, and examination for volume overload will be performed as shown in the Time and Events Schedule for Procedures to be Performed or at any time clinically indicated. After the start of study agents, clinically relevant abnormalities in these evaluations are to be reported as an adverse event.

Complete Physical Examinations and Height

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

Physical examination includes head, eyes, ears, nose, and throat (HEENT); chest; cardiac; abdominal; extremities; neurologic; and lymph node examinations. After the start of study agents, clinically relevant abnormalities noted on physical examinations are to be reported as an adverse event.

Physical examinations will be conducted as shown in the Time and Events Schedule for Procedures to be Performed. Height will be recorded at screening only.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the Core Study Treatment Phase after collection of his PSA level after 6 cycles of treatment, or at the time of radiographic evidence of disease progression prior to completion of the End of Core Study Treatment Visit procedures. A subject will be considered to have completed the Pre-metastatic Disease Follow-up Phase of the study upon the development of metastatic disease, and if participating in the ODHP, after 2 years of follow-up.

10.2. Discontinuation of Study Agent(s)

10.2.1. Discontinuation of Abiraterone Acetate

Abiraterone acetate will be continued in subjects who have increasing PSA values in the absence of radiographic progression. Although serial PSAs will be measured in this study, progression or change in PSA values should not be used as an indication to discontinue study agents.

An investigator may discontinue a subject from abiraterone acetate at any time based on clinical judgment or for any of the following:

- ☐ Sustained side effects: Subjects who have sustained toxicities that do not return to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE version 4.0) Grade 1 or less with appropriate medical management, should be discontinued from abiraterone acetate.
- ☐ Administration of prohibited treatments as described in Section 8.2.2.
- ☐ Metastatic disease progression.
- ☐ Participation in the Optional Drug Holiday Phase
- ☐ In the event abiraterone acetate is discontinued, prednisone should also be discontinued.

Procedures to be performed if abiraterone acetate is discontinued are dependent upon the time of discontinuation as follows:

- ☐ If a subject discontinues abiraterone acetate prior to the End of Core Study Treatment Visit, when possible, all End of Core Study Treatment Visit procedures should be performed, and the subject will be required to return to the site for the 30-day Safety Follow-up Visit.
- ☐ If a subject discontinues abiraterone acetate during the Pre-metastatic Disease Follow-up Phase or the Optional Drug Holiday Phase of the Study, the subject will be required to return to the study site for the 30-day Safety Follow-up Visit.

Subjects who discontinue abiraterone acetate at any time during the study are to be discontinued from the study following the 30-day Safety Follow-up Visit.

10.2.2. Discontinuation of Prednisone

An investigator may discontinue a subject from prednisone at any time during the study based on clinical judgment; however, where possible, the investigator should discuss discontinuation of prednisone with the sponsor's medical monitor prior to discontinuation. In the event prednisone is discontinued, a subject may continue to receive abiraterone acetate and continue on study as scheduled, unless as otherwise described in Section 10.3.

10.3. Withdrawal From the Study

Study participation may end for any of the following reasons:

- ☐ Discontinuation of abiraterone acetate. If a subject discontinues abiraterone acetate, procedures to be followed prior to discontinuation from the study are described in Section 10.2.
- ☐ A subject may withdraw from the study for any reason. A subject'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. These decisions will not affect his future medical care or medical benefits.
- ☐ The investigator feels that it is no longer in the subject's best interest to remain in the trial.
- ☐ Lost to follow-up. In case a subject is lost to follow-up, every possible effort must be made by the site personnel to contact the subject and determine the reason for discontinuation/ withdrawal. The measures taken to follow up must be documented.
- ☐ Death

If the subject withdraws prior to the End of Core Study Treatment Visit, when possible, all End of Core Study Treatment Visit procedures should be completed prior to withdrawal from the study. In addition, when possible, the subject should return for the 30-day Safety Follow-up Visit prior to withdrawal from the study.

If the subject withdraws during the Pre-metastatic Disease Follow-up Phase, when possible, the subject should return for the 30-day Safety Follow-up Visit prior to withdrawal from the study with evaluations to be completed as shown in the Time and Events Schedule for Procedures to be Performed.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document.

Study agents assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

11. STATISTICAL METHODS

Specific details of the analyses and data handling rules will be provided in the Statistical Analysis Plan (SAP).

Demographic and baseline information will be summarized descriptively.

11.1. Subject Information

There are 3 analysis populations for the Core Study Treatment Phase: an efficacy-evaluable population, a Per Protocol (PP) population, and a Safety population.

- ☐ The efficacy-evaluable population is defined as all subjects who completed at least one cycle of treatment
- ☐ The PP population is defined as all subjects who did not have a major protocol violation during the Core Study Treatment Phase (as defined in the SAP) and completed at least 6 cycles of treatment
- ☐ The Safety population is defined as all subjects exposed to study agents

11.2. Efficacy Analyses

11.2.1. Primary Endpoint

The primary endpoint of this study is the proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit. The proportion of subjects will be analyzed using a normal approximation to the binomial distribution comparing the observed proportion to a reference of 0.35, and the 95% confidence interval (CI) interval will also be computed. The primary analysis will be performed using the efficacy-evaluable population, and an additional sensitivity analysis will be performed on the PP population.

11.2.2. Secondary Endpoints

Time to radiographic evidence of disease progression and time to PSA progression will be summarized using the Kaplan-Meier method.

The proportion of subjects with a ≥ 50% reduction in PSA after 3 cycles of treatment will be summarized and the 95% CI will be computed.

The proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit will be summarized by local therapy status (with or without local therapy) and the 95% CI will be computed.

PSA levels at each time point, and change from baseline, will be summarized descriptively.

Testosterone levels after 3 and 6 cycles of treatment, and change from baseline will be summarized descriptively.

All secondary endpoints will be analyzed using the efficacy-evaluable population.

From the time of the End of the Core Study Treatment Phase until the end of the study, secondary endpoints collected during the Pre-metastatic Disease Follow-up Phase will be updated on an annual basis. After radiographic disease progression, the duration and type of subsequent cancer therapy will be summarized descriptively.

For the Optional Drug Holiday Phase, descriptive statistics will be provided

11.3. Sample Size Determination

The sample size estimate for this study is based upon testing the primary endpoint of the proportion of subjects with a ≥ 50% reduction in PSA after 6 cycles of treatment or by the End of Core Study Treatment Visit. Assuming a null hypothesis proportion equals 0.35 vs the alternative of 0.50; a 1-sided, alpha equal to 0.025; and 90% power, a sample size of 111 subjects will be required. Accounting for an approximate dropout rate of 10%, 125 subjects are planned for enrollment.

11.4. Biomarker Analyses

Blood samples collected at pre-metastatic and metastatic time points, including the Optional Drug Holiday Phase, may be analyzed for a selective panel of molecular changes (androgen receptor anomalies such as mutation and splice variants etc.) and associations may be made with clinical endpoints.

The association biomarkers with clinical response or relevant survival endpoints may be assessed using appropriate statistical methods (eg, analysis of variance, categorical, or survival models), depending on the endpoints.

11.5. Safety Analyses

All safety analyses will be performed on the Safety population. All safety endpoints will be reported through the end of the Core Study Treatment Phase and then in an Annual Addendum.

Adverse Events

The original terms used in the CRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least one occurrence of the given event will be summarized overall and by NCI CTCAE Grade.

Special attention will be given to those subjects who died, who discontinued treatment due to an adverse event, or who experienced a serious adverse event (eg, summaries, listings, and narrative preparation may be provided, as appropriate).

The proportion of subjects with mineralocorticoid excess (those with hypokalemia, hypertension, and/or volume overload [edema, refractory edema, or pulmonary edema]) will be summarized and the 95% CI interval will be computed.

The proportion of subjects for each component of mineralocorticoid excess as described above will be summarized and the 95% CI computed.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test and cycle. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point including change from baseline.

Vital Signs

Descriptive statistics of vital sign values (including bodyweight) and changes from baseline will be summarized at each scheduled time point.

11.6. Interim Analysis

No interim analysis is planned.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

In this study any suspected drug-drug interaction with abiraterone acetate should be recorded as an adverse event and the sponsor notified.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (ICF, refer to Section 12.2.1, All Adverse Events for time of last adverse event recording).

Serious Adverse Event

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- ☐ Results in death
- ☐ Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- ☐ Requires inpatient hospitalization or prolongation of existing hospitalization ☐
  Results in persistent or significant disability/incapacity, or ☐ Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a serious adverse event). Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Associated With the Use of the Drug

An adverse event is considered associated with the use of study agent(s) if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of study agent(s).

Doubtful

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

Possible

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

Probable

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

Very likely

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

12.1.3. Severity Criteria

Adverse event severity is a clinical determination of the intensity of an adverse event or a serious adverse event. The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE version 4.0; a link to the CTCAE is provided in Attachment 1).

An adverse event/serious adverse event not listed in the NCI CTCAE version 4.0 is to be graded as follows:

SEVERITY OF EVENT	
Grade	**Definition**
1	Mild: Symptoms that do not interfere with the subject's daily activities
2	Moderate: Symptoms that may interfere with the subject's daily activities
3	Severe: Events that interrupt the subject's daily activities
4	Life-threatening or disabling
5	Death

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

12.2. Procedures

12.2.1. All Adverse Events

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained to 30 days after the last dose of study agents. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study agents, must be reported using the Serious Adverse Event Form. During the Optional Drug Holiday Phase, all adverse events, whether serious or non-serious will continue to be collected. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

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

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study agents, the study number, the investigator's name, a 24-hour emergency contact number, and excluded concomitant medications.

12.2.2. Serious Adverse Events

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

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

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

☐ The event resolves ☐

The event stabilizes

☐ The event returns to baseline, if a baseline value is available

☐ The event can be attributed to agents other than the study agents or to factors unrelated to study conduct

☐ It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Suspected transmission of an infectious agent by a medicinal product should be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

☐ Rehabilitation facilities

☐ Hospice facilities

☐ Skilled nursing facilities

☐ Nursing homes

☐ Routine emergency room admissions

☐ Same day surgeries (as outpatient/same day/ambulatory procedures)

- ☐ Social reasons in absence of an adverse event (eg, the subject has no place to sleep)
- ☐ Surgery or procedure planned before entry into the study (must be documented in the CRF)

12.2.3. Pregnancy

Because abiraterone acetate may have an effect on sperm, or if the effect is unknown, pregnancies in partners of subjects included in the study are to be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form.

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

In the case of paternal exposure, investigators will be asked to do the following:

- ☐ Obtain the subject's permission to have his partner complete the Authorization for Disclosure of Medical Information Form and provide information on the pregnancy and its outcome. The subject must be informed that information about the study drug and its indication will be provided to his partner and her treating physician and/or health care professional (HCP).

- ☐ Document in the subject's medical chart whether or not he agreed to the follow-up and that he was fully informed about the study information that will be provided to his partner and her treating physician and/or HCP.

If the subject agrees to pregnancy follow-up, the investigator will have the subject's partner complete the Authorization for Disclosure of Medical Information Form.

- ☐ *If partner's consent is obtained*, the investigator will file the Authorization for Disclosure of Medical Information Form in the Trial Center File. The Drug Exposure During Pregnancy Collection Form A (Clinical Trial Section completed) will be sent to the investigator to provide to the treating physician and/or HCP identified on the Authorization for Disclosure of Medical Information Form.

- ☐ *If partner's consent is not obtained*, no further follow-up information on the pregnancy will be requested.

At the estimated time of delivery, or if delivery has not already occurred:

- ☐ The End of Pregnancy Collection Form B (Clinical Trial Section completed) will be sent to the investigator.

☐ The investigator will provide the treating physician and/or HCP identified on the Authorization for Disclosure of Medical Information Form with a copy of the signed form and the End of Pregnancy Collection Form B.

If there was an abnormal pregnancy outcome, a Serious Adverse Event form will need to be completed by the investigator.

12.3. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. INFORMATION ON STUDY AGENTS

14.1. Physical Description of Study Agents/Packaging/Labeling/Storage

For detailed information regarding the physical description of the study agents, as well as their packaging, labeling, and storage refer to the Pharmacy Reference Manual. An overview of this information is provided below.

Abiraterone acetate tablets and prednisone tablets will be packaged and provided to each site such that subjects will receive a sufficient supply to allow for visits to occur every 28 days.

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

Labeling for study agents will contain information to meet the applicable regulatory requirements.

The study agents must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol.

At the study site and while the subject is at home, bottles of study agents should be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted in the range from 15°C to 30°C (59°F to 86°F) in the original container with the cap, as applicable, on tightly; abiraterone acetate and prednisone should not be refrigerated. Subjects should be advised to keep all medications out of the reach and out of sight of children.

14.2. Drug Accountability

The investigator is responsible for ensuring that all study agents received at the site are inventoried and accounted for throughout the study. The dispensing of study agents to the subject, and the return of study agents from the subject, must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study agents. Study agents returned by study subjects will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study agents' containers.

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

Study agents should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study agents will be supplied only to subjects participating in the study. Returned study agents must not be dispensed again, even to the same subject. Study agents may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study agents from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- ☐ Study Reference Materials, including but not limited to, online access to electronic CRFs, a Trial Center File, a Pharmacy Reference Manual, a Laboratory Manual
- ☐ Study card

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

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

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Institutional Review Board (IRB)

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

- ☐ Final protocol and, if applicable, amendments
- ☐ Sponsor-approved ICF (and any other written materials to be provided to the subjects)

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

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

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

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

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

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

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

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

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

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

All subjects who continue the study when a protocol amendment is installed need to be re-consented with the revised ICF or an ICF addendum.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study agents used in this study.

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

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

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In

all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Pre-study Documentation

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

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

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

- ☐ Completed investigator financial disclosure forms from all clinical subinvestigators
- ☐ Documentation of subinvestigator qualifications (eg, curriculum vitae)

- ☐ Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- ☐ Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

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

It is recommended that the author of an entry in the source documents be identifiable.

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

17.5. Case Report Form Completion

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor. The electronic file will be considered to be the CRF. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English.

Designated site personnel must complete CRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

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

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

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

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

17.8. Monitoring

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

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

17.9. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon

study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

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

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

- ☐ Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- ☐ Inadequate recruitment of subjects by the investigator
- ☐ Discontinuation of further abiraterone acetate development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

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

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

information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

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

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1:
Link to National Cancer Institute Common Terminology Criteria for Adverse Events

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

Attachment 2:
Modified Response Evaluation Criteria in Solid Tumors

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

Evaluation of Progression

In this study, patients will have no evidence of metastatic disease at baseline. Scans (CT, MRI, and bone) performed up to 28 days prior to Cycle 1 Day 1 may be used for screening assessments. If disease progression is observed on a scan, a confirmatory scan is required 6 weeks later. Study treatment should continue in the interim.

Measurability of tumor lesions

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 2 cm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Measurement of lesions

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

New lesions denote progression

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Attachment 3:
Calculation of PSADT in the Electronic Screening Tool

Three PSA values are used to calculate the PSADT. In order for the calculation to be valid, the following requirements must be met:

1. All of the 3 dates must be provided.

2. All of the 3 dates must be in the specified format (dd-MMM-yyyy). No partial date is accepted.

3. The 3 dates must be in chronological order. The first PSA date must be the oldest, and the last PSA date (the most recent date) must be within the study screening period.

4. There should be a period of at least 2 weeks between each PSA date.

5. There should be a period of at least 8 weeks between the first and the third value.

6. All of the 3 PSA values must be provided.

7. All of the 3 PSA values must be numeric and greater than 0.

8. The first of the 3 PSA values must be $\geq$ 2 ng/mL.

9. All of the 3 PSA values must be provided in the same lab units (ng/mL).

Attachment 4:
Protocol History

Original Protocol: 08 Dec 2010

Amendment 1: 14 Apr 2011

Amendment 2: 01 Nov 2011

Amendment 3: 15 Jan 2014

Amendment 4: 05 Apr 2016

Amendment 5: 17 Apr 2017

Amendment 6: 28 Nov 2018

Amendment 6 - 28 Nov 2018

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

1. Description/Rationale

With protocol Amendment 4 (April 2016), 33 subjects remained on study and were considered long-term responders with a median duration of response of 44.4 months (29.5-58.4 months). The microarray profile of these subjects (n=30) is suggestive of enhanced immune surveillance. As of July 2018, 16 subjects remained on study with a median duration of response of 69.3 months (60.4-86.3 months). Continuous androgen pathway signaling suppression suggests association with long term response of subjects. Additionally, long term response also suggests that subjects may no longer require or benefit from administration of these medications. Improvement in subjects' quality of life may be observed by no longer being subjected to the side effects of these medications. The Optional Drug Holiday Phase is consistent with a standard of care approach and with other chemotherapies.

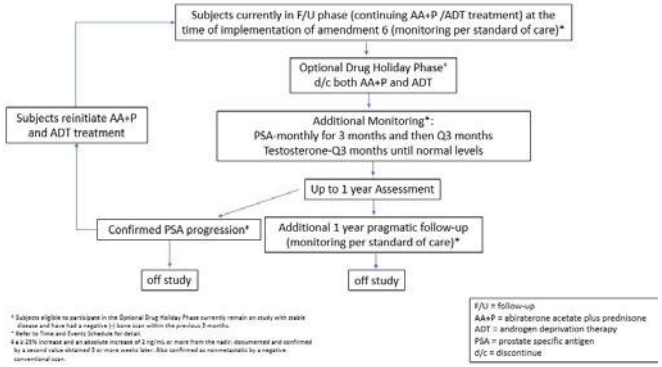
Prior to amendment 6, the study was designed such that subjects would continue treatment until the development of metastasis. The study design has now been modified to provide subjects an option to elect to participate in an Optional Drug Holiday Phase and discontinue all CRPC agents. Subjects can however decline to enter the Optional Drug Holiday Phase and continue to receive current treatment (abiraterone acetate, prednisone, and androgen depravation therapy [ADT]), as per protocol prior to this amendment.

If subjects elect to participate in the Optional Drug Holiday Phase, subjects will be monitored throughout the first year, per the time and events schedule. Subjects that demonstrate signs of disease progression up to 1 year (confirmed as nonmetastatic by a negative conventional scan), may return to treatment with abiraterone plus prednisone and ADT or choose other treatments and discontinue from study. If subjects remain free from signs of disease progression, subjects may continue in the Optional Drug Holiday Phase for an additional second year and will be monitored per standard of care as directed by their treating physician. If no disease progression is detected within 2 years, subjects will exit the study.

Sections Affected	Original Content	Amended/New Content
SYNOPSIS Exploratory Objectives (new third bullet and sub bullets)	*(None)*	☐ Optional Drug Holiday Phase – To evaluate if patients who demonstrate no signs of disease progression (radiographic or PSA) after > 5 years of treatment for non-metastatic CRPC may no longer require medications that suppress the androgen signaling pathway.

		– To evaluate PSA kinetics after withdrawal of abiraterone acetate plus prednisone and androgen deprivation therapy (ADT) in patients participating in this study phase.
SYNOPSIS HYPOTHESIS Optional Drug Holiday	*(None)*	Optional Drug Holiday Phase: Subjects who demonstrate no signs of disease progression after > 5 years of treatment may no longer require medications that suppress the androgen signaling pathway and may benefit by not being subjected to the side effects of these medications (abiraterone acetate, prednisone, and ADT.
SYNOPSIS OVERVIEW OF STUDY DESIGN (para 2)	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28-day cycles); a Pre-metastatic Disease Follow-up Phase and a 30-day Safety Follow-up Visit. A study treatment cycle is 28 days.	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28-day cycles); a Pre-metastatic Disease Follow-up Phase, an Optional Drug Holiday Phase; and a 30-day Safety Follow-up Visit. A study treatment cycle is 28 days.
SNYOPSIS OPTIONAL DRUG HOLIDAY PHASE:	*(None)*	**OPTIONAL DRUG HOLIDAY PHASE:** During the Pre-metastatic Disease Follow-up Phase, subjects who demonstrate no signs of radiographic or PSA disease progression after > 5 years of study treatment may choose to participate in this phase. During the Optional Drug Holiday Phase, subjects will discontinue abiraterone acetate plus prednisone and ADT. During the first year in this phase, subjects will be monitored closely for signs of PSA progression and will have the option to return to study medication if there is evidence of disease progression, confirmed as nonmetastatic by a negative conventional scan. Refer to the Time and Events Schedule for procedures to be performed and timing of assessments. If after one year, there are no signs of PSA progression, subjects will be followed for an additional year but will not have the option to return to study medication if progression is noted after 12 months off medication.
SNYOPSIS OPTIONAL DRUG HOLIDAY PHASE:	This Phase has been eliminated from the current protocol; however, those subjects who are currently in the Optional Post-Metastatic Follow-up Phase as of the date of this protocol amendment may remain on study.	While the option to enter the Post-metastatic Disease Follow-up Phase no longer exists, subjects who continue in the Post-metastatic Disease Follow-up Phase at the time of Protocol Amendment 6, may remain on trial.

SNYOPSIS OPTIONAL DRUG HOLIDAY PHASE: (para 4)	A schedule of events showing the timing of procedures is provided in the Time and Events Schedule for Procedures to be Performed and a flow chart depicting subject participation in the study is provided in the Time and Events Schedule for Subject Participation in the Study.	A schedule of events showing the timing of procedures is provided in the Time and Events Schedule for Procedures to be Performed and a flow chart depicting subject participation in the study is provided in the Time and Events Schedule for Subject Participation in the Study and for the Optional Drug Holiday Phase.
SNYOPSIS OPTIONAL DRUG HOLIDAY PHASE: (para 5)	Subjects may remain on abiraterone acetate until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws or the sponsor determines it is necessary to stop the study.	Subjects may remain on abiraterone acetate until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, the subject elects to participate in the Optional Drug Holiday Phase as described in Protocol Amendment 6, or the sponsor determines it is necessary to stop the study.
SNYOPSIS OPTIONAL DRUG HOLIDAY PHASE: (para 6)	The duration of study participation is anticipated to be approximately 2 years. The completion of the entire Core Study Treatment Phase is defined as the time at which the last subject completes the End of Core Study Treatment Visit. The end of the study is defined as the point at which all subjects have progressed to metastatic disease.	The completion of the entire Core Study Treatment Phase is defined as the time at which the last subject completes the End of Core Study Treatment Visit. The end of the study is defined as the point at which all subjects have progressed to metastatic disease or for those participating in the Optional Drug Holiday Phase, the end of the 2-year period.
SNYOPSIS Optional Drug Holiday Phase Inclusion:	*(None)*	Optional Drug Holiday Phase Inclusion: ☐ Patients on study who demonstrate no signs of disease progression (radiographic or PSA) after > 5 years of treatment ☐ Negative scan within the previous 3 months ☐ PSA values < 25% above nadir or < 10 ng/mL, within the previous 3 months
SYNOPSIS EFFICACY EVALUATIONS/CRITERIA (2nd para, 1st sent)	During the Pre-metastatic Disease Follow-up Phase imaging studies for disease status will be done locally per standard of care.	During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, imaging studies for disease status will be done locally per standard of care.
SNYOPSIS BIOMARKER ANALYSIS (1st para, 1st sent)	During the Pre-metastatic Disease Follow-up Phase a blood sample for biomarker analysis will be collected prior to and at the time of metastatic disease progression.	During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, a blood sample for biomarker analysis will be collected prior to and at the time of metastatic disease progression.

SNYOPSIS SAFETY EVALUATIONS (2nd para)	During the Pre-metastatic Disease Follow-up Phase safety evaluations will be conducted per standard of care; laboratory evaluations will be conducted using a local laboratory.	During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, safety evaluations will be conducted per standard of care; laboratory evaluations will be conducted using a local laboratory.
SNYOPSIS Biomarker Analyses	Blood samples collected at pre-metastatic and metastatic time points may be analyzed for a selective panel of molecular changes (androgen receptor anomalies such as mutation and splice variants etc.) and associations may be made with clinical endpoints.	Blood samples collected at pre-metastatic, including at the time of the start of the Optional Drug Holiday Phase, and metastatic time points may be analyzed for a selective panel of molecular changes (androgen receptor anomalies such as mutation and splice variants etc.) and associations may be made with clinical endpoints.
Time and Events Schedule for Procedures to be Performed	The Time and Events Schedule for Procedures to be Performed per Protocol Amendment 6 with changes highlighted in blue is shown first, followed by the original version. Both at shown at the bottom of the amendment detail.	
TIME AND EVENTS SCHEDULE FOR SUBJECT PARTICIPATION IN THE STUDY	*(None)*	Per Protocol Amendment 6, during the Pre-metastatic Disease Follow-up Phase, subjects who demonstrate no signs of radiographic or PSA disease progression after > 5 years of study treatment may choose to participate in the Optional Drug Holiday Phase. Refer to the study schematic for the Optional Drug Holiday Phase.
STUDY SCHEMATIC FOR THE OPTIONAL DRUG HOLIDAY PHASE	*(None)*	
1.2.Abiraterone and Abiraterone Acetate	*(None)*	In addition, per Protocol Amendment 6, an Optional Drug Holiday Phase has been added to the protocol; further details on this phase of the study are provided in section 1.3. Rationale for Optional Drug Holiday Phase and the study schematic for the Optional Drug Holiday Phase.

1.3 Rationale for Drug Optional Holiday Phase (2 new paras)	*(None)*	As of July 2018, 16 subjects remain on study with a median duration of response of 69.3 months (60.4 - 86.3 months). This prolonged response may suggest that the subjects no longer require medication and may benefit from a period where they are not subject to the side effects of the medications (abiraterone acetate, prednisone, and ADT). The option for a "drug holiday" is consistent with other oncologic therapies and with a standard of care approach (Li et al, 2015; Petrioli et al, 2015). If subjects choose to enroll in the Optional Drug Holiday Phase , they will have the option to return to study drug if a relapse (defined as PSA increase and confirmed as nonmetastatic by a negative conventional scan) occurs within the first year. In this first year, subjects will be closely monitored. In the second year of the Optional Drug Holiday Phase , they will follow standard of care disease management as directed by their physician. If no disease progression is detected within 2 years, patients will be considered as stable and at low risk of progression and will have completed this study. If patients later experience increases in PSA, there are now FDA approved treatment options (apalutamide [Erleada™] or enzalutamide [Xtandi®]) as well as clinical trials for patients with non-metastatic CRPC at their physician's discretion, whereas when the study was initiated, there were no options.
2 Objectives Exploratory Objectives (new third bullet)	*(None)*	• Optional Drug Holiday Phase: - To evaluate if patients who demonstrate no signs of disease progression (radiographic or PSA) after > 5 years of treatment for non-metastatic CRPC may no longer require medications that suppress the androgen signaling pathway. - To evaluate PSA kinetics after withdrawal of abiraterone acetate plus prednisone and androgen deprivation therapy (ADT) in patients participating in this study phase

2 Objectives Hypothesis (new para)	*(None)*	Optional Drug Holiday Phase: Subjects who demonstrate no signs of disease progression after > 5 years of treatment may no longer require medications that suppress the androgen signaling pathway and may benefit by not being subjected to the side effects of these medications (abiraterone acetate, prednisone, and ADT.
3.1. Study Design	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28 day cycles); a Pre-metastatic Disease Follow-up Phase, and a 30-day Safety Follow-up Visit as described in further detail below. A study treatment cycle is 28 days.	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28 day cycles); a Pre-metastatic Disease Follow-up Phase, an Optional Drug Holiday Phase; and a 30-day Safety Follow-up Visit as described in further detail below. A study treatment cycle is 28 days.
	If abiraterone acetate is discontinued, prednisone should also be discontinued as described in Section 10.2, and the subject should be discontinued from the study as described in Section 10.3.	If abiraterone acetate is discontinued, prednisone should also be discontinued as described in Section 10.2, and the subject should be discontinued from the study as described in Section 10.3 unless the subject has consented to the participate in the Optional Drug Holiday Phase.
	(None)	If the subject elects to participate in the Optional Drug Holiday Phase, subject will discontinue abiraterone acetate plus prednisone and ADT.
	(None)	OPTIONAL DRUG HOLIDAY PHASE: During the Pre-metastatic Disease Follow-up Phase subjects who demonstrate no signs of radiographic or PSA disease progression after > 5 years of study treatment may choose to participate in this phase. During the Optional Drug Holiday Phase, subjects will discontinue abiraterone acetate plus prednisone and ADT. During the first year in this phase, subjects will be monitored closely for signs of PSA progression and will have the option to return to study medication if there is evidence of disease progression, confirmed as nonmetastatic by a negative conventional scan. Refer to the Time and Events Schedule for procedures to be performed and timing of assessments. If after one year, there are no signs of PSA progression, subjects will be followed for an additional year but will not have the option to return to study medication if progression is noted after 12 months off medication.

	This Phase has been eliminated from the current protocol; however, those subjects who are currently in the Optional Post-Metastatic Follow-up Phase as of the date of this protocol amendment may remain on study. Subjects may remain on abiraterone acetate until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, or until the sponsor determines it is necessary to stop the study. A schedule of events showing the timing of procedures is provided in the Time and Events Schedule for Procedures to be Performed, and a flow chart depicting subject participation in the study is provided in the Time and Events Schedule for Subject Participation in the Study. The duration of study participation is anticipated to be approximately 2 years.	While the option to enter the Post-metastatic Disease Follow-up Phase no longer exists, subjects who continue in the Post-metastatic Disease Follow-up Phase at the time of Protocol Amendment 6, may remain on study. Subjects may remain on abiraterone acetate until the subject elects to participate in the Optional Drug Holiday Phase or until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, or until the sponsor determines it is necessary to stop the study. A schedule of events showing the timing of procedures is provided in the Time and Events Schedule for Procedures to be Performed, and a flow chart depicting subject participation in the study is provided in the Time and Events Schedule for Subject Participation in the Study and the Study schematic for the Optional Drug Holiday Phase. The duration of study participation was anticipated to be approximately 2 years.
4.2.1 Optional Drug Holiday Phase Inclusion	*(None)*	4.2.1. Optional Drug Holiday Phase Inclusion 1.Patients on study who demonstrate no signs of disease progression (radiographic or PSA) after >5 years of treatment. 2.Negative scan within the previous 3 months. 3.PSA values < 25% above nadir or < 10 ng/mL within the previous 3 months. 4.Have signed an informed consent document indicating that the subject understands the purpose of and procedures required for this phase of the study and are willing to participate in this phase of the study.
6.1. Description of Study Agents and Administration (fourth para, 3rd sent)	If abiraterone acetate is discontinued, prednisone should also be discontinued as described in Section 10.2, and the subject should be discontinued from the study as described in Section 10.3.	If abiraterone acetate is discontinued, prednisone should also be discontinued as described in Section 10.2, and the subject should be discontinued from the study as described in Section 10.3 unless the subject has elected to participate in the Optional Drug Holiday Phase as described in Section 3.1 Optional Drug Holiday Phase.

9.1. Overview (1st para, 2nd sent)	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28 day cycles); a Pre-metastatic Disease Follow-up Phase, and a 30-day Safety Follow-up Visit, as described in further detail in Section 3.1. A study treatment cycle is 28 days. Refer to the Time and Events Schedule for Procedures to be Performed for the frequency and timing of procedures to be conducted during each phase of the study.	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28 day cycles); a Pre-metastatic Disease Follow-up Phase, an Optional Drug Holiday Phase; and a 30-day Safety Follow-up Visit, as described in further detail in Section 3.1. A study treatment cycle is 28 days. Refer to the Time and Events Schedule for Procedures to be Performed for the frequency and timing of procedures to be conducted during each phase of the study.
(last para.)	*(None)*	Sample collection times are shown in the Time and Events Schedule for Procedures to be Performed.
9.2. Efficacy (new paras, 4-6)	*(None)*	During the Optional Drug Holiday Phase, potential signs of disease progression (defined as a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir, documented and confirmed by a second value obtained 3 or more weeks later, and confirmed as nonmetastatic by a negative conventional scan) will be monitored by PSA levels monthly, for 3 months, and then once every 3 months thereafter, testosterone levels every 3 months until recovery (ie, within normal ranges), and imaging studies (bone scans, CT or MRI of the chest, abdomen, and pelvis) done locally per standard of care, for a period of 1 year. Subjects who demonstrate no signs of disease progression may continue on study in the Optional Drug Holiday Phase for an additional 1-year period and will be monitored and have samples collected per standard of care, and will exit from study after completion of the additional 1 year follow up period. Subjects that demonstrate signs of disease progression up to 1 year, may return to treatment with abiraterone plus prednisone and ADT or choose other treatments and discontinue from study. Blood samples will be collected at the time of clinical relapse or discontinuation from study
9.3. Sample Collection for Biomarker Analysis (new fourth sentence)	*(None)*	Blood samples may also be collected during the Optional Drug Holiday Phase. Samples will be collected at the time of study drug discontinuation, at confirmed PSA progression at any point during year 1, and at “off study” if no signs of disease progression.

9.4. Safety Clinical laboratory tests	During the Pre-metastatic Disease Follow-up Phase laboratory evaluations will be conducted locally per the Time and Events Schedule	During the Pre-metastatic Disease Follow-up Phase and the Optional Drug Holiday Phase, laboratory evaluations will be conducted locally per the Time and Events Schedule.
9.4. Safety Scans-	During the Core Study Treatment Phase, the Pre-metastatic Disease Follow-up Phase scans (bone scans, and CT or MRI of the chest, abdomen, and pelvis) will be performed as shown in the Time and Events Schedule for Procedures to be Performed or at any time clinically indicated	During the Core Study Treatment Phase, the Pre-metastatic Disease Follow-up Phase, and the Optional Drug Holiday Phase, scans (bone scans, and CT or MRI of the chest, abdomen, and pelvis) will be performed as shown in the Time and Events Schedule for Procedures to be Performed or at any time clinically indicated
10.1. Completion	*A subject will be considered to have completed the Pre-metastatic Disease Follow-up Phase of the study upon the development of metastatic disease.*	A subject will be considered to have completed the Pre-metastatic Disease Follow-up Phase of the study upon the development of metastatic disease, and if participating in the ODHP, after 2 years of follow-up.
10.2.1. Discontinuation of Abiraterone Acetate (new fourth bullet)	*(None)*	• Participation in the Optional Drug Holiday Phase
10.2.1. Discontinuation of Abiraterone Acetate	*If a subject discontinues abiraterone acetate during the Pre-metastatic Disease Follow-up Phase, the subject will be required to return to the study site for the 30-day Safety Follow-up Visit.*	If a subject discontinues abiraterone acetate during the Pre-metastatic Disease Follow-up Phase or the Optional Drug Holiday Phase of the Study, the subject will be required to return to the study site for the 30-day Safety Follow-up Visit.
11.2.2. Secondary Endpoints (new final sentence)	*(None)*	For the Optional Drug Holiday Phase, descriptive statistics will be provided
11.4. Biomarker Analyses, (para 1, sentence 1)	Blood samples collected at pre-metastatic and metastatic time points may be analyzed for a selective panel of molecular changes (androgen receptor anomalies such as mutation and splice variants etc.) and associations may be made with clinical endpoints.	Blood samples collected at pre-metastatic and metastatic time points, including the Optional Drug Holiday Phase, may be analyzed for a selective panel of molecular changes (androgen receptor anomalies such as mutation and splice variants etc.) and associations may be made with clinical endpoints.
12.2.1 All Adverse Events, (para 1, sentence 3)	*(None)*	During the Optional Drug Holiday Phase, all adverse events, whether serious or non-serious will continue to be collected
REFERENCES	*(None)*	Li YF, Zhang SF, Zhang TT, et al. Intermittent tri-weekly docetaxel plus bicalutamide in patients with castration-resistant prostate cancer: a single-arm prospective study using a historical control for comparison. Asian J Androl. 2013 Nov;15(6):773-779.
	(None)	Petrioli R, Francini E, Roviello G, Is there still a place for docetaxel rechallenge in prostate cancer? World J Clin Oncol. 2015;6(5):99-103.

2. **Description/Rationale:** Prior references to Protocol Amendment 5 as the "current protocol" have been edited wherever needed to clarify that there is now Amendment 6.

TIME AND EVENTS SCHEDULE FOR PROCEDURES TO BE PERFORMED

Procedures and Evaluations	Screening Phase (Days)	Core Study Treatment Phase										Pre-metastatic Disease Follow-up Phase [b]	30-day Safety Follow-up Visit [b]	Optional Drug Holiday Phase
		Cycle (Day)									End of Core Study Treatment Visit [b]			
		1		2		3		4	5	6				
	(-28 to -1)	(1)	(15)	(1)	(15)	(1)	(15)	(1)	(1)	(1)				
Informed consent	X													X
Dispense study card [c]	X													
Medical history, prior medications including prior prostate cancer therapies [d]	X													
Height	X													
ECOG status	X													
MUGA scan or Cardiac ECHO [e]	X													
Demography	X													
Complete physical exam [f]	X										X	per standard of care [a]		
Vital signs/weight/and examination for volume overload [g]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [a]	per standard of care [a]	per standard of care [a]
12 Lead ECG	X							X			X			per standard of care [a]
Coagulation factors PT/PTT (INR)	X		X										per standard of care [a]	
Biomarker sample												X [a]	X [a]	X [a]
Hematology	X	X	X	X	X	X		X	X	X	X	per standard of care [a]	per standard of care [a]	
Serum chemistry [h]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [a]	per standard of care [a]	
Fasting glucose	X	X	X	X	X	X		X	X	X	X	per standard of care [a]	per standard of care [a]	
Serum lipids	X					X			X		X	per standard of care [a]	per standard of care [a]	
Liver function tests [i]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [a]	per standard of care [a]	

Procedures and Evaluations	Screening Phase (Days)	Core Study Treatment Phase									End of Core Study Treatment Visit [b]	Pre-metastatic Disease Follow-up Phase [b]	30-day Safety Follow-up Visit [b]	Optional Drug Holiday Phase
		Cycle (Day)												
		1		2		3		4	5	6				
	(-28 to -1)	(1)	(15)	(1)	(15)	(1)	(15)	(1)	(1)	(1)				
Serum testosterone	X	X						X			X	per standard of care [o]	per standard of care [o]	X[d]
PSA [j]	X	X						X			X	per standard of care [o]	per standard of care [o]	X[d]
CT/MRI	X [k]							X [k]			X [k]	per standard of care [o]		X[d]
Bone scan	X [k]							X [k]			X [k]	every cycle per standard of care [k,o]		X[d]
Abiraterone acetate and prednisone distribution [l]		X		X		X		X	X	X	X	every cycle		
Study agents compliance assessment												every cycle		
Concomitant medications [d]	X	X	X	X	X	X	X	X	X	X	X	every cycle	X	X
Adverse events [m]	X	X	X	X	X	X	X	X	X	X	X	every cycle	X	X
Changes in prostate cancer therapy												every cycle [n]	X	X
Disease status												per standard of care [o]		per standard of care [o]

a. A cycle is defined as 28 days.

b. The End of Core Study Treatment Visit is to occur at the following times:

- On Day 1 of Cycle 7;
- At the time of discontinuation of abiraterone acetate if discontinuation occurs prior to completion of the Core Study Treatment Phase;
- If possible, at the time of withdrawal from the study if withdrawal occurs prior to completion of the Core Study Treatment Phase; or
- In the event of radiographic evidence of disease progression prior to completion of the Core Study Treatment Phase.

At the time of the current protocol, the Core Study Treatment Phase has been completed.

After the Core Study Treatment Phase, subjects may enter the Pre-metastatic Disease Follow-up Phase and continue to receive abiraterone acetate until metastatic disease progression is confirmed. At the time of metastatic disease progression, the subject is to be discontinued from abiraterone acetate.

Note that prior to Protocol Amendment 4, subjects may have continued to receive abiraterone acetate in an Optional Post-metastatic Disease Follow-up Phase. This Phase has been eliminated from the current protocol; however, those subjects who are currently in the Optional Post-Metastatic Follow-up Phase as of the date of this protocol may remain on study. For these subjects, procedures to be followed are listed under the Pre-metastatic Disease Follow-up Phase column.

All subjects will be required to return to the study site 30 days after receiving their last dose of abiraterone acetate for safety follow-up.

The duration of study participation was anticipated to be approximately 2 years. The completion of the entire Core Study Treatment Phase is defined as the time at which the last subject completes the End of Core Study Treatment Visit. The end of the study is defined as the point at which all subjects have progressed to metastatic disease or for those participating in the Optional Drug Holiday Phase, the end of the 2-year period.

c. Subjects must be provided with a study card indicating the name of the investigational study agents, the study number, the investigator's name, a 24-hour emergency contact number, and, excluded concomitant medications.

d. Refer to Section 8 for further details on reporting prior and concomitant medications.

e. MUGA or ECHO scan should be obtained at baseline (existing documented MUGA or ECHO scan up to 28 days prior to Cycle 1 Day 1 may be used for this screening assessment). A cardiac ECHO may be used if MUGA is not available, when ECHO is standard of care for the institution, or due to the time interval between the MUGA and bone scan that is required by the institution.

f. Complete physical examination includes head, eyes, ears, nose, and throat; chest; cardiac; abdominal; extremities; neurologic; and lymph node examinations.

g. Vital signs include upright blood pressure, heart rate, respiratory rate, and body temperature. Weight and an examination for volume overload will also be performed at these visits. If signs of volume overload are noted, and a diuretic is initiated, potassium will need to be monitored more frequently (refer to Section 6.2.3 for further details); similarly, if a subject is treated with a diuretic for hypertension, potassium will need to be monitored more frequently (refer to Section 6.2.2 for further details).

h. Subjects who enter the study on exogenous potassium supplementation or who experience low potassium may need more frequent monitoring for hypokalemia; refer to Section 6.2.1 for further details.

i. Liver function tests must include: alkaline phosphatase, ALT, AST, LDH, and direct and total bilirubin. Subjects who experience an abnormal liver function test result may need more frequent monitoring; refer to Section 6.2.4 for further details.

j. If a digital rectal examination is performed, PSA must be sampled prior to the examination.

k. Scans (existing documented bone scans, and CT or MRI of the chest, abdomen, and pelvis) performed up to 28 days prior to Cycle 1 Day 1 may be used for screening assessments. If disease progression is observed on a postbaseline scan, confirmatory scan is required within 6 to 8 weeks after the initial diagnosis (see Section 9.2 for further details). Study agents should continue in the interim.

l. Study agents include abiraterone acetate and prednisone. Subjects will also continue to receive their GnRH monotherapy as prescribed. Subjects will begin taking study agents on Day 1 of Cycle 1. If prednisone and/or GnRH monotherapy are discontinued, subjects may continue to receive abiraterone acetate and continue on study as scheduled. If a subject needs to discontinue either of these therapies, the appropriate medical management of the subject needs to be discussed with the Medical Monitor. If a subject prematurely discontinues abiraterone acetate, prednisone should also be discontinued. Refer to Sections 10.2 and 10.3 for reasons for permanently discontinuing study agents or withdrawal from the study, respectively.

Subjects may remain on abiraterone acetate until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, or until the sponsor determines it is necessary to stop the study.

m. Adverse events should be collected from the date informed consent is signed until 30 days after the last dose of study agents. For the Optional Drug Holiday Phase, AEs will continue to be collected for the full duration. Refer to Section 6.2 for abiraterone acetate dose adjustment in the event of toxicity.

n. Prior to metastatic disease progression, new therapy for prostate cancer is prohibited as described in Section 8.2.2.1; for those currently on study who have metastatic disease progression, new therapy is prohibited as described in Section 8.2.2.2.

o. All imaging studies, laboratory tests, or other safety monitoring as noted in the column above for the Pre-metastatic Disease Follow-Up Phase, the Optional Drug Holiday Phase, and the 30-day Safety Follow-up Visit will be done locally per standard of care, except as noted in "p" below for analysis of biomarker data. Note that while bone scans to determine disease status will be performed locally per standard of care, disease progression is to be confirmed using RECIST criteria as described in Section 9.2.

p. For subjects who do not have metastatic disease progression, a blood sample for biomarker analysis will be collected prior to and at the time of metastatic disease progression. For subjects currently enrolled in the study who have metastatic disease progression, a single sample will be obtained. A blood sample may also be collected at the 30-day Safety Follow-up Visit, if not previously. For the Optional Drug Holiday Phase, samples will be collected at the time of study drug discontinuation, at confirmed PSA progression at any point during year 1, and at "off study" if no signs of disease progression.

q. Serum testosterone will be monitored every 3 months until return to normal levels for up to 1 year.

r. PSA will be monitored monthly for 3 months and then once every 3 months thereafter for up to 1 year, and thereafter per standard of care.

s. Subjects with a negative bone scan within the previous 3 months and have been on study for > 5 years, are eligible to participate in the Optional Drug Holiday Phase, and thereafter per standard of care

TIME AND EVENTS SCHEDULE FOR PROCEDURES TO BE PERFORMED

Procedures and Evaluations	Screening Phase (Days)	Core Study Treatment Phase									End of Core Study Treatment Visit [b]	Pre-metastatic Disease Follow-up Phase [b]	30-day Safety Follow-up Visit [b]
		Cycle (Day)											
		1[a]		2		3		4	5	6			
	(-28 to -1)	(1)	(15)	(1)	(15)	(1)	(15)	(1)	(1)	(1)			
Informed consent	X												
Dispense study card [c]	X												
Medical history, prior medications including prior prostate cancer therapies [d]	X												
Height	X												
ECOG status	X												
MUGA scan or Cardiac ECHO [e]	X												
Demography	X												
Complete physical exam [f]	X										X	per standard of care [o]	
Vital signs/weight/and examination for volume overload [g]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [o]	per standard of care [o]
12 Lead ECG	X							X			X		
Coagulation factors PT/PTT (INR)	X		X										per standard of care [o]
Biomarker sample												X [p]	X [p]
Hematology	X	X	X	X	X	X		X	X	X	X	per standard of care [o]	per standard of care [o]
Serum chemistry [h]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [o]	per standard of care [o]
Fasting glucose	X	X	X	X	X	X		X	X	X	X	per standard of care [o]	per standard of care [o]
Serum lipids	X					X			X		X	per standard of care [o]	per standard of care [o]
Liver function tests [i]	X	X	X	X	X	X	X	X	X	X	X	per standard of care [o]	per standard of care [o]
Serum testosterone	X	X						X			X	per standard of care [o]	per standard of care [o]
PSA [j]	X	X						X			X	per standard of care [o]	per standard of care [o]
CT/MRI	X [k]							X [k]			X [k]	per standard of care [k,o]	
Bone scan	X [k]							X [k]			X [k]	every cycle per standard of care [k,o]	

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Procedures and Evaluations	Screening Phase (Days)	Core Study Treatment Phase										Pre-metastatic Disease Follow-up Phase [b]	30-day Safety Follow-up Visit [b]
		Cycle (Day)									End of Core Study Treatment Visit [b]		
		1[a]		2		3		4	5	6			
	(-28 to -1)	(1)	(15)	(1)	(15)	(1)	(15)	(1)	(1)	(1)			
Abiraterone acetate and prednisone distribution [l]		X		X		X		X	X	X	X	every cycle	
Study agents compliance assessment				X		X		X	X	X	X	every cycle	
Concomitant medications [d]	X	X	X	X	X	X	X	X	X	X	X	every cycle	X
Adverse events [m]	X	X	X	X	X	X	X	X	X	X	X	every cycle	X
Changes in prostate cancer therapy												every cycle [n]	X
Disease status												per standard of care [o]	

a. A cycle is defined as 28 days.

b. The End of Core Study Treatment Visit is to occur at the following times:

- On Day 1 of Cycle 7;
- At the time of discontinuation of abiraterone acetate if discontinuation occurs prior to completion of the Core Study Treatment Phase;
- If possible, at the time of withdrawal from the study if withdrawal occurs prior to completion of the Core Study Treatment Phase; or
- In the event of radiographic evidence of disease progression prior to completion of the Core Study Treatment Phase.

At the time of the current protocol, the Core Study Treatment Phase has been completed.

After the Core Study Treatment Phase, subjects may enter the Pre-metastatic Disease Follow-up Phase and continue to receive abiraterone acetate until metastatic disease progression is confirmed. At the time of metastatic disease progression, the subject is to be discontinued from abiraterone acetate.

Note that prior to Protocol Amendment 4, subjects may have continued to receive abiraterone acetate in an Optional Post-metastatic Disease Follow-up Phase. This Phase has been eliminated from the current protocol; however, those subjects who are currently in the Optional Post-Metastatic Follow-up Phase as of the date of this protocol may remain on study. For these subjects, procedures to be followed are listed under the Pre-metastatic Disease Follow-up Phase column.

All subjects will be required to return to the study site 30 days after receiving their last dose of abiraterone acetate for safety follow-up.

The duration of study participation is anticipated to be approximately 2 years. The completion of the entire Core Study Treatment Phase is defined as the time at which the last subject completes the End of Core Study Treatment Visit. The end of the study is defined as the point at which all subjects have progressed to metastatic disease.

c. Subjects must be provided with a study card indicating the name of the investigational study agents, the study number, the investigator's name, a 24-hour emergency contact number, and, excluded concomitant medications.

d. Refer to Section 8 for further details on reporting prior and concomitant medications.

e. MUGA or ECHO scan should be obtained at baseline (existing documented MUGA or ECHO scan up to 28 days prior to Cycle 1 Day 1 may be used for this screening assessment). A cardiac ECHO may be used if MUGA is not available, when ECHO is standard of care for the institution, or due to the time interval between the MUGA and bone scan that is required by the institution.

f. Complete physical examination includes head, eyes, ears, nose, and throat; chest; cardiac; abdominal; extremities; neurologic; and lymph node examinations.

g. Vital signs include upright blood pressure, heart rate, respiratory rate, and body temperature. Weight and an examination for volume overload will also be performed at these visits. If signs of volume overload are noted, and a diuretic is initiated, potassium will need to be monitored more frequently (refer to Section 6.2.3 for further details); similarly, if a subject is treated with a diuretic for hypertension, potassium will need to be monitored more frequently (refer to Section 6.2.2 for further details).

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h. Subjects who enter the study on exogenous potassium supplementation or who experience low potassium may need more frequent monitoring for hypokalemia; refer to Section 6.2.1 for further details.

i. Liver function tests must include: alkaline phosphatase, ALT, AST, LDH, and direct and total bilirubin. Subjects who experience an abnormal liver function test result may need more frequent monitoring; refer to Section 6.2.4 for further details.

j. If a digital rectal examination is performed, PSA must be sampled prior to the examination.

k. Scans (existing documented bone scans, and CT or MRI of the chest, abdomen, and pelvis) performed up to 28 days prior to Cycle 1 Day 1 may be used for screening assessments. If disease progression is observed on a postbaseline scan, confirmatory scan is required within 6 to 8 weeks after the initial diagnosis (see Section 9.2 for further details). Study agents should continue in the interim.

l. Study agents include abiraterone acetate and prednisone. Subjects will also continue to receive their GnRH monotherapy as prescribed. Subjects will begin taking study agents on Day 1 of Cycle 1. If prednisone and/or GnRH monotherapy are discontinued, subjects may continue to receive abiraterone acetate and continue on study as scheduled. If a subject needs to discontinue either of these therapies, the appropriate medical management of the subject needs to be discussed with the Medical Monitor. If a subject prematurely discontinues abiraterone acetate, prednisone should also be discontinued. Refer to Sections 10.2 and 10.3 for reasons for permanently discontinuing study agents or withdrawal from the study, respectively.

   Subjects may remain on abiraterone acetate until metastatic disease progression, the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, or until the sponsor determines it is necessary to stop the study.

m. Adverse events should be collected from the date informed consent is signed until 30 days after the last dose of study agents. Refer to Section 6.2 for abiraterone acetate dose adjustment in the event of toxicity.

n. Prior to metastatic disease progression, new therapy for prostate cancer is prohibited as described in Section 8.2.2.1; for those currently on study who have metastatic disease progression, new therapy is prohibited as described in Section 8.2.2.2.

o. All imaging studies, laboratory tests, or other safety monitoring as noted in the column above for the Pre-metastatic Disease Follow-Up Phase and the 30-day Safety Follow-up Visit will be done locally per standard of care, except as noted in "p" below for analysis of biomarker data. Note that while bone scans to determine disease status will be performed locally per standard of care, disease progression is to be confirmed using RECIST criteria as described in Section 9.2.

p. For subjects who do not have metastatic disease progression, a blood sample for biomarker analysis will be collected prior to and at the time of metastatic disease progression. For subjects currently enrolled in the study who have metastatic disease progression, a single sample will be obtained. A blood sample may also be collected at the 30-day Safety Follow-up Visit, if not previously obtained.

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; GnRH = gonadotropin-releasing hormone; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PSA = prostate-specific antigen; PT/PTT (INR) = prothrombin time/partial thromboplastin time (international normalized ratio); RECIST = Response Evaluation Criteria in Solid Tumors

Amendment 5 - 17 Apr 2017

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below.

1. Description/Rationale: To be aligned with current Janssen prostate cancer clinical trials, and in consideration of optimal bone health, supportive therapy with calcium/vitamin D, bisphosphonates or denosumab are now allowed/may be initiated, as appropriate and in accordance with label indications.

Sections Affected	Original Content	Amended/New Content
Section 8.2.1, Permitted Therapy: Prior to or Following Metastatic Disease Progression (3rd bullet)	Bisphosphonate and denosumab usage is allowed only if subjects are on the medication prior to Day 1 of Cycle 1	Bisphosphonate and denosumab usage is allowed ~~only if subjects are on the medication prior to Day 1 of Cycle 1~~

2. Description/Rationale: Prior references to Protocol Amendment 4 as the "current protocol" have been edited wherever needed to clarify that there is now Amendment 5.

Amendment 4 - 05 Apr 2016

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study and therefore are not described below.

Description/Rationale: Prior to this amendment, the protocol included an Optional Post-metastatic Disease Follow-up Phase. At this time, only a very limited number of subjects have taken advantage of this option, and as abiraterone acetate with prednisone is approved and available for metastatic CRPC, this optional phase has been eliminated from the current protocol.

At the time of this amendment the Core Study Treatment Phase has been completed and text was updated to reflect that the remaining subjects are currently in the Follow-up Phase of the study. In accordance with this, and following the sensitivity analysis for rPFS, the current protocol was also modified to streamline procedures in the Pre-metastatic Disease Follow-up Phase such that imaging and safety evaluations are to be conducted locally per standard of care.

As acquired genetic mutations in the androgen pathway may lead to resistance to drug treatment, biomarker evaluation may provide information on these changes that are associated with resistance to drug treatment and disease progression. Hence, blood sample collection has been added to the current protocol to evaluate gene expression from a panel of RNA and DNA biomarker candidates. Additional markers associated with the disease and treatment may be evaluated based on emerging evidence.

Additional changes were made for clarity.

Sections Affected	Original Content	Amended/New Content
Synopsis, Exploratory Objectives, new 2nd bullet and Section 2, Objectives, Exploratory Objectives, new 2nd bullet	*(None)*	• To evaluate exploratory biomarkers predictive of resistance to abiraterone acetate treatment.
Synopsis, Overview of Study Design: 2nd paragraph; Section 3.1, Study Design, 2nd paragraph; and Section 9.1 Overview, 1st paragraph	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28-day cycles); a Pre-metastatic Disease Follow-up Phase; and an Optional Post-metastatic Disease Follow-up Phase. A study treatment cycle is 28 days.	The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six, 28-day cycles); a ***Pre-metastatic Disease Follow-up Phase; and a 30-day Safety Follow-up Visit***. A study treatment cycle is 28 days.
New 4th paragraph Previously 4th and 5th	*(None)* After the Core Study Treatment Phase, subjects may enter	***At the time of the current protocol (Protocol Amendment 4), the Core Study Treatment Phase has been completed.*** After the Core Study Treatment Phase, subjects may enter

paragraphs, now 5th paragraph	the Pre-metastatic Disease Follow-up Phase and continue to receive abiraterone acetate until metastatic disease progression is confirmed. At this time, subjects may opt to continue to receive abiraterone acetate in the Optional Post-metastatic Disease Follow-up Phase. During the Optional Post-metastatic Disease Follow-up Phase, subjects will be required to return to the study site at the start of each cycle to receive study agents. Assessments will be limited to monitoring of study treatment compliance, safety reporting, and documentation of changes in prostate cancer disease status and therapy. Subjects may receive additional therapies at the investigator's discretion during this phase, with the exception of those noted in Section 8.2.2.2.	the Pre-metastatic Disease Follow-up Phase and continue to receive abiraterone acetate until metastatic disease progression is confirmed. During the ***Pre***-metastatic Disease Follow-up Phase, subjects will be required to return to the study site at the start of each cycle to receive study agents. Assessments will be limited
New 6th paragraph	*(None)*	
9th paragraph	Subjects may remain on abiraterone acetate until the end of the study, the investigator decides that continuing on abiraterone acetate is not in the subject's best interest, the subject withdraws, or until the sponsor determines it is necessary to stop the study.	