Janssen Research & Development*

Clinical Protocol

A Phase 3b Multicenter, Open-label Abiraterone Acetate Long-term Safety Study

Protocol 212082PCR3010; Phase 3b

JNJ-212082 (abiraterone acetate)

Amendment INT-2

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Only sites in the United States (U.S.) will conduct this study under U.S. Food & Drug Administration (FDA) IND regulations (21 Code of Federal Regulations [CFR] Part 312).

EudraCT NUMBER: 2011-005243-28

Issue/Report Date: 11 March 2015
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-ERI-29599689:5.0

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

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Peter De Porre, M.D.

Institution: Janssen Research & Development, LLC

Signature: PPD Date: PPD

(Day Month Year)

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

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LIST OF IN-TEXT TABLES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	30 November 2011
Amendment INT-1	9 April 2012
Amendment INT-2	11 March 2015

Amendments are listed beginning with the most recent amendment.

Amendment INT-2 (11 March 2015)

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

The overall reason for the amendment: The overall reason for the amendment is to extend the period for long-term safety follow up.

Applicable Section(s)	Description of Change(s)
Rationale: Specified that follow-up for safety will continue for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012)	
Synopsis Rationale, Objective, Overview; 1.1 Rationale; 2.1. Objective; 3.1. Overview; 3.2 Rationale; 9.1.1.2. End-of-Treatment Visit; 10.1. Completion; 16.1. Design Considerations	Updated follow-up for safety to a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012).
Rationale: To provide updated drug-drug interaction information for CYP3A4	
Section 8.1 Drug-Drug Interaction	Text updated to include current CYP3A4 drug-drug interaction information
Rationale: To comply with current internal standards for protocol development	
Throughout the protocol	Mandatory protocol text was updated
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (9 April 2012)

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

The overall reason for the amendment: The overall reason for the amendment is to add long-term safety data collection in this study.

Applicable Section(s)	Description of Change(s)
Rationale: Changed this study from a long-term access study to a long-term safety follow-up study, per Medicines and Healthcare products Regulatory Agency (MHRA) request.	
Title page; Synopsis Protocol Title	Replaced the word “access” with the word “safety” in the protocol title.
Synopsis Rationale, Objective, Hypothesis, Overview; 1.1 Rationale; 2.1. Objective; 2.2. Hypothesis; 3. Design and Rationale; 3.1. Overview; 3.2 Rationale; 16.1. Design Considerations	Specified that this is a long-term safety follow-up study.
Rationale: Specified that follow-up for safety will continue for a maximum duration of 3 years from the protocol issue date of 9 April 2012, per MHRA request.	
Synopsis Rationale, Objective, Overview; 1.1 Rationale; 2.1. Objective; 3.1. Overview; 3.2 Rationale; 9.1.1.2. End-of-Treatment Visit; 10.1. Completion; 16.1. Design Considerations	Updated follow-up for safety to a maximum of 3 years from the protocol issue date of 9 April 2012.
Rationale: To allow for potential extension of study duration following review of the safety data at 3 years.	
Synopsis Rationale, Overview; 1.1 Rationale; 3.1. Overview; 3.2 Rationale; 9.1.1.2. End-of-Treatment Visit; 10.1. Completion; 16.1. Design Considerations	Added statement that consideration will be given to extend the study duration following review of the safety data at 3 years.

Applicable Section(s)	Description of Change(s)
Rationale: To ensure subject's anonymity.	
17.3. Subject Identification	Indicated that subject will be identified by subject ID and date of birth instead of the assigned number.
Rationale: To comply with current standards for safety reporting.	
16.2.2. IEC/IRB	Replaced "Annual Safety Reports" with "Development Safety Update Report."
Rationale: To comply with current internal standards for the company name (new legal entity).	
Title page; Investigator Signature Page	Replaced with Janssen Research & Development, LLC.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3b Multicenter, Open-label Abiraterone Acetate Long-term Safety Study

Abiraterone [17-(3-pyridyl) androsta-5, 16-dien-3β-ol] is an irreversible inhibitor of CYP17 (17α-hydroxylase/C17, 20-lyase), a dual function enzyme that catalyzes 2 critical reactions in the synthesis of testosterone. Abiraterone acetate is the prodrug of the active drug abiraterone. Abiraterone acetate has received marketing approval in the United States, European Union, Canada, Brazil, and Switzerland for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel treatment. It is being investigated for the treatment of mCRPC in men who have not previously received chemotherapy for mCRPC and in women with metastatic breast cancer.

The rationale for this study is to collect follow-up safety data from subjects in completed abiraterone acetate studies (eg, studies in which the final analysis of the primary endpoint has been performed) for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012).

OBJECTIVE AND HYPOTHESIS

Objective

To collect long term follow-up safety data from subjects in completed abiraterone acetate studies for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012).

Hypothesis

This is an open-label uncontrolled long-term safety follow-up study to provide continued abiraterone acetate access to subjects who are receiving treatment in an abiraterone acetate clinical study at the time the study is considered complete. No hypothesis is being tested.

OVERVIEW OF STUDY DESIGN

This Phase 3b multicenter, open-label study is designed to collect long-term follow-up safety data from subjects in completed abiraterone acetate studies for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012).The subjects will continue with the same abiraterone acetate and low dose corticosteroid regimen they were receiving in the previous abiraterone acetate clinical study until the investigator determines that the subject is not receiving benefit from continued treatment, the study is terminated by the sponsor or for other reasons as defined in the protocol. Subjects can be withdrawn from the study if an alternative access (eg, patient-assistance program or commercial source of abiraterone acetate) is available and feasible.

Subjects will sign the informed consent and be screened for eligibility during the Screening Phase. Eligibility in this study requires that subjects would have already received at least 3 months (3 cycles) of treatment. During the Treatment Phase, abiraterone acetate should be taken each day at least 2 hours after eating and no food should be eaten for at least 1 hour after taking abiraterone acetate. All subjects will also take a low dose corticosteroid (eg, 5 mg of prednisone or prednisolone orally twice daily); it is not required for the low dose corticosteroid to be taken at the same time as abiraterone acetate. For consistency, at the first dose of study medication all subjects will restart cycle count as Cycle 1, Day 1. Each cycle of treatment will be 28 days.

Investigators should monitor and assess the subjects for response to treatment or progression according to routine practice. Suggested timing and assessments are outlined in the Time and Events Schedule. The timing of assessments may be modified if clinically indicated or based on local label requirements. No efficacy data are being collected by the sponsor. Any serious adverse event should be reported to the sponsor by investigational staff within 24 hours of their knowledge of the event as outlined in the protocol. No other safety data are being collected by the sponsor.

SUBJECT POPULATION

The subjects enrolled in this study are participating in an abiraterone acetate clinical study that is now considered complete and will have received at least 3 months of abiraterone acetate and low dose corticosteroid treatment. Eligibility criteria also include the investigator's assessment that continued abiraterone acetate therapy may provide clinical benefit. The subjects should not have laboratory evaluations or medical conditions that would preclude them from continuing to receive abiraterone acetate.

DOSAGE AND ADMINISTRATION

Abiraterone acetate and low dose corticosteroids will be given orally as tablets according to the regimen established in the prior abiraterone acetate clinical study (eg, abiraterone acetate 1,000 mg [4 tablets] once daily without food with prednisone 5 mg orally twice daily). Lower doses of abiraterone acetate (500 mg or 750 mg daily) and lower doses of corticosteroids are permitted per the regimen established in the prior study. Study treatment will continue until the investigator determines the subject is no longer receiving benefit from continued treatment, or other reasons as described in the protocol.

EFFICACY EVALUATIONS

Investigators should monitor and assess the subjects for response to treatment or progression according to routine practice to determine whether continued treatment with abiraterone acetate is warranted. Suggested timing and assessments are outlined in the Time and Events Schedule. All assessments and evaluations should be documented in the source medical record. No efficacy data will be collected and analyzed by the sponsor.

SAFETY EVALUATIONS

Vital signs, physical examinations, clinical laboratory tests, and adverse events should be monitored and evaluated by the investigator according to routine practice. Suggested timing and assessments are outlined in the Time and Events Schedule. The timing of assessments may be modified if clinically indicated or based on local label requirements. All safety evaluations and adverse events should be documented in the source medical record.

Any serious adverse event occurring during the study must be reported to the sponsor by investigational staff within 24 hours of their knowledge of the event. The sponsor will only collect serious adverse events by the serious adverse event reporting process outlined in the protocol. No other safety data will be collected and analyzed by the sponsor.

STATISTICAL METHODS

The sample size for this study is not powered according to statistical calculation. It is estimated that approximately 300 subjects may participate in this study. The number of subjects enrolled will depend on the number of subjects from other abiraterone acetate studies who are receiving treatment at the time that a study is considered complete. No efficacy analyses are planned for this study.

SUGGESTED TIME AND EVENTS SCHEDULE

Phase 3b		Treatment Phase		
	Screening Phase	Cycle 1[a]	Every Third Cycle Until Treatment Discontinuation	End-of-Treatment Visit
	Day -30 to -1	Day 1	Day 1	
Study Procedures				
Informed consent	X			
Inclusion/exclusion criteria	X			
Hematology		X[b]	X[c]	
Serum chemistry, electrolytes, LFTs		X[b]	X[c]	
Dispense/administer study drug		X	X	
Drug accountability			X	
Tumor assessment/PSA response			X[d]	
Physical examination		X	X	
Vital signs		X	X	
Concomitant therapy		X	X	
Adverse events[e]	X	X	X	X

LFT=liver function test; PSA=prostate-specific antigen

[a]While the subjects enrolling in this study would have already received at least 3 months (3 cycles) of treatment, for consistency, all subjects will restart cycle count at Cycle 1, Day 1.

[b]Use laboratory assessments from the last visit in the previous abiraterone acetate study if the visit occurred 30 days or less from Cycle 1, Day 1.

[c]The suggested timing of laboratory assessments may be more frequent as clinically indicated or modified to meet local label requirements.

[d]Tumor assessment/PSA response evaluations are to be performed at the discretion of the investigator based on routine treatment or as clinically indicated.

[e]Serious adverse events should be reported to the sponsor by investigational staff within 24 hours of their knowledge of the event using the instructions provided with the Serious Adverse Event Form. An End-of-Treatment Visit (or phone call) for a safety assessment should take place at least 30 days after the last dose of study medication.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mCRPC	metastatic castration-resistant prostate cancer
NCI	National Cancer Institute
PQC	Product Quality Complaint
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

1. INTRODUCTION

Abiraterone [17-(3-pyridyl) androsta-5, 16-dien-3β-ol] is an irreversible inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase), a dual function enzyme that catalyzes 2 critical reactions in the synthesis of testosterone. Abiraterone acetate is the prodrug of the active drug abiraterone. Abiraterone acetate has received marketing approval in the United States, European Union, Brazil, Switzerland, and Canada for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel treatment. It is being investigated for the treatment of mCRPC in men who have not previously received chemotherapy for mCRPC and in women with metastatic breast cancer.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of abiraterone acetate, refer to the latest version of the Investigator's Brochure for abiraterone acetate.[1]

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

The rationale for this study is to collect follow-up safety data from subjects in completed abiraterone acetate studies (eg, studies in which the final analysis of the primary endpoint has been performed) for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012). The early Phase 1 and 2 studies have only a few subjects continuing to receive treatment. Moving these subjects and the subjects from completed Phase 3 studies to a single access study improves coordination of the management of these subjects.

2. OBJECTIVE AND HYPOTHESIS

2.1. Objective

To collect long term follow-up safety data from subjects in completed abiraterone acetate studies for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012).

2.2. Hypothesis

This is an open-label uncontrolled long-term safety follow-up study to provide continued abiraterone acetate access to subjects who are receiving treatment in an abiraterone acetate clinical study at the time the study is considered complete. No hypothesis is being tested.

3. STUDY DESIGN AND RATIONALE

This is a Phase 3b, multicenter, open-label, long-term safety follow-up study. Approximately 300 subjects from other abiraterone acetate clinical studies will participate in this study. Subjects must have received at least 3 months of treatment with abiraterone acetate and low dose corticosteroid (eg, prednisone or prednisolone) and, based on investigator assessment, may benefit from continued treatment.

3.1. Overview of Study Design

This study is designed to collect long-term follow-up safety data from subjects who received at least 3 months of abiraterone acetate treatment in completed abiraterone acetate studies and are still deriving benefit from continued treatment based on investigator assessment. Follow-up for safety in this study will continue for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012). The subjects will continue with the same abiraterone acetate and low dose corticosteroid dosing regimen they were receiving in the previous abiraterone acetate clinical study until the investigator determines that the subject is no longer receiving benefit, the sponsor terminates the study, or for other reasons as defined in Section 10. Subjects can be withdrawn from the study if an alternative access (eg, patient-assistance program or commercial source of abiraterone acetate) is available and feasible.

Subjects will sign the informed consent and be screened for eligibility during the Screening Phase. Subjects enrolling in this study would have received at least 3 months (3 cycles) of treatment. During the Treatment Phase, abiraterone acetate should be taken each day at least 2 hours after eating and no food should be eaten for at least 1 hour after taking abiraterone acetate. All subjects will also take a low dose corticosteroid (eg, 5 mg of prednisone or prednisolone orally twice daily); it is not required for the low dose corticosteroid to be taken at the same time as abiraterone acetate. For consistency, all subjects will restart cycle count as Cycle 1, Day 1. Each cycle of treatment will be 28 days.

Suggested timing and assessments are outlined in the Time and Events Schedule. While the protocol has recommendations, the timing of assessments is at the discretion of the investigator as clinically indicated or modified to meet local label requirements. Investigators should monitor and assess the subjects for response to treatment or progression according to routine practice or as clinically indicated to determine whether continued treatment with abiraterone acetate is warranted. No efficacy data are being collected by the sponsor. Serious adverse events should be reported to the sponsor by investigational staff within 24 hours of their knowledge of the event using instructions provided in the Serious Adverse Event Report Form (see Section 12.3.2). No other safety data will be collected and analyzed by the sponsor. An End-of-Treatment Visit or phone call for a safety assessment should take place at least 30 days after the last dose of abiraterone acetate.

3.2. Rationale for Study Design

This long-term safety study was designed to collect follow-up safety data from subjects in completed abiraterone acetate studies for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012). The sponsor recommends tumor assessments to take place every 3 months as was done after 4 cycles of treatment in the Phase 3 studies. For laboratory evaluations, the sponsor also recommends evaluations at least every 3 months unless more frequent evaluations are required per the local label. The dispensing of study medication and drug accountability also occur every 3 months, thus making it more convenient for the subject.

End of study definition: The study is considered completed with the last End-of-Treatment safety assessment for the last subject participating in the study (maximum study duration of 6

years from the protocol INT-1 issue date of 9 April 2012) or upon a decision by the sponsor to terminate the study.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

4.1. Inclusion Criteria

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

1. Currently participating in an abiraterone acetate clinical study considered complete and had received at least 3 months of treatment with abiraterone acetate tablets

2. Investigator's assessment that continued abiraterone acetate therapy will be safe and beneficial

3. If a man is sexually active with a woman of childbearing potential (eg, premenarchal, non-postmenopausal), he must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study drug

4. Sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Medical conditions that require hospitalization

2. Any condition or situation which, in the opinion of the investigator, may put the subject at significant risk, may confound the study results, or may interfere significantly with subject's participation in the study

4.3. Prohibitions and Restrictions

Subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- If a man is sexually active with a woman of childbearing potential (eg, premenarchal, non-postmenopausal), he must use a double barrier method of birth control and not donate sperm during the study and for 3 months after receiving the last dose of study drug.

- Treatment restrictions outlined in Section 8.

5. TREATMENT ALLOCATION AND BLINDING

This is an open-label study; subjects will continue the same treatment regimen they were receiving during their participation in the previous abiraterone acetate clinical study.

6. DOSAGE AND ADMINISTRATION

Abiraterone acetate will be given orally as tablets once daily continuously according to the regimen established in the previous abiraterone acetate clinical study (eg, abiraterone acetate 1,000 mg taken as four 250-mg tablets). Abiraterone acetate should be taken at least 2 hours after eating. Also, no food should be eaten for at least 1 hour after taking the dose. Lower doses of abiraterone acetate (500 mg or 750 mg daily) are permitted per the regimen established for a subject in the previous study. Each cycle consists of 28 days. Sufficient study drug for 3 cycles will be dispensed and taken outside the clinic. A missed dose of abiraterone acetate should be omitted and not made up. Study treatment will continue until the investigator decides the subject is no longer receiving benefit from continued treatment or other reasons as defined in Section 10.

Prednisone or prednisolone (5 mg tablet twice daily) or other corticosteroid need not be taken at the same time as abiraterone acetate. Lower doses of corticosteroids are permitted per the regimen established for the subject in the previous study. A change in the dose of abiraterone acetate does not necessarily warrant a change in the dose of corticosteroid. If a corticosteroid dose is missed, it should be omitted and will not be made up.

Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol (see Section 14).

6.1. Dose Modification and Management of Adverse Events

In clinical studies, abiraterone acetate was generally well tolerated. The most common abiraterone acetate-related adverse events included fatigue (cortisol reduced by CYP17 inhibition) and mineralocorticoid-related hypertension, fluid retention, and hypokalemia (compensatory adrenocorticotropic hormone [ACTH] drive). Low dose prednisone/prednisolone or other glucocorticoids are expected to mitigate these effects through cortisol supplementation and abrogation of the ACTH drive.

For the management of adverse events known to be associated with abiraterone acetate treatment follow the local label instructions. In areas where abiraterone acetate does not yet have marketing authorization, follow the management guidelines outlined in Sections 6.1.1 through 6.15 (as applicable).

Adverse events may be related to progressing prostate cancer. Therefore, investigators are strongly encouraged to use approaches other than dose reduction to address adverse events. Up to 2 dose reductions are allowed for adverse events if the dose at the time of the adverse event was the full dose (ie, 1,000 mg [4 tablets]); doses of abiraterone acetate lower than 500 mg/day (2 tablets) are not allowed. At each dose reduction the dose will be reduced by 1 tablet, eg, 4 tablets (1,000 mg) to 3 tablets (750 mg), and 3 tablets (750 mg) to 2 tablets (500 mg). After an

abiraterone acetate dose reduction, the abiraterone acetate dose should not be increased without documentation of adverse event resolution. If interruption of abiraterone acetate is required, dosing should not be resumed until resolution of the adverse event is documented.

Subjects receive low-dose prednisone/prednisolone (or other corticosteroid) taken with abiraterone acetate. Following prolonged glucocorticoid therapy, subjects may develop Cushing's syndrome, characterized by central obesity, thin skin, easy bruising, bone loss, avascular necrosis of the hip, cataracts, and proximal myopathy. With long-term glucocorticoid therapy, a rapid withdrawal may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise, which may occur even without evidence of obvious adrenal insufficiency.

6.1.1. Management of Hypokalemia

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

Table 1: **Hypokalemia Management**

Serum Potassium	Grade of Hypokalemia	Action	Further Action or Maintenance
Low K+ or history of hypokalemia		At least weekly laboratory electrolyte evaluations	Titrate potassium supplement dose to serum K+ ≥3.5 to ≤5.0 mM; maintenance at ≥4.0 mM is recommended.
<3.5 to 3.0 mM	Grade 1 to 2	Initiate oral K+ supplementation	Titrate potassium supplement dose to serum K+ ≥3.5 to ≤5.0 mM; maintenance at ≥4.0 mM is recommended.
<3.0 to 2.5 mM	Grade 3	Withhold abiraterone acetate and initiate IV K+ and cardiac monitoring	Recommended to discuss reinitiation of abiraterone acetate with the medical monitor.
<2.5 mM	Grade 4	Withhold abiraterone acetate and initiate IV K+ and cardiac monitoring	Recommended to discuss reinitiation of abiraterone acetate with the medical monitor.

6.1.2. Management of Hypertension

- If Grade 1 or 2 adverse events occur, supportive management per investigator. No abiraterone acetate dose reduction.
- If Grade 3 or 4 adverse events occur, withhold abiraterone acetate. Adjust or add medications to mitigate the toxicity or consider the specific mineralocorticoid receptor blocker, eplerenone. When toxicity resolves to ≤Grade 1, resume abiraterone acetate at the previous dose.
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume abiraterone acetate at with the first dose level reduction (eg, if 1,000 mg [4 tablets] adjust to 750 mg [3 tablets] if at 750 mg [3 tablets] adjust to 500 mg [2 tablets]).

- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume study drug with the second dose level reduction (2 tablets, 500 mg of study drug) unless the dose was already at 500 mg (2 tablets), in this case discontinue abiraterone acetate.
- If toxicity recurs despite optimal medical management and at a dose of 500 mg (2 tablets), then discontinue abiraterone acetate.

6.1.3. Management of Edema and Fluid Retention

- If pedal edema occurs, supportive management per investigator. No abiraterone acetate dose reduction.
- If anasarca or pulmonary edema requiring supplemental oxygen occurs withhold abiraterone acetate. Adjust or add medications to mitigate the toxicity or consider the specific mineralocorticoid receptor blocker, eplerenone. When toxicity resolves to ≤Grade 1, resume abiraterone acetate at the previous dose.
- If toxicity recurs, withhold abiraterone acetate and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume abiraterone acetate with the first dose level reduction (eg, if 1,000 mg [4 tablets] adjust to 750 mg [3 tablets] or if at 750 mg [3 tablets] adjust to 500 mg [2 tablets]).
- If toxicity recurs, withhold study drug, and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume study drug with the second dose level reduction (2 tablets, 500 mg of study drug) unless the dose was already at 500 mg (2 tablets), in this case discontinue abiraterone acetate.
- If toxicity recurs despite optimal medical management and at a dose of 500 mg (2 tablets), then discontinue abiraterone acetate.

6.1.4. Management of Abnormal Liver Function Tests

- If Grade 1 increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT) or bilirubin occur (eg, increase in AST or ALT from ULN to 2.5X Upper limit of normal (ULN); increase in total bilirubin from ULN to 1.5X ULN): The frequency of liver function test monitoring should be increased, if the investigator assesses that the laboratory abnormalities are potentially related to abiraterone acetate. No abiraterone acetate dose reduction is required.
- If Grade 2 increases in AST, ALT or bilirubin occur (eg, increase in AST or ALT to >2.5-5X ULN; increase in total bilirubin from >1.5-3X ULN): The frequency of liver function test monitoring should be increased to once a week or more, if the investigator assesses that the laboratory abnormalities are potentially related to abiraterone acetate. No abiraterone acetate dose reduction is required.
- If Grade 3 increases in AST, ALT, or bilirubin occur (eg, increase in AST or ALT to >5X-20X ULN; increase in total bilirubin to >3X-10X ULN), withhold abiraterone acetate and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to ≤Grade 1 or baseline. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.

- If study abiraterone acetate resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin, then resume abiraterone acetate with first dose level reduction (eg, if 1,000 mg [4 tablets] adjust to 750 mg [3 tablets] or if at 750 mg [3 tablets] adjust to 500 mg [2 tablets]) when Grade 3 toxicities resolve to ≤Grade 1 or baseline value.
- If Grade 3 increases in AST, ALT, or bilirubin recur after the first dose reduction, withhold abiraterone acetate and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the liver function tests return to ≤Grade 1 or baseline value. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.
- If abiraterone acetate resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin with the first dose reduction, resume abiraterone acetate with the second dose level reduction (500 mg, 2 tablets) unless the dose was already at 500 mg (2 tablets), in this case discontinue abiraterone acetate (see below). Resumption should not occur until AST, ALT, or bilirubin returns to ≤Grade 1 or baseline value.
- If Grade 3 increases in AST, ALT, or bilirubin recur at the second dose reduction (500 mg [2 tablets]) dose reduction, subjects must discontinue abiraterone acetate immediately and will not be rechallenged. The subject should be followed until resolution of abnormal liver function tests.

- If Grade 4 increases in AST, ALT, or bilirubin occur (eg, increase in AST or ALT to >20X ULN; increase in total bilirubin to >10X ULN), subjects must discontinue abiraterone acetate immediately and not be rechallenged. The subject should be followed until resolution of abnormal liver function tests.

6.1.5. Management of Non-Mineralocorticoid Side Effects

- If Grade 1 or 2 toxicities occur, supportive management per investigator. No abiraterone acetate dose reduction.
- If Grade 3 or higher toxicities occur, including headache (interferes with activities of daily living), nausea (total parenteral nutrition/intravenous fluids), vomiting (6 or more episodes in 24 hours, total parenteral nutrition/intravenous fluids), diarrhea (intravenous fluids, hospitalization, hemodynamic collapse), or any other toxicity judged related to study drug is observed where the subjects safety is jeopardized, hold abiraterone acetate.
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume abiraterone acetate with the first dose level reduction.
- If toxicity recurs, withhold abiraterone acetate, and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume study drug with the second dose level reduction (500 mg [2 tablets]) unless the dose was already at 500 mg (2 tablets), in this case discontinue abiraterone acetate.
- If toxicity recurs despite optimal medical management and at a dose of 500 mg (2 tablets), then discontinue abiraterone acetate.

7. TREATMENT COMPLIANCE

Accurate records of all drug shipments as well as tablets dispensed and returned will be maintained. This inventory must be available for inspection by designated sponsor or regulatory authority representatives at any time. Drug supplies are to be used only in accordance with this protocol and under the supervision of the investigator. Study drug administration and dosing compliance should be assessed every 3 months. A count of all study drug provided by the sponsor will be conducted in the Treatment Phase.

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

8. CONCOMITANT THERAPY

- Supportive care medications should be used according to institutional guidelines. Subjects with prostate cancer who did not undergo orchiectomy, must receive concurrent treatment with a luteinizing hormone-releasing hormone (LHRH) agonist.
- Anti-bone resorptive therapies, such as bisphosphonates are permitted; calcium and vitamin D supplementation are permitted.
- Other anticancer cytotoxic, immunotherapy or hormonal (except LHRH) agents should not be used during treatment with abiraterone acetate (however, concomitant radiation therapy is permitted). Use of investigational drug therapy for any reason is prohibited.
- Concomitant therapy with aldactone or spironol should not be prescribed.

8.1. Potential for Drug-Drug Interactions

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing cytochrome P450 enzyme, CYP2D6. In a CYP2D6 drug-drug interaction study, the Cmax and AUC of dextromethorphan (CYD2D6 substrate) were increased 2.8-fold 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.

Based on *in vitro* data, abiraterone is a substrate of CYP3A4. In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer, rifampicin, 600 mg daily for 6 days followed by a single dose of abiraterone acetate 1,000 mg, the mean plasma AUC∞ of abiraterone was decreased by 55%. Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [Hypericum perforatum]) during treatment with abiraterone acetate are to be avoided, or used with careful evaluation of clinical efficacy. In a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Investigators may consult listings of medications that may have the potential for cytochrome P450 drug-drug interactions at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. If at any time an investigator suspects a drug-drug interaction due to abiraterone acetate therapy, an adverse event report should be filed.

For the most accurate and current information regarding potential drug-drug interactions with abiraterone acetate, refer to the latest version of the Investigator Brochure for abiraterone acetate.[1]

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of suggested evaluations applicable to this study.

9.1.1.1. Screening and Treatment Phase

All subjects must sign informed consent before conduct of any study procedure, and must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 4.1 and 4.2 respectively, before starting the Treatment Phase. During the Treatment Phase, subjects will receive daily treatment with the abiraterone acetate and low dose corticosteroid dosing regimen they received in the previous study. Subjects enrolling in this study are moving over from a completed abiraterone acetate study and would have received at least 3 months (3 cycles) of abiraterone acetate treatment. For consistency, the subjects will restart at Cycle 1, Day 1 when they receive the first dose of study medication in this study.

9.1.1.2. End-of-Treatment Visit

Safety follow-up will continue for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012). Subjects should be followed for a safety assessment at least 30 days after the last dose of abiraterone acetate. The follow-up can take place as a scheduled visit or phone call at the discretion of the investigator.

9.2. Efficacy Evaluations

Investigators should monitor and assess the subjects for response to treatment or progression according to routine practice or as clinically indicated to determine whether continued treatment with abiraterone acetate is warranted. Suggested timing and assessments are outlined in the Time and Events Schedule. Any evaluations or findings should be documented in the source medical record. No efficacy data will be collected and analyzed by the sponsor for this study.

9.3. Safety Evaluations

Vital signs, physical examinations, clinical laboratory tests, and adverse events should be monitored and evaluated by the investigator according to routine practice. Suggested timing and assessments are outlined in the Time and Events Schedule. The timing of assessments should be

modified to meet local label requirements or as clinically indicated. Safety evaluations and adverse events should be documented in the source medical record. Any serious adverse event occurring during the study must be reported to the sponsor by investigational staff within 24 hours of their knowledge of the event. The sponsor will only collect serious adverse event data by the serious adverse event reporting process as described in Section 12.3.2. No other safety data will be collected and analyzed by the sponsor.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject is considered to have completed the study once they have discontinued treatment for any reason and had a follow-up safety assessment at least 30 days after the last dose of abiraterone acetate. Safety follow-up will continue for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012).

10.2. Withdrawal From the Study

Subjects can be withdrawn from the study if an alternative access (eg, patient-assistance program or commercial source of abiraterone acetate) is available and feasible.

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

- Lost to follow-up
- Withdrawal of consent
- Discontinuation of study treatment. A subject's study treatment will be discontinued if:
  - The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) that it is in the best interest of the subject to stop treatment
  - The investigator believes the subject is no longer receiving clinical benefit from continued abiraterone acetate treatment
- The sponsor terminates the study

11. STATISTICAL METHODS

No formal statistical analyses are planned.

11.1. Sample Size Determination

The sample size for this study is not powered according to statistical calculation. It is estimated that approximately 300 subjects may participate in this study. The number of subjects enrolled will depend on the number of subjects from other abiraterone acetate studies who are still receiving treatment at the time that a study is considered complete.

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.

For this study, the investigators should document adverse events in the source medical records and report serious adverse events as specified in Section 12.3.2.

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.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject

or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if 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. For a non-sponsor investigational medicinal product (eg, a comparator product) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is doubtful, 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 the drug.

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

The NCI-CTCAE Version 4.0 may be used to grade the severity of adverse events. Adverse events not listed in the NCI-CTCAE may be graded as follows.

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

12.2. Special Reporting Situations

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

- Overdose of a sponsor medicinal product
- Suspected abuse/misuse of a sponsor medicinal product
- Inadvertent or accidental exposure to a sponsor medicinal product
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor medicinal product
- Unexpected therapeutic or clinical benefit from use of a sponsor medicinal product
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor medicinal product, eg, name confusion)

Special reporting situations should be recorded in the source medical record. Any special reporting situation that meets the criteria of a serious adverse event should also be reported to the sponsor as indicated in Section 12.3.2.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be recorded in the source medical record from the time a signed and dated informed consent form is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of abiraterone acetate, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Disease progression should not be reported as an adverse event. However, the signs and symptoms of clinical sequelae resulting from disease progression should be reported if they fulfill the serious adverse event definition (see Section 12.1.1, Adverse Event Definitions and Classification). 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 medical record. 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 source medical record 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 medical record 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 (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

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

12.3.2. Serious Adverse Events

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

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

Any serious adverse event that has not resolved by the end of the study, or that has 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/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the source medical record)

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (see Section 12.1.1, Adverse Event Definitions and Classifications).

12.4. Contacting Sponsor Regarding Safety

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

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, or reliability of a product, including its labeling or package integrity. A PQC 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 12.3.2, 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. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The abiraterone acetate 250-mg tablets supplied for this study are oval, white to off-white, and contain abiraterone acetate and compendial-grade (USP/NF/EP) lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide. Refer to the Investigator's Brochure for additional information.

Prednisone (or prednisolone in regions where prednisone is not marketed), 5mg tablets will be prescribed by the investigator. In some regions, prednisone/prednisolone may be provided by the sponsor. Any other low dose corticosteroids will be prescribed by the investigator.

14.2. Packaging

Abiraterone acetate will be supplied by the sponsor as 250-mg tablets packaged in high-density polyethylene bottles with child-resistant closures. There are 120 tablets per bottle.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

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

Bottles of abiraterone acetate should be stored at room temperature between 15º to 30º C with the cap on tightly and should not be refrigerated.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug preparation and handling.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for abiraterone acetate
- Pharmacy manual/site investigational product manual
- NCI-CTCAE Version 4.0
- Interactive Web Response System (IWRS) Manual
- Subject cards

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This study is designed to collect long-term follow-up safety data from subjects in completed abiraterone acetate studies for a maximum duration of 6 years from the protocol INT-1 issue date (9 April 2012). The study requires that serious adverse events are reported as outlined in Section 12.3.2. The study is not designed to evaluate efficacy.

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.

The total blood volume to be collected is considered to be within the normal range allowed for this subject population over this time frame.

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 well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials and subject information cards
- 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 the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the informed consent form, applicable recruiting materials, subject information cards and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)

- Revision(s) to informed consent form 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
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

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 IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects

will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her 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 informed consent form the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

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

When prior consent of the subject is not possible, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject must be informed about the study as soon as possible and give consent to continue.

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 fulfill the objectives of the study.

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

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

The subject has the right to request through the investigator access to his or her 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.

16.2.5. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

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

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

- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, informed consent form, 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 (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, 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, if applicable
- 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 subject ID and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

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

17.4. Source Documentation

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

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

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

17.5. Case Report Form Completion

No case report forms will be provided. All information will be documented in the source medical record.

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 sites, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain 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 site visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. The nature and location of all source documents will be identified to ensure that all sources of original data 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.

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 Completion/Termination

17.9.1. Study Completion

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

17.9.2. Study Termination

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

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

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

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

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. 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.

A minimum Clinical Study Report (CSR) will be generated by the sponsor at the completion of the study. This synoptic report will include a description of the study, the number of subjects enrolled and treatment administered, and a listing of serious adverse events. 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. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such 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, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

REFERENCES

1. JNJ-212082 (abiraterone acetate) Investigator's Brochure. Janssen Research and Development. Document ID No. EDMS-144937303.

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