

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

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**Randomized, Open-Label Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone With or Without Exemestane in Postmenopausal Women With ER+ Metastatic Breast Cancer Progressing After Letrozole or Anastrozole Therapy**

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**Protocol 212082BCA2001; Phase 2****Amendment INT-7****JNJ-212082 (abiraterone acetate)**

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

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

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

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## PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	11 March 2011
Amendment INT-1	25 March 2011
Amendment INT-2	20 June 2011
Amendment INT-3	4 November 2011
Amendment INT-4	19 September 2012
Amendment INT-5	18 March 2013
Amendment INT-6	20 January 2014
Amendment INT-7	27 April 2015

Amendments are listed beginning with the most recent amendment.

### Amendment INT-7 (27 April 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 to a maximum of 5 years from the final analysis clinical cut off.

Applicable Section(s)	Description of Change(s)
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**Rationale:** Specified that follow-up for safety will continue for an additional duration of up to 3 years from the existing date of 20<sup>th</sup> Sep 2015 in the current protocol (i.e., up to 20 September 2018)

Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 5 Treatment Allocation and Randomization; 16.2.3 Informed Consent;	Individual subjects who continue to derive benefit from the treatment they are currently receiving, will be offered the opportunity to continue on their existing study medication and followed-up for safety for an additional duration of up to 3 years (ie, up to 20 September 2018) from the date previously stated (20 September 2015) in the Amendment INT-6 protocol. The situation may be reassessed periodically for subjects still receiving study medication
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**Rationale:** To comply with current internal standards for protocol development

Throughout the protocol	Mandatory protocol text was updated
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**Rationale:** Minor errors were noted

Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
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**Amendment INT-6** (20 January 2014)

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

**The overall reason for the amendment:** The final analysis of the primary endpoint, progression-free survival (PFS) was performed after the predefined total of 150 PFS events were reported in the abiraterone plus exemestane group and in the exemestane alone group; the clinical cutoff date for the final analysis (CCO-FA) was 20 September 2013. The results did not show a clinically meaningful or statistically significant advantage of abiraterone acetate plus exemestane or abiraterone acetate alone over exemestane alone. There was also a slight increase in the incidence of adverse events in subjects treated with abiraterone acetate or with the combination of abiraterone acetate plus exemestane versus single-agent exemestane. However, individual subjects may derive benefit from the treatment they are currently receiving with continued control of disease in the absence of significant toxicity. Therefore, it was decided to offer all subjects still on study treatment the opportunity to continue on their existing study medication for up to 2 years from the CCO-FA (ie, up to 20 September 2015), at which point the situation will be reassessed for subjects still receiving study medication. Subjects who do not continue on study medication and those in long-term follow up will be discontinued from the study. The decision to continue on study medication or withdraw from the study will be made by the subject and the investigator.

Applicable Section(s)	Description of Change(s)
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**Rationale:** Based on the results of the final analysis, the primary endpoint of the study was not met.

Synopsis (Overview of Study Design; Time and Events Schedule); 3.1	The study is being amended to allow remaining subjects to continue to receive study medication for up to 2 years after the CCO-FA and to reduce the number of study-related procedures and amount of data to be collected.
Overview of Study Design; 5 Treatment Allocation and Randomization; 9.1.1	Subjects will be required to sign an updated informed consent form to continue participation under Amendment INT-6.
Overview (of Study Evaluations); 9.1.5 Follow-Up Phase; 10.1 Completion; 16.2.3 Informed Consent; Attachment 10	Attachment 10 has been added which includes a description of all procedures to be performed under Amendment INT-6. The Schedule of Events in this Attachment supersedes the Time and Events Schedule in the previous version of the protocol (Amendment INT-5).

**Rationale:** To advise investigators where potential new information regarding drug-drug interactions for abiraterone acetate may be found.

8.3 Special Concomitant Therapy	A reference to the Investigator Brochure has been added.
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**Amendment INT-5** (18 March 2013)

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 incorporate the recommendations of the Data Review Committee (DRC) following their review of the efficacy and safety results from the protocol-specified interim analysis of progression-free survival (PFS) (110 [50%] of progression or death events).

Applicable Section(s)	Description of Change(s)
	<p><b>Rationale:</b> The criterion for futility was met for the abiraterone acetate group and the DRC recommended that subjects no longer be randomized to this group. The sponsor is stopping randomization of subjects to the abiraterone acetate group. The criteria for futility or efficacy were not met for the abiraterone acetate plus exemestane group; the DRC recommended that this group continue per protocol. The sponsor will continue per protocol. Based on the findings in the 2 groups noted above, the DRC stated the study team may consider that subjects who progress in the exemestane alone group be allowed to crossover to the abiraterone acetate plus exemestane group. The sponsor considered this option but decided not to allow crossover and for subjects who progress on exemestane to discontinue study treatment. The sponsor also decided that subjects in the abiraterone acetate group be informed of the sponsor decision to discontinue randomized assignment to the abiraterone acetate group and to allow ongoing subjects to make their own decision about whether or not to continue further study treatment.</p>
Synopsis Overview of Study Design; Sample Size Determination; Section 3.1 Overview of Study Design; Section 11.1 Sample Size Determination	<p>Added a description of the DRC recommendations in the overview of study design. Added Attachment 9 to explain the revisions to the protocol based on the DRC recommendations.</p> <p>Added a revised sample size and number of events for the final analysis of PFS based on 2 treatment groups.</p>
	<p><b>Rationale:</b> Added cautionary wording for women who are pregnant or may be pregnant to avoid handling of abiraterone acetate tablets without protection. This wording is being incorporated into all new or amended abiraterone acetate protocols.</p>
Section 14.4 Preparation, Handling and Storage	<p>To avoid inadvertent exposure, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, eg, gloves. It is not known if either abiraterone acetate or its metabolites are excreted in human breast milk.</p>
	<p><b>Rationale:</b> Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. A drug-drug interaction study of abiraterone acetate and ketoconazole showed no clinically meaningful influence on abiraterone pharmacokinetics (PK). A drug-drug interaction study of abiraterone acetate and rifampicin showed reduced mean abiraterone plasma <math>AUC_{\infty}</math>. This information is being incorporated into all new or amended abiraterone acetate protocols.</p>
Section 8.3 Special Concomitant Therapy	<p>Added this wording to Section 8.3: 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 <math>AUC_{\infty}</math> of abiraterone was decreased by 55%. Strong inducers of CYP3A4 (eg, phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with abiraterone acetate are to be avoided, or used with careful evaluation of clinical efficacy.</p>

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> Removed cautionary wording regarding CYP3A4 inhibitors because drug interaction studies did not show any clinically meaningful effects of the strong CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics of either exemestane or abiraterone.
Section 4.3 Prohibitions and Restrictions	Removed reference to CYP3A4 inhibitors in text and in Table 1.
	<b>Rationale:</b> The storage conditions for prednisone and prednisolone were not correct and have been updated.
Section 14.4 Preparation, Handling and Storage	The correct temperature for storage of prednisone is 20 to 25°C (68 to 77 °F) and for prednisolone is below 25°C
	<b>Rationale:</b> Updated Attachment 5: Progressive Disease Notification Fax Sheet; Tom Griffin has replaced Margaret Yu as the project physician.
Attachment 5	Updated contact information.
	<b>Rationale:</b> Made minor editorial revisions for consistency with other protocols and incorporated minor changes from revised protocol template.
Throughout the protocol	Minor editorial changes and incorporation of new template language.

**Amendment INT-4** (19 September 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:** A prothrombin time (PT) is not done by many sites in Belgium, France, the Netherlands, and Spain, but an international normalized ratio (INR) is done instead. In addition, some subjects have abnormal but not clinically significant PT, which strictly per the current wording, would violate the protocol. This amendment allows an INR to be done whenever PT is not available. It also allows subjects with out of range PTs that are of no clinical significance to be eligible for the study.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> To allow INR to be done in place of PT, and to allow for subjects with PTs/ INRs, or PTT out of normal range but not clinically significant to be eligible for enrollment.
Time and Events Schedule	Specified coagulation as PT or INR, and PTT; defined INR in footnote.
4.1 Inclusion Criteria bullet 7	Changed criterion to: Clinically normal prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT) per investigator assessment.
	<b>Rationale:</b> To fix the discrepancy between the Time and Events Schedule and Section 9.4.4 on the timing of the tumor biopsy.
Time and Events Schedule, Tumor Biopsy row and footnote w	Changed timing of tumor biopsy from Day 1 of Cycle 1 to screening

Applicable Section(s)	Description of Change(s)
9.4.4 Fresh Tumor Biopsies	Changed timing of tumor biopsy from 14 days within randomization to screening
<b>Rationale:</b> To avoid the risk of the fax number changing again before the study is done.	
Attachment 5	Replaced fax numbers with "Janssen LTM include number".
<b>Rationale:</b> To comply with current internal standards for the company name (new legal entity).	
Title page; Investigator Signature Page; Attachment 5	Replaced Johnson & Johnson Pharmaceutical Research & Development, LLC with Janssen Research & Development, LLC.
<b>Amendment INT-3</b> (4 November 2011)	
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.	
<b>The overall reason for the amendment:</b> To collect circulating tumor cells (CTCs) from all subjects on study in order to improve the power of the CTC sub-study.	
Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Blood samples will be collected for CTC analysis from all subjects at baseline. Additional blood samples will be collected only if the CTCs meet the required minimum threshold at baseline.	
Synopsis Overview; Synopsis Biomarker Evaluations ;Time and Events Schedule footnote <sup>r</sup> ; 9.1.1 Overview Table 3; 9.4.3 Circulating Tumor Cells	Modified language to indicate that CTCs will be assessed from all subjects. The sites will be notified if a subject's Day 1 Cycle 1 sample does not meet a minimum threshold and no further CTC sampling should be done for the subject.
9.1.1 Table 3	Blood volumes increased.
<b>Rationale:</b> In certain countries, drawing of 40 mL of blood per timepoint may not be acceptable by their Ethics Committee.	
Time and Events Schedule footnote <sup>r</sup> ; 9.1.1 Overview; Table 3; 9.4.3 Circulating Tumor Cells	Added " <b>where local regulations permit</b> ".
<b>Rationale:</b> Clarified Type I error.	
Synopsis Sample Size; 11.1 Sample Size	Indicated that for each of the pair-wise comparisons, the statistical tests of treatment effects on primary endpoint of PFS will be conducted independently at the 2-sided 0.10 level of significance.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> Stratified log-rank test provides a method to adjust for the possible effect of prognostic factors on treatment responsiveness.
Synopsis Statistical Methods; 11.4.3 Analysis Methods	Nonstratified log-rank test was modified to stratified log-rank test.
	<b>Rationale:</b> No further assessment of endocrine markers, pharmacogenomics, PK, or CTCs will be done for subjects who have progressed on exemestane because there is no expectation that these tests will provide valuable information for the study.
Time and Events Schedule and footnotes <sup>r, s, t, and v</sup> ; 10.2 Discontinuation	Samples for evaluating the endocrine markers, pharmacogenomics, PK, or CTCs will not be collected from subjects receiving abiraterone acetate after crossing over from the exemestane treatment.
	<b>Rationale:</b> Specified the assays to be done on the CTCs.
3.2 Rationale	Added language to indicated that CTC samples will be taken to characterize AR, ER, PR, CYP17, CYP19, and other candidate markers related to abiraterone or to breast cancer.
	<b>Rationale:</b> Timing of cardiac evaluations using MUGA or ECHO and the timing of imaging to confirm disease progression were specified.
Time and Events Schedule and footnote <sup>g</sup> ; 9.3 Safety Evaluation	MUGA (or ECHO) will be captured at baseline and at every 3rd cycle thereafter.
3.2 Rationale	Imaging will be done on Day 1 of Cycles 3, 5 and 7, then on Day 1 of every 3rd cycles thereafter.
	<b>Rationale:</b> Clarified eligibility criteria for consistency with other sections in the study protocol.
4.1 Inclusion Criteria	<p>Criterion 2 indicated that in a subject with multiple biopsies of metastatic sites, the most recent biopsy prior to study entry should be submitted for evaluation of hormone receptor status.</p> <p>Criterion 3 specified that subjects with purely sclerotic lesions may not participate in the study as indicated in Section 9.2.1 of the protocol.</p> <p>Criterion 7 was modified for subjects to meet the hemoglobin, neutrophils, and platelets criteria, independent of growth factors and transfusions.</p> <p>Criterion 10 specified that bisphosphonate or denosumab may be initiated on the same day as the assigned study treatment.</p>
4.2 Exclusion Criteria	<p>Criterion 1 indicated prior treatment with ketoconazole for <math>\leq 7</math> days is permitted and topical formulations of ketoconazole are permitted.</p> <p>Criterion 2 specified that potential subjects must not have taken anastrozole, letrozole, fulvestrant, or any chemotherapy for at least 2 weeks (bevacizumab for at least 3 weeks) before randomization to be consistent with the other therapies.</p> <p>Criterion 10 specified that subjects with any active or uncontrolled disease that may require oral corticosteroid therapy should be excluded.</p>

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarified that CYP3A4 inhibitors and inducers should be avoided and not prohibited.	
4.3 Prohibitions	Modified language in the first bullet and in the title of Table 1 to indicate that CYP3A4 inhibitors and inducers should not be prohibited, but rather used with caution or avoided.
<b>Rationale:</b> Clarified which food and beverages were allowed during the PK substudy.	
4.3 Prohibitions	Specified which food and beverages are prohibited during the PK sampling.
<b>Rationale:</b> Specified that 2 dose reductions are allowed for drug-related adverse events, and not those attributable to disease progression.	
6.1 Dose Reduction	Up to 2 dose reductions <b>of abiraterone acetate</b> are allowed for adverse events <b>that the investigator attributes to abiraterone acetate</b> .
<b>Rationale:</b> Deleted to avoid redundancy with Section 12.1.3 of the protocol.	
6.1 Dose Reduction	<del>Adverse events including laboratory adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.</del>
<b>Rationale:</b> Made consistent with the U.S. package insert (USPI) for ZYTIGA.	
6.1.1 Management of Hypokalemia	Changed "the subject hospitalized" to "hospitalization considered".
<b>Rationale:</b> Further revised permitted supportive care and interventions for subjects enrolled in the study.	
8.2 Permitted Supportive Care	Conventional multivitamins, <del>selenium, and soy supplements.</del>
8.2 Permitted Supportive Care	<del>Bisphosphonates or denosumab is permitted for bone disease, provided a stable dose is documented for at least 2 doses before randomization.</del>
8.2 Permitted Supportive Care	Deleted the wording referring to the use of anti-infectives, hematopoietic cytokines, blood transfusions, and any medications to treat serious adverse events, because all details pertaining to these concomitant medications are to be documented in the eCRF.
8.2 Permitted Supportive Care	Language has been modified to indicate that if a subject is suspected of having progressed but has a not fully met all criteria for progression then certain treatment options are available.
8.2 Permitted Supportive Care	Changed "documented" to "suspected".
<b>Rationale:</b> The occurrence of neutropenia is unlikely in this study.	
8.3 Special Concomitant Therapy	Deleted language concerning the use of colony stimulating factors.
<b>Rationale:</b> Provided the details around the collection of tumor samples for molecular analyses.	
9.1.1 Overview	<b>Tumor samples are collected for ER subtyping and other molecular analyses.</b>
<b>Rationale:</b> Specified when the End-of-Treatment visit should occur.	
9.1.4 End-of-Treatment	<b>....occurs when the subject has met the criteria for discontinuation of study drug(s).</b>

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> Clarified language regarding the assessment of response in subjects with only bone metastasis.
9.2.1 Progression-Free Survival	<b>Disease progression should not be based on assessments of new sclerotic bone lesions. When bone disease is the only basis for determination of progression or response, only lytic bone lesions should be used. All disease progressions should be confirmed by the sponsor company via a faxed confirmation form (Attachment 5).</b>
	<b>Rationale:</b> Revised to reflect current biomarker storage policy.
9.5 Pharmacogenomic Evaluation;	Stored DNA samples <del>and relevant clinical data are made non-identifiable</del> <b>will be double-coded and stored for a period of 5 years.</b>
10.3 Withdrawal	Deleted language that indicated that all samples would be made unidentifiable.
	<b>Rationale:</b> Laboratory requisition forms and not the eCRFs will be used to record sample collection.
9.7 Sample Collection	...sample collection must be recorded on the <del>eCRF</del> <b>laboratory requisition forms.</b>
	<b>Rationale:</b> Clarified that the fax should document discontinuation due to disease progression only.
10.2 Discontinuation	Specified that the study drug discontinuation due to disease progression only should be communicated to the Sponsor via a fax; and only after the reasons are accepted by the sponsor, the study drugs can be discontinued.
	<b>Rationale:</b> Specified the subject's options regarding pharmacogenomic research at the time of withdrawal from the study.
10.3 Withdrawal	DNA extracted will be retained and used in accordance with the subject's original pharmacogenomic informed consent or if a subject withdraws the consent then the DNA sample will be destroyed.
	<b>Rationale:</b> Revised for consistency with the storage conditions specified in the ZYTIGA label.
14.4 Preparation, Handling, and Storage	Modified to state that abiraterone acetate, exemestane, and prednisone/prednisolone are all stored at room temperature (15 to 30°C; 59 to 86°F).
	<b>Rationale:</b> Subjects and not their legally accepted representative need to be able to complete the PRO scales in this study.
14.5 Accountability	Deleted language regarding the subjects' legally accepted representative.
	<b>Rationale:</b> Results from tests and procedures that are considered part of standard of care that were performed before signing of the ICF may be used for the study.
16.2.3 Informed Consent	<b>Results from laboratory tests, medical procedures and imaging or scans done as part of standard of care that have been performed before the consent form signature date may be used for the study.</b>
	<b>Rationale:</b> For compliance reasons, subjects should not be able to be identified by their initials.
17.3 Subject Identification, Enrollment, and Screening Logs	...will identify subjects by <del>initials and</del> assigned number. <del>only.</del>
	<b>Rationale:</b> To clarify response assessment.
Attachment 1	<b>Confirmations of PR and CR will be documented by a second CT or MRI at least 4 weeks after the initial response.</b>

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Provided the Progressive Disease Notification FAX form.	
Attachment 5	Attachment 5 was added.
<b>Rationale:</b> Specified the clinical laboratory tests to be performed. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) were missing in the previous amendment.	
Attachment 7	Added Clinical Laboratory: luteinizing hormone (LH), follicle stimulating hormone (FSH).
<b>Rationale:</b> Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Abbreviations	Made abbreviations consistent throughout.
<b>Amendment INT-2</b> (20 June 2011)	
This amendment is considered to be nonsubstantial 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, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.	
<b>The overall reason for the amendment:</b> To clarify the language regarding concomitant therapies with CYP2D6 substrates and dosing of abiraterone acetate to be consistent with the existing label.	
Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Added language to provide consistency with the USPI regarding concomitant therapies with CYP2D6 substrates	
Section 8.3 Special Concomitant Therapy	Added the following: "Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate."
<b>Rationale:</b> Added language to provide consistency with USPI regarding the dosing of abiraterone acetate with respect to food consumption	
Synopsis, Dosage and administration; Time and Events Schedule footnote f; Section 6.1 Dosage and administration	Clarified the dosing of abiraterone acetate with respect to consumption of food. "Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken."
<b>Rationale:</b> Consistency within the protocol. This was an oversight during the last amendment.	
Section 6.1 Dose Reduction and Toxicity Management	Removed incorrect text stating that the first level dose reductions of abiraterone acetate due to toxicity is from 1 g/day to 500 mg/day. Clarified the language with respect to dose reductions of abiraterone acetate, and provided consistency with the USPI.
<b>Rationale:</b> Consistency within the protocol. This was an oversight during the last amendment.	
Section 6.1 Dose Reduction and Toxicity Management	Adverse events including laboratory adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Additional clarity provided regarding prednisone discontinuations.	
Section 6.1 Dose Reduction and Toxicity Management	Discontinuation of prednisone will be individualized depending on investigator judgment. Abrupt discontinuation of prednisone after chronic therapy may trigger symptoms and signs consistent with adrenal insufficiency.
<b>Rationale:</b> Not previously defined in the protocol. This is now defined to be consistent within the abiraterone acetate program.	
Section 7 Treatment compliance	Added the language “Drug non-compliance is defined as missing $\geq 75\%$ of doses in 2 consecutive cycles or more than 14 days of therapy in 1 cycle”
<b>Rationale:</b> Inclusion criteria clarification based on questions from investigators.	
Section 4.1 Inclusion criteria	Divided the inclusion criteria #2 to 2 separate criteria; Subjects with disease confined only to bone may be included and Subjects with ER+, Her2- metastatic breast cancer, confirmed within 7 days before randomization with FFPE tissue from either primary or metastatic breast cancer site, that recurred during or within 6 months of discontinuing anastrozole or letrozole therapy in adjuvant or metastatic setting.
<b>Rationale:</b> The End-of-Treatment blood sample for PK evaluation is not needed.	
Pharmacokinetic Evaluation Section of the synopsis; Time and Events Schedule and footnote “u”; Section 9.1.1. Overview of Study procedures; Section 9.6 Pharmacokinetics Evaluation	Removed the language referring to PK sampling at End-of-Treatment
<b>Rationale:</b> Some sites identified for PK sampling cannot support overnight stays for patients.	
Time and Events Schedule footnote “u”; Section 9.1.1 Overview of Study procedures; Section 9.6 Pharmacokinetics Evaluation	Added language to specify that sites that are not capable of overnight stays for subjects will not collect the 12, 16, and 22 hour PK sampling timepoints on Days 1 and 15 of Cycle 1. Added “approximate” to the total volumes of blood collected per subject
<b>Rationale:</b> Increased blood volume is needed to be taken for CTC analyses	
Time and Events Schedule footnote “v”; Section 9.1.1 Overview of Study procedures and Table 3; Section 9.4.3 Circulating Tumor Cells	The blood sample volume was changed from 20 mL to 40 mL to be taken on Day 1 of Cycles 1 and 2 and at End-of-Treatment for CTC analyses.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> Analyses for CTC only to be performed on samples from subjects on the monotherapy arms of the study
Time and Events Schedule footnote “v”; Section 9.4.3 Circulating Tumor Cells	Clarification that blood for circulating tumor cell (CTC) analyses will only be taken from subjects randomized from the abiraterone/prednisone and exemestane treatment groups.
	<b>Rationale:</b> Biopsy of tumor more convenient with procedures done on Day 1 Cycle 1
Time and Events Schedule footnote “w”;	Eliminated the biopsy of tumor at baseline time point
	<b>Rationale:</b> Minor errors were noted.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

**Amendment INT-1** (25 March 2011)

This amendment is considered to be nonsubstantial 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, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

**The overall reason for the amendment:** The overall reason for the amendment is to clarify the description of the Follow-up phase versus the anticipated total study duration and to revise the timing of the CTC collection.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> The description of the study’s Follow-up phase versus the anticipated total study duration has been clarified.
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 9.1.5 Follow-Up Phase; 10.1 Completion	Whenever study drug is discontinued, subjects should be evaluated within 30 days during the End-of-Treatment visit and entered into the Follow-Up phase regardless of reason for study drug discontinuation, and monitored every 3 months ( $\pm 7$ days) until death, loss to follow-up, consent withdrawal, or abiraterone acetate development in this indication is discontinued. The total duration of the study is anticipated to be up to 3 years.
	<b>Rationale:</b> The CTC collection at Cycle 3 Day 1 has been removed.
Time and Events Schedule, Circulating Tumor Cells line entry and Footnote u; 9.4.3 Circulating Tumor Cells (Selected Study Sites)	Blood samples (20 mL) will be taken Day 1 of Cycles 1 and 2 and during the End-of-Treatment visit for CTC enumeration and molecular characterization.

Applicable Section(s)	Description of Change(s)
9.1.1 Overview, Table 3: Approximate Blood Volume Through Four Treatment Cycles	Circulating tumor cells (CTCs): Samples per subject=2; volume per subject (mL)=40. The total blood volume to be drawn with PK, CTC, DNA=220-320 mL.
<b>Rationale:</b> Minor modifications were made to reduce the exploratory biomarker analyses and provide flexibility in identifying which exploratory analyses may be performed.	
3.2 Study Design Rationale, DNA and Biomarker Collection; 9.4.1 Formalin-Fixed Paraffin-Embedded Tumor Tissue; 11.5 Biomarker Analyses	The text was revised from “will be performed” to “may be performed” and “will be analyzed” to “may be analyzed.” Also “and” has been replaced with “or” in some instances to provide flexibility.
3.2 Study Design Rationale, DNA and Biomarker Collection; 9.4.3 Circulating Tumor Cells (Selected Study Sites)	Ki-67 and 3 $\beta$ -hydroxysteroid dehydrogenase were removed from the CTC analysis and replaced with “other candidate markers.”
<b>Rationale:</b> To simplify the study, blood pressure home monitoring for subjects with suspected anxiety-induced hypertension has been removed, and study inclusion blood pressure was clarified as <160/95 mm Hg.	
Time and Events Schedule, Footnote j; 9.3 Safety Evaluation, Vital Signs	Upright sitting blood pressure, heart rate, respiratory rate, and oral or aural body temperature, should be recorded. <del>If anxiety induced hypertension is suspected, subject must document systolic blood pressure &lt;140 mm Hg and diastolic blood pressure &lt;90 mm Hg with at least two home morning measurements within 7 days before a scheduled visit.</del>
4.1 Inclusion Criteria Criterion #7	Subjects must have systolic blood pressure <160 mm Hg and diastolic blood pressure <95 mm Hg [Note: Hypertension controlled by antihypertensive therapy is permitted]. <del>For patients with suspected anxiety induced hypertension, systolic blood pressure &lt;140 mm Hg and diastolic blood pressure &lt;90 mm Hg may be confirmed via home monitoring within 14 days of randomization.</del>
6.1.2 Management of Hypertension	<u>Grade 1-2:</u> Management per investigator; investigators should maintain blood pressure <160/95 mm Hg with antihypertensive agents; do not reduce abiraterone acetate dose.
<b>Rationale:</b> To correct an inconsistency, specific details regarding the timing of blood sampling have been removed.	
Time and Events Schedule, Footnote f; 6 Dosage and Administration	All study drugs are oral and should be taken once daily. Abiraterone acetate 1 g/day must be taken as four 250-mg tablets on an empty stomach and subjects must not eat for at least 1 hour after abiraterone acetate; prednisone (prednisolone when prednisone is not available) 5 mg/day should be taken daily with abiraterone acetate; if gastric intestinal upset occurs, prednisone may be taken with food and separately from abiraterone acetate. Exemestane 25 mg/day should be taken as a single tablet, preferably after a meal. <del>Pre-dose review of clinical laboratory results will be done Day 1 of every cycle.</del>

Applicable Section(s)	Description of Change(s)
<b>Rationale (Cont.):</b> To correct an inconsistency, specific details regarding the timing of blood sampling have been removed.	
3.1 Overview of Study Design	During the Treatment phase, study visits and study procedures are scheduled Day 1 of every 28-day cycle ( $\pm 2$ days) as well as Day 15 ( $\pm 2$ days) of Cycles 1 through 3. <del>Because review of clinical laboratory results should precede dosing every visit, subjects are instructed not to take study drugs at home on visit days.</del> Study drug treatment will continue until the earliest of the following events: disease progression, unacceptable toxicity, or death. Subjects with no disease progression for 12 treatment cycles may continue study treatment at the discretion of the investigator, in which case study visits will continue every 3 cycles.
9.1.1 Overview	The Time and Events Schedule summarizes the frequency and timing of all study evaluations. When study procedures occur on the same visit day, PROs should be completed before any other procedures or consultations for that visit <del>and blood sampling should follow all visit procedures.</del>
9.3 Safety Evaluation, Clinical Laboratory Tests	Blood samples for hematology and chemistry will be taken for evaluation of laboratory safety parameters (Attachment 6). The investigator must review the laboratory report <del>before visit day dosing</del> , document this review, and record any clinically relevant changes during the study in the adverse event section of the eCRF. Baseline values, including Screening coagulation and dipstick urinalysis, should be measured within 7 days before randomization.
<b>Rationale:</b> The term “Data Monitoring Committee (DMC)” has been revised to “Data Review Committee (DRC)” in alignment with a new SOP coming into effect.	
Synopsis, Interim Analysis and Data Review Committee; Abbreviations; 11.8 Interim Analysis; 11.9 Data Review Committee; 16.1 Study-Specific Design Considerations	After review of interim data, the Data Review Committee (DRC) will make recommendations regarding study continuation.
<b>Rationale:</b> To correct an inconsistency, the term “Study Pharmacy Manual” has been revised to “Study Laboratory Manual.”	
9.7 Sample Collection and Handling	PK sample collection, processing, storage, and shipping instructions are detailed in the Study Laboratory Manual.
<b>Rationale:</b> To clarify the intended protocol conduct, check marks for survival status assessment during the Treatment phase have been removed from the Time and Events Schedule.	
Time and Events Schedule, Survival Status line entry	Survival Status to be assessed during Follow-up (every 3 months)

## SYNOPSIS

### **Randomized, Open-Label Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone With or Without Exemestane in Postmenopausal Women With ER+ Metastatic Breast Cancer Progressing After Letrozole or Anastrozole Therapy**

Abiraterone [17-(3-pyridyl)androsta-5,16-dien-3 $\beta$ -ol] is an irreversible inhibitor of cytochrome P450 (CYP)17 (17 $\alpha$ -hydroxylase/ C17,20-lyase), a dual-function enzyme that catalyzes 2 critical reactions in the synthesis of testosterone. Abiraterone acetate (JNJ-212082) is the prodrug of the active drug abiraterone (JNJ-589485). Once absorbed after oral administration, abiraterone acetate is rapidly converted to the active form, abiraterone.

### **OBJECTIVES AND HYPOTHESIS**

This Phase 2 study evaluates whether estrogen receptor (ER) signaling remains important to breast cancer growth in the setting of aromatase inhibition failure in postmenopausal women with estrogen-receptor-positive (ER+) metastatic breast cancer. This study also evaluates if continued aromatase inhibition, through the use of exemestane, is required to maximally suppress estrogen biosynthesis when abiraterone acetate is used.

#### **Primary Objective**

The primary objective is to assess the safety and efficacy of abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone, in postmenopausal women with ER+ metastatic breast cancer progressing after letrozole or anastrozole therapy.

#### **Secondary Objectives**

Secondary objectives are to assess abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone, in postmenopausal women with ER+ metastatic breast cancer progressing after letrozole or anastrozole therapy, with respect to the following:

- Overall survival
- Overall response rate
- Patient-reported outcomes (PROs), EORTC-C30, EQ-5D-5L, and BPI-SF pain intensity scale
- Endocrine markers estradiol, testosterone, estrone, and other biomarkers
- Pharmacokinetics (PK) characterization of abiraterone and exemestane

#### **Hypothesis**

Abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone, are safe and prolong progression-free survival (PFS) in postmenopausal women with ER+ metastatic breast cancer still sensitive to treatment with endocrine therapy.

### **OVERVIEW OF STUDY DESIGN**

This is a randomized, open-label, parallel-group, multicenter Phase 2 study of abiraterone acetate plus prednisone (or prednisolone when prednisone is not available) and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone, in postmenopausal women with ER+ metastatic breast cancer progressing after letrozole or anastrozole therapy. This study is divided into 3 phases: Screening, Treatment, and Follow-Up. The Treatment phase comprises a series of 28-day cycles with continuous study treatment until disease progression, when an End-of-Treatment visit is completed before the Follow-Up phase begins. At selected study sites, PK and fresh tumor biopsies are assessed. Circulating tumor cells (CTC) will be assessed in samples from all subjects at baseline. Sites will be notified if a subject's Day 1 Cycle 1 sample does not meet a minimum threshold. If low CTCs are found in the baseline sample, no further CTC sampling should be done for the subject.

During Screening, potential study subjects are assessed for study eligibility after providing signed informed consent. Eligible subjects, stratified by number of prior therapies in the metastatic setting (0 or 1 versus 2) and by setting of prior letrozole or anastrozole treatment (adjuvant versus metastatic), are randomly assigned in a 1:1:1 ratio to 3 treatment groups: abiraterone acetate plus prednisone, abiraterone acetate plus prednisone combined with exemestane, or exemestane alone.

During Treatment, study visits are scheduled Day 1 of every 28-day cycle ( $\pm 2$  days) as well as Day 15 ( $\pm 2$  days) of Cycles 1 through 3. Treatment will continue until the earliest of the following events: disease progression, unacceptable toxicity, or death. At disease progression, subjects randomized to exemestane alone may be switched

to abiraterone acetate plus prednisone at the discretion of the investigator; if not switched, these subjects must be discontinued from study drug. At disease progression, subjects randomized to either abiraterone acetate plus prednisone or abiraterone acetate plus prednisone combined with exemestane must be discontinued from study drug. Whenever study drug is discontinued, subjects should be evaluated within 30 days during the End-of-Treatment visit and entered into the Follow-Up phase regardless of reason for study drug discontinuation, and monitored every 3 months ( $\pm 7$  days) until death, loss to follow-up, consent withdrawal, or abiraterone acetate development in this indication is discontinued. The total duration of the study will be extended up to September 2018. Subjects with no disease progression for 12 treatment cycles may continue study treatment at the discretion of the investigator, in which case, study visits will continue every 3 cycles to measure safety and efficacy parameters.

The clinical cutoff for the planned interim analysis (110 [50%] of progression or death events) occurred on 14 December 2012. At the time of the clinical cutoff, safety data were available for 231 subjects. The DRC reviewed the efficacy and safety outcomes of the interim analysis. They also reviewed biomarker data in relation to the PFS data. On 08 March 2013, the DRC recommended the study continue as follows:

- abiraterone acetate + exemestane group: The interim analysis criteria were not met for either for futility nor efficacy. The DRC therefore recommends that this group continue as stipulated in the protocol.
- abiraterone acetate group: The interim analysis criterion for futility was met. The DRC therefore recommends that randomized assignment to this group be discontinued.
- exemestane group: Patients with progressive disease in this group are offered crossover to abiraterone acetate alone. Given the findings regarding the other 2 groups noted above, the study team may consider crossover to the combination of exemestane + abiraterone acetate.
- The biomarker studies should continue as planned.

Protocol Amendment INT-5 incorporates the recommendations of the DRC. The sponsor considered the crossover option but decided not to allow crossover and for subjects who progress on exemestane to discontinue study treatment. The sponsor also decided that subjects in the abiraterone acetate group be informed of the decision to discontinue randomized assignment to the abiraterone acetate group and to allow ongoing subjects to make their own decision about whether or not to continue further study treatment. The changes in randomization and crossover are outlined in Attachment 9 of the protocol.

The clinical cutoff for the final analysis for the study (after the predefined total of 150 PFS events were reported in the abiraterone plus exemestane group and in the exemestane alone group) occurred on 20 September 2013. The results of the analysis did not show a significant benefit in PFS (the primary endpoint of the study) of adding abiraterone acetate to exemestane, while a slight increase in the incidence of reported adverse events was observed in the combination treatment group and in the abiraterone acetate group versus the exemestane alone group.

However, individual subjects in the study may derive benefit from the treatment they are currently receiving with continued control of disease in the absence of significant toxicity. Therefore, the study has been amended to allow subjects to continue receiving their existing study medication and to reduce the number of required study-related procedures and amount of data collected (Attachment 10). The decision to continue to receive study medication or withdraw from the study will be based on updated study information and made together with the subject and the investigator. Subjects who elect not to continue on study medication and those currently in long-term follow-up will be discontinued from the study. Under Amendment 7, individual subjects who may continue to derive benefit from the treatment they are currently receiving, will be offered the opportunity to continue on their existing study medication and followed-up for safety for an additional duration of up to 3 years (ie, up to 20 September 2018) from the date previously stated (20 September 2015) in the Amendment INT-6. The situation may be reassessed periodically for subjects still receiving study medication.

## **SUBJECT POPULATION**

Postmenopausal women at least 18 years of age with ER+, Her2- metastatic breast cancer (confirmed with prerandomization formalin-fixed paraffin-embedded [FFPE] tissue) will be enrolled in this study. Subjects with disease confined only to bone may be included. Their disease must have been sensitive to anastrozole or letrozole therapy prior to disease progression, defined as either stable disease or better for  $\geq 6$  months in the metastatic setting or relapse free for  $\geq 2$  years in the adjuvant setting. Subjects must have had no more than 2 prior lines of therapy in the metastatic setting, of which no more than 1 was chemotherapy; simultaneous combination treatment is

considered 1 line of therapy. They must have an Eastern Cooperative Oncology Group (ECOG) performance status score of  $\leq 1$ .

### **DOSAGE AND ADMINISTRATION**

All study drugs are oral and should be taken once daily. Abiraterone acetate 1,000 mg/day should be taken as four 250-mg tablets and must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. Prednisone 5 mg/day should be taken daily with abiraterone acetate; if gastric intestinal upset occurs, prednisone may be taken with food and separately from abiraterone acetate. Exemestane 25 mg/day should be taken as a single tablet, preferably after a meal.

### **EFFICACY EVALUATION**

Determination of PFS will use radiographic progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) on measurable lesions captured by computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and, using the same modality, repeated every 2 cycles initially (Day 1 Cycle 3, Day 1 Cycle 5, and Day 1 Cycle 7) and every 3 cycles thereafter (eg, Day 1 Cycle 10, Day 1 Cycle 13) until, and including, the End-of-Treatment visit. Since disease progression should be documented by CT or MRI, imaging with whichever modality was used at baseline should be completed as soon as possible if a new breast-cancer-related symptom appears that requires medical intervention. Determination of long-term benefit will use survival status and PRO scores throughout the study and during Follow-Up.

### **BIOMARKER EVALUATION**

Tumor samples (FFPE) will be assessed for ER, progesterone receptor (PR), and Her2 at randomization. These tumors may also be analyzed for microRNA (miRNA) expression patterns, mutations or amplification of the ER, or for other biomarkers. Serum samples are analyzed for estrogens or androgens. At selected study sites, fresh tumor biopsies will be taken. Blood samples for CTC analysis will be collected from all subjects. Biomarker studies are designed to identify markers predictive of response (or resistance) to abiraterone.

### **PHARMACOGENOMICS EVALUATION**

Where local regulations permit, if separate consent is granted, blood samples will be taken for pharmacogenomics research.

### **SAFETY EVALUATION**

Evaluations include periodic physical examination, vital sign measurement, and clinical laboratory tests. Cardiac function is assessed by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO) and 12-lead electrocardiogram (ECG). Adverse events, including laboratory adverse events, are graded and summarized. 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.

### **PHARMACOKINETICS EVALUATION**

At selected study sites, serial PK blood samples for determination of abiraterone and exemestane concentrations will be collected Days 1 and 15 of Cycle 1. Predose samples will also be collected Day 1 of Cycles 2 through 4. From PK profiles obtained Days 1 and 15 of Cycle 1, the following parameters will be calculated:  $C_{max}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $t_{last}$ , and  $AUC_{24h}$ . Additional PK parameters may be determined and exploratory analyses may be performed, as deemed appropriate.

### **SAMPLE SIZE DETERMINATION**

The primary analysis consists of 2 pair-wise comparisons of the experimental treatment groups (abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane) with the reference treatment group (exemestane alone). For each of the pair-wise comparisons, the statistical tests of treatment effects on primary endpoint of PFS will be conducted independently at the 2-sided 0.10 level of significance. This study is event driven and will complete for primary analysis after a total of 220 PFS events in the 3 treatment groups have occurred over a total study duration of 19 months. It is assumed that the PFS follows an exponential distribution with a constant hazard ratio. Assuming an underlying hazard ratio of any pair-wise comparison (abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone) is 0.65 (median PFS 6.2 and 4.0 months, respectively), the study has 80% power at a significance level of 0.10 (2-sided) to demonstrate a treatment difference with approximately 150 PFS events in each pair-wise comparison. Assuming an enrollment rate of 20 subjects per month for 15 months, a total sample size of approximately 300 subjects

(100 subjects per group) is planned. In the case that randomization to 1 treatment group is discontinued based on the DRC recommendation after the interim analysis, the study may stop randomization when approximately 200 subjects are enrolled to the remaining 2 treatment groups. The final analysis would then be performed after the occurrence of 150 death or progression events within the remaining 2 treatment groups.

### **STATISTICAL METHODS**

An intent-to-treat (ITT) analysis including all randomized subjects will be used to evaluate efficacy. The primary efficacy endpoint, PFS, is measured from time of randomization to first occurrence of either disease progression or death from any cause. Secondary endpoints include overall survival, overall response rate, PRO scores, and biomarkers, and PK. Distributions of time-to-event variables will be estimated using the Kaplan-Meier product-limit method. Median times to event with 2-sided 95% confidence intervals will be estimated. The stratified log-rank test will be used as the primary analysis for treatment comparison. A Cox proportional-hazards model will provide estimates of hazard ratios with 95% confidence intervals. The relative risk of overall response rate (treatment:control) will be reported along with the associated 95% confidence interval. Statistical inference will be evaluated using the Chi-square statistic. PRO scores and biomarker concentrations will be descriptively summarized by treatment group; statistical tests may be carried out as appropriate.

Plasma concentrations of abiraterone and exemestane and PK parameter estimations will be descriptively summarized by treatment group. Association of biomarkers with clinical response or time-to-event endpoints will be assessed using the appropriate statistical methods (analysis of variance [ANOVA], categorical, or survival model), depending on endpoint.

Subjects who receive at least 1 study drug dose will be analyzed for safety. Treatment-emergent adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Adverse events will be summarized by system organ class and preferred term, and will be presented overall and by treatment group. Deaths and other serious adverse events will be provided in a listing. Other safety endpoints, including vital signs, clinical laboratory parameters, and ECG, will be summarized descriptively.

### **Interim Analysis and Data Review Committee**

One interim analysis is scheduled when approximately 110 (50%) of the PFS events have occurred. Gamma-family spending functions determined the Type I error rate of 10% (2-sided) and Type II error rate of 20% for each pair-wise comparison. After review of interim data, the Data Review Committee (DRC) will make recommendations regarding study continuation. In addition to the planned interim analysis, the DRC will meet periodically to review the cumulative safety data collected. One DRC safety review will occur after the tenth subject in each treatment group (~30 subjects) has received study drug for 28 days (Cycle 1); subject accrual will continue only if no safety concerns arise. When baseline and at least 1 posttreatment ECG are available for the first 25 subjects in each treatment group (75 subjects total), the DRC will determine if additional ECGs are needed for these and subsequent subjects.

Abiraterone acetate: Clinical Protocol 212082BCA2001 – Amendment INT-7

**TIME AND EVENTS SCHEDULE**

The Time and Events Schedule below became obsolete under Amendment INT-6 and has been replaced with a new Schedule of Events provided in [Attachment 10](#).

\*Except where noted otherwise, study visits/procedures have a  $\pm 2$ -day time window.

PHASE:	Screen	Treatment						4 to disease progression <sup>a</sup>	End	Follow-Up
		1		2		3				
CYCLE (28 days):		1	15	1	15	1	15	1		
*CYCLE DAY:		1	15	1	15	1	15	1		
<b>Screening</b>										
Informed consent <sup>b</sup>	X									
Inclusion/exclusion criteria	X									
Prestudy anticancer therapy <sup>c</sup>	X									
Medical history and demographics	X									
Urinalysis (dipstick)	X									
Immunohistochemistry, FFPE <sup>d</sup>	X									
<b>Study Drug Administration<sup>e</sup></b>										
Randomization		X								
Dispense study drug <sup>f</sup>		X		X		X		X		
<b>Safety</b>										
MUGA (or ECHO) <sup>g</sup>	X							every 3 cycles	X	
Electrocardiogram, 12-lead <sup>h</sup>	X							every 3 cycles	X	
Physical examination <sup>i</sup>	X			X		X		X	X	
Vital signs <sup>j</sup>	X			X		X		X	X	
<b>Efficacy</b>										
CT or MRI <sup>k</sup>	X					X		X <sup>k</sup>	X	
ECOG	X			X		X		X	X	
PROs <sup>l</sup>		X		X		X		X	X	X
Survival status <sup>m</sup>										X
<b>Clinical Laboratory</b>										
Coagulation (PT or INR, and PTT)	X									
Serology (hepatitis B and C) <sup>n</sup>	X									
LH	X									
FSH	X									
Lipid profile <sup>o</sup>	X							every 6 cycles	X	
Hematology/Glucose <sup>p</sup>	X			X		X		X	X	
Chemistry with electrolytes <sup>p</sup>	X		X	X		X		X	X	
Liver function tests <sup>q</sup>	X		X	X	X	X	X	X	X	
Circulating tumor cells <sup>r</sup>		X		X					X	
Serum endocrine markers <sup>s</sup>		X		X		X		every 3 cycles	X	
Pharmacogenomics <sup>t</sup>		X								
<b>Ongoing Subject Review</b>										
Dosing compliance			X	X		X		X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	
Adverse events <sup>u</sup>	X	X	X	X	X	X	X	X	X	
<b>Selected Centers Only</b>										
Pharmacokinetics <sup>v</sup>		X	X	X		X		Cycle 4		
Tumor biopsy <sup>w</sup>	X					X		Cycle 5		

CT=computed tomography; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed paraffin-embedded; FSH=follicle-stimulating hormone; INR=international normalized ratio; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition scan; LH=luteinizing hormone; PT=prothrombin time; PRO=patient-reported outcome; PTT=partial thromboplastin time

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- <sup>a</sup> For subjects continuing study drug after 12 months with no disease progression, physical examinations, vital signs, CT or MRI, ECOG, fasting glucose, hematology, chemistry with electrolytes, and LFTs to be every 3 cycles; PROs and lipid profiles to continue every cycle and every 6 cycles, respectively.
- <sup>b</sup> Written informed consent to be obtained within 4 weeks before randomization.
- <sup>c</sup> Potential subjects must not have taken anastrozole, letrozole, fulvestrant, or any chemotherapy for at least 2 weeks (bevacizumab for at least 3 weeks) before randomization.
- <sup>d</sup> FFPE tumor tissue to be collected within 7 days before randomization for androgen receptor (AR), ER, progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2), CYP17, CYP19, Ki-67, 3 $\beta$ -hydroxysteroid dehydrogenase (HSD), and future molecular analyses.
- <sup>e</sup> At disease progression, subjects randomized to exemestane alone may be switched to abiraterone acetate plus prednisone at the discretion of the investigator; if not switched, these subjects must be discontinued from study drug. At disease progression, subjects randomized to either abiraterone acetate plus prednisone or abiraterone acetate plus prednisone combined with exemestane must be discontinued from study drug. In either case, subjects should be evaluated within 30 days during End-of-Treatment visit and entered into the Follow-Up phase.
- <sup>f</sup> Study drug to be dispensed Day 1 of each 28 $\pm$ 2-day cycle and taken outside clinic. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. Prednisone (prednisolone when prednisone is not available) should be taken daily with abiraterone acetate; if gastric intestinal upset occurs, prednisone may be taken with food and separately from abiraterone acetate; exemestane should be taken after a meal. Subjects continuing study drug treatment after 12 months without disease progression will be dispensed sufficient study drug for visits every 3 cycles.
- <sup>g</sup> MUGA (ECHO when MUGA unavailable) to be done within 4 weeks before randomization and, using the same modality, End-of-Treatment. Subjects with prior anthracycline  $\geq$ 350 mg/m<sup>2</sup> will have MUGA or ECHO done at baseline and every 3 cycles thereafter (eg, Day 1 Cycle 4, Day 1 Cycle 7).
- <sup>h</sup> ECGs to be done within 4 weeks before randomization and every 3 cycles thereafter (eg, Day 1 Cycle 4, Day 1 Cycle 7), and End-of-Treatment; serum potassium <3.5 mM should be corrected before any ECG. At selected study sites, when PK sampling is Day 1 Cycle 1, an ECG will be recorded 2 hours after study drug dose.
- <sup>i</sup> Physical examination to be done within 2 weeks before randomization, Day 1 Cycle 2 and every cycle thereafter (eg, Day 1 Cycle 2, Day 1 Cycle 3), and End-of-Treatment; height to be recorded only at baseline.
- <sup>j</sup> Vital signs (upright blood pressure, heart rate, respiratory rate, and oral/aural body temperature) to be done within 2 weeks before randomization, every cycle thereafter (eg, Day 1 Cycle 2, Day 1 Cycle 3), and End-of-Treatment.
- <sup>k</sup> Radiographic disease to be measured within 4 weeks before randomization as close as possible to Day 1 Cycle 1 and, using the same modality (CT or MRI), repeated every 2 cycles (Day 1 Cycle 3, Day 1 Cycle 5, and Day 1 Cycle 7), and every 3 cycles thereafter (eg, Day 1 Cycle 10, Day 1 Cycle 13), and End-of-Treatment; positron emission tomography (PET) not acceptable.
- <sup>l</sup> PROs (EORTC-C30, EQ-5D-5L, BPI-SF pain intensity scale) to be done before any other visit procedure within 2 days before randomization, repeated every cycle thereafter (eg, Day 1 Cycle 2, Day 1 Cycle 3), End-of-Treatment, and every 3 months during Follow-Up.
- <sup>m</sup> Survival status and nonstudy anticancer therapy to be monitored by telephone or chart review during Follow-Up.
- <sup>n</sup> Full hepatitis panel to be done during Screening to include hepatitis B surface antigen and hepatitis C antibody; to be repeated during Continuing Treatment only if subject develops Grade 3 or higher LFT increase.
- <sup>o</sup> Lipids to be done within 7 days before randomization, every 6 cycles thereafter (eg, Day 1 Cycle 7, Day 1 Cycle 13), and End-of-Treatment.
- <sup>p</sup> Fasting glucose, hematology, and chemistry to be done within 7 days before randomization, every cycle thereafter (eg, Day 1 Cycle 2, Day 1 Cycle 3), and End-of-Treatment; blood chemistry also to be done Day 15 Cycle 1.
- <sup>q</sup> Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, total bilirubin) to be done within 7 days before randomization, every cycle thereafter (eg, Day 1 Cycle 2, Day 1 Cycle 3), Day 15 of Cycles 1 through 3, and End-of-Treatment.
- <sup>r</sup> At all study sites, blood samples (40 mL where local regulations permit) to be taken Day 1 of Cycles 1 and 2 and End-of-Treatment for CTC enumeration and molecular characterization. Circulating tumor cells will be assessed in samples from all subjects at baseline. Sites will be notified if a subject's Day 1 Cycle 1 sample does not meet a minimum threshold. If low CTCs are found in the baseline sample, no further CTC sampling should be done for the subject. NOTE: CTC samples will not be collected from subjects receiving abiraterone acetate after crossing over from exemestane treatment.
- <sup>s</sup> Endocrine biomarker (estradiol, testosterone, and estrone) blood samples (15 mL) to be taken Day 1 of Cycles 1 through 3, and every 3 cycles thereafter (eg, Day 1 Cycle 6, Day 1 Cycle 9) up to and including Day 1 Cycle 12,
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and at End-of-Treatment. NOTE: Endocrine biomarker samples will not be collected from subjects receiving abiraterone acetate after crossing over from exemestane treatment.

<sup>t</sup> Where local regulations permit, if separate consent is granted, blood samples (10 mL) to be taken for pharmacogenomics research; a sample collected at a later time point will not be a protocol deviation. NOTE: Pharmacogenomic samples will not be collected from subjects receiving abiraterone acetate after crossing over from exemestane treatment.

<sup>u</sup> Adverse events will be recorded from time of Consent Form signature until 30 days after last study drug dose.

<sup>v</sup> At selected study sites, 20 subjects/treatment group to remain overnight Days 1 and 15 of Cycle 1 for blood samples (2 mL, abiraterone acetate; 4 mL, exemestane) to be taken before and 1, 1.5, 2, 3, 4, 8, 12, 16, 22, and 24 hours after study drug dosing; sites that do not have the capability of overnight stays will not collect blood samples at 12, 16, and 22 hours after study drug dosing on Days 1 and 15 of Cycle 1; predose samples also to be taken Day 1 of Cycles 2 through 4. Study drug will be given at the study site and subjects will be instructed to record study drug dosing times and meal times for 2 days before each sampling visit. NOTE: Pharmacokinetic samples will not be collected from subjects receiving abiraterone acetate after crossing over from exemestane treatment.

<sup>w</sup> At selected study sites, consent will be sought to biopsy metastasized or primary tumor at screening, Day 1 Cycle 3, and Day 1 Cycle 5 for biomarker studies. Consent should be obtained for a biopsy at baseline and at least 1 Treatment phase time point; a missing time point will not be considered a protocol deviation.

**ABBREVIATIONS**

ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AR	androgen receptor
AST	aspartate aminotransferase (SGOT)
BPI-SF	Brief Pain Inventory – Short Form
CCO-FA	clinical cutoff for the final analysis
CT	computed tomography
CTC	circulating tumor cells
CYP	cytochrome P450
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone sulphate
DNA	deoxyribonucleic acid
DRC	Data Review Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EORTC-C30	European Organization for Research and Treatment of Cancer core quality-of-life questionnaire
EQ-5D-5L	Euro-QoL quality-of-life questionnaire
ER+	estrogen receptor positive
EU	European Union
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
Her2	human epidermal growth factor receptor 2
HSD	hydroxysteroid dehydrogenase
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
Ki-67	cellular marker for proliferation
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	microRNA
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PQC	product quality complaint
PR+	progesterone receptor positive
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
U.S.	United States

## 1. INTRODUCTION

Breast cancer is the most frequent cancer among women with an estimated 1.38 million cases newly diagnosed worldwide in 2008 (23% of all cancers) (Ferlay 2010); incidence and mortality rates per 100,000 person years were 109.4/21.0 (Belgium), 99.7/17.6 (France), 81.8/16.9 (Germany), 86.3/16.1 (Italy), 82.7/14.7 (Sweden), 96.8/19.6 (Netherlands), and 87.9/18.6 (United Kingdom). Breast cancer is estimated to account for 28% of newly diagnosed cancers in women in the United States (U.S.) and 15% of deaths from cancer in U.S. women in 2010 (American Cancer Society 2010a). In the U.S. (1999 to 2006), among patients with breast cancer, 60% were diagnosed with localized Stage 1 or 2 disease, 33% with Stage 2 or 3, and 5% with Stage 4 (National Cancer Institute 2010). About 70% of primary breast cancers are estrogen receptor positive (ER+) (National Breast Cancer Coalition 2010), which correlates most often with postmenopausal status (Kamangar 2006). Survival rates decrease with stage of disease. The 5-year survival rate for women with metastatic breast cancer is 15% (American Cancer Society 2010b), which reflects a substantial unmet medical need for more effective therapy.

Several lines of evidence support investigation of abiraterone acetate (JNJ-212082) for treatment of women with ER+ breast cancer. Breast cancers ER+ and progesterone-receptor-positive (PR+) positively correlate with circulating levels of adrenal steroids, including dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S) (Eliassen 2006; Key 2002) and in vitro data indicate these ligands stimulate proliferation of breast cancer cell lines in a low-estrogen environment (Maggiolini 1999). Although adrenalectomy and hypophysectomy were effective for treatment of ER+ breast cancer, abiraterone acetate is the first compound specifically designed to inhibit cytochrome P450 (CYP)17 with resultant inhibition of sex hormone biosynthesis. Hypothetically, depletion of androgens and estrogens by abiraterone acetate may inhibit tumor growth by disruption of ER-dependent growth signaling.

The role of androgens and androgen receptor (AR) function in ER+ breast cancer is not entirely clear. Proliferation of certain breast tumor cell lines has been suppressed with antiandrogen- and androgen-like steroids (Hackenberg 1996). Expression of AR has been correlated with smaller tumors, less aggressive disease, and lack of lymph node involvement (Ogawa 2008). However, high serum levels of adrenal androgens (DHEA and androstenedione) also have been correlated with increased breast cancer risk in postmenopausal women (Hankinson 1998; Kaaks 2005), which may result from androgen signaling via either AR or ER (Maggiolini 1999).

Patients with ER+ disease have limited options once disease progresses after treatment with available endocrine therapy. Although chemotherapy may be used following progression during aromatase inhibitor therapy, toxicities are severe and overall survival is not extended substantially. In addition, patients with disease still driven by ER or AR signaling may not yet have the extensive visceral disease or the rapid clinical progression requiring immediate therapy

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with systemic chemotherapy. Since CYP17 is upstream from aromatase in the steroid synthesis pathway, theoretically, abiraterone acetate more completely inhibits sex steroid synthesis. Abiraterone acetate may inhibit synthesis of adrenal sources of hormones (eg, androstenedione) whereas other available endocrine therapies may not.

Twenty-five postmenopausal subjects with refractory metastatic breast cancer, who had been treated with both tamoxifen and aromatase inhibitors before study entry, have been treated with abiraterone acetate in an ongoing Cancer Research Phase 1/2 study sponsored by the United Kingdom (CR9304-21). This dose-escalation study has 4 planned dose levels: 250, 500, 1000, and 2,000 mg/day with 6 evaluable subjects treated at each dose level; subjects are discontinued from study drug and replaced before completion of a 28-day cycle when an event other than toxicity occurs. The majority of subjects recruited into the Phase 1 portion of the study are ER+. At the time of the poster presentation (Basu 2010), abiraterone acetate at all dose levels resulted in suppression of serum testosterone by Day 15 Cycle 1 of study treatment. Serum estradiol also declined with treatment but concentrations greater than 15 pmol/L were maintained by 3 subjects. Mechanism-based toxicities such as hypokalemia were the most frequent adverse events and were medically manageable. Preliminary antitumor efficacy in breast cancer was observed: of the 6 subjects given 1,000 mg/day, 1 ER+ subject has achieved a partial response for more than 8 months with corresponding reduction in breast cancer tumor marker CA 15.3; another ER+ subject has had stable disease for more than 11 months.

Exemestane is an oral, irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione, and lowers circulating estrogen concentrations in postmenopausal women without affecting adrenal biosynthesis of corticosteroids, aldosterone, or other enzymes in the steroidogenic pathway (Aromasin 2008, 2009). It is approved in the U.S., Europe, and Canada for adjuvant treatment of ER+ early breast cancer in postmenopausal women after 2 to 3 years of tamoxifen therapy. Exemestane is commonly prescribed for treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. As with other estrogen-lowering agents, bone mineral density may decrease with exemestane therapy. Patients taking exemestane experienced a significant increase in the overall fracture rate when compared with those taking tamoxifen (Lønning 2005).

The present Phase 2 study is designed to evaluate whether ER signaling remains important to breast cancer growth in the setting of aromatase inhibition failure in postmenopausal women with ER+ metastatic breast cancer. This study also evaluates if continued aromatase inhibition, through the use of exemestane, is required to maximally suppress estrogen biosynthesis when abiraterone acetate is used.

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## **Abiraterone Acetate (JNJ-212082)**

Abiraterone acetate is a prodrug of abiraterone [17-(3-pyridyl) androsta-5,16-dien-3 $\beta$ -ol], a novel selective irreversible inhibitor of cytochrome P450 CYP17, a dual-function enzyme that catalyzes 2 critical reactions in testosterone synthesis.

A Phase 3, multinational, randomized, double-blind, placebo-controlled study of oral abiraterone acetate and oral prednisone demonstrated that abiraterone acetate 1,000 mg/day was an effective therapy for subjects (N=1,195) with metastatic castration-resistant prostate cancer whose disease had progressed following treatment with a docetaxel-containing treatment regimen (Study COU-AA-301). Compared with placebo-plus-prednisone treatment, abiraterone acetate plus prednisone reduced risk of death by 35% and significantly improved time to prostate-specific antigen (PSA) progression, radiographic progression-free survival (rPFS), and PSA response.

This was the first study to demonstrate conclusively the importance of inhibition of CYP17 targeting of AR-mediated signaling persisting or up-regulated after conventional androgen-deprivation therapy and docetaxel chemotherapy. The results substantiate the hypothesis that abiraterone improves survival in patients with metastatic castration-resistant prostate cancer by CYP17 inhibition lowering testosterone concentrations below those achieved with androgen-deprivation therapies.

In addition, treatment with abiraterone acetate and prednisone resulted in a highly desirable safety profile and benefit/risk ratio, consistent with findings of earlier Phase 1/2 and Phase 2 studies. Toxicities associated with mineralocorticoid excess secondary to the mechanism of abiraterone action were amenable to medical management and resulted in infrequent dose interruptions, dose reductions, or treatment discontinuations. Infrequent liver function test (LFT) abnormalities were managed with careful laboratory monitoring, treatment interruptions and retreatment only after return to baseline values. A daily dose of 1,000 mg was selected for further Phase 2 and 3 evaluation based on its consistent pharmacologic and endocrinologic effects.

For the most accurate and current information regarding the efficacy and safety of abiraterone acetate, refer to the latest Investigator Brochure for abiraterone acetate.

## **2. OBJECTIVES AND HYPOTHESIS**

### **2.1. Objectives**

The primary objective is to assess safety and efficacy of abiraterone acetate plus prednisone and abiraterone acetate plus prednisone plus exemestane, each compared with exemestane alone, in postmenopausal women with ER+ metastatic breast cancer progressing after letrozole or anastrozole therapy.

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Secondary objectives are to assess abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone, in postmenopausal women with ER+ metastatic breast cancer progressing after letrozole or anastrozole therapy, with respect to the following:

- Overall survival
- Overall response rate
- Patient-reported outcomes (PROs) EORTC-C30, EQ-5D-5L, and BPI-SF pain intensity scale
- Endocrine markers estradiol, testosterone, estrone, and other biomarkers
- Pharmacokinetic (PK) characterization of abiraterone and exemestane

## **2.2. Hypothesis**

Abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone, are safe and prolong PFS in postmenopausal women with ER+ metastatic breast cancer still sensitive to treatment with endocrine therapy.

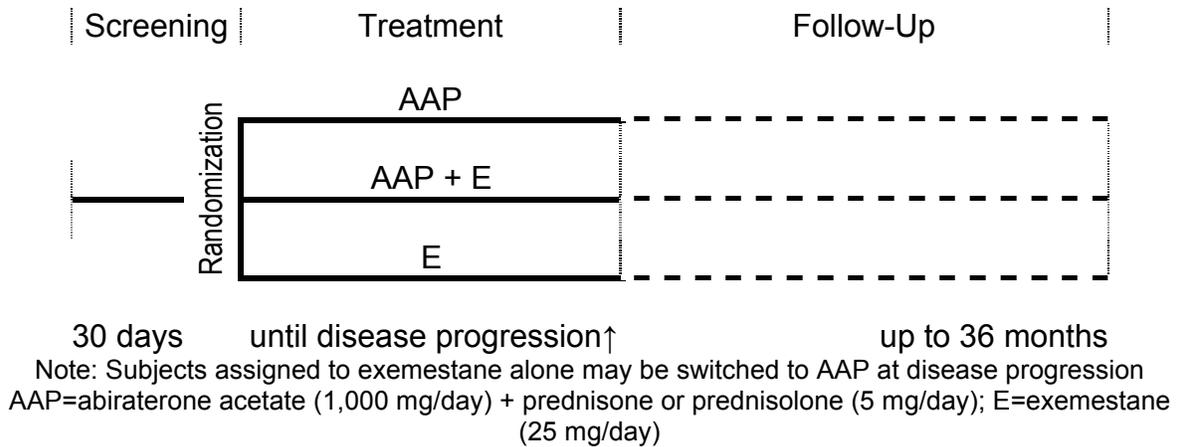
## **3. STUDY DESIGN AND RATIONALE**

This is a randomized, open-label, parallel-group, multicenter Phase 2 study of abiraterone acetate plus prednisone (or prednisolone when prednisone is not available) and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone, in postmenopausal women with ER+ metastatic breast cancer progressing after letrozole or anastrozole therapy. From approximately 65 sites in North America, Europe, and Asia, approximately 300 subjects will be randomized to 3 treatment groups (100 subjects per group).

### **3.1. Overview of Study Design**

This study is divided into 3 phases: Screening, Treatment, and Follow-Up. Timing of study assessments and procedures is detailed in the Time and Events Schedule (following the Synopsis). The Treatment phase comprises a series of 28-day cycles with continuous study treatment until disease progression, when an End-of-Treatment visit is completed before the Follow-Up phase begins.

During Screening, potential study subjects are assessed for study eligibility (Section 4) after providing signed informed consent. Eligible subjects will be stratified by 2 factors: number of prior therapies in the metastatic setting (0 or 1 versus 2); and whether letrozole or anastrozole was administered in the adjuvant or metastatic setting. Subjects will be assigned randomly in a 1:1:1 ratio as follows:



During the Treatment phase, study visits and study procedures are scheduled Day 1 of every 28-day cycle ( $\pm 2$  days) as well as Day 15 ( $\pm 2$  days) of Cycles 1 through 3. Study drug treatment will continue until the earliest of the following events: disease progression, unacceptable toxicity, or death. Subjects with no disease progression for 12 treatment cycles may continue study treatment at the discretion of the investigator, in which case study visits will continue every 3 cycles.

Response Evaluation Criteria in Solid Tumors (RECIST) will define disease progression on measurable lesions captured by computed tomography (CT) or magnetic resonance imaging (MRI) ([Attachment 1](#)). At disease progression, subjects randomized to exemestane alone may be switched to abiraterone acetate plus prednisone at the discretion of the investigator; if not switched, these subjects must be discontinued from study drug. At disease progression, subjects randomized to either abiraterone acetate plus prednisone or abiraterone acetate plus prednisone combined with exemestane must be discontinued from study drug. In either case, subjects should be evaluated within 30 days during the End-of-Treatment visit and entered into the Follow-Up phase.

Subjects should enter the Follow-Up phase regardless of reason for study drug discontinuation and should be monitored every 3 months ( $\pm 7$  days) until death, loss to follow-up, consent withdrawal, or abiraterone acetate development in this indication is discontinued. The total duration of the study will be extended up to September 2018.

Samples to assess circulating tumor cells (CTC) will be collected from all subjects. At selected study sites, fresh tumor biopsies and samples to assess pharmacokinetics (PK) will be obtained.

The study will end on the date of the last follow-up of the last subject participating in the study.

The clinical cutoff for the planned interim analysis (110 [50%] of progression or death events) occurred on 14 December 2012. At the time of the clinical cutoff, safety data were available for

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231 subjects. The Data Review Committee (DRC) reviewed the efficacy and safety outcomes of the interim analysis. They also reviewed biomarker data in relation to the PFS data. On 08 March 2013, the DRC recommended the study continue as follows:

- abiraterone acetate + exemestane group: The interim analysis criteria were not met for either for futility nor efficacy. The DRC therefore recommends that this group continue as stipulated in the protocol.
- abiraterone acetate group: The interim analysis criterion for futility was met. The DRC therefore recommends that randomized assignment to this group be discontinued.
- exemestane group: Patients with progressive disease in this group are offered crossover to abiraterone acetate alone. Given the findings regarding the other 2 groups noted above, the study team may consider crossover to the combination of exemestane + abiraterone acetate.
- The biomarker studies should continue as planned.

Protocol Amendment INT-5 incorporates the recommendations of the DRC. The sponsor considered the crossover option but decided not to allow crossover and for subjects who progress on exemestane to discontinue study treatment. The sponsor also decided that subjects in the abiraterone acetate group be informed of the decision to discontinue randomized assignment to the abiraterone acetate group and to allow ongoing subjects to make their own decision about whether or not to continue further study treatment. The changes in randomization and crossover are outlined in [Attachment 9](#) of the protocol.

### **Post-Clinical Cutoff for the Final Analysis**

Based upon the results of the final analysis, the protocol has been amended to allow subjects to continue on study medication for up to 2 years from the CCO-FA (ie, up to 20 September 2015), at which point the situation will be reassessed for subjects still receiving study medication. Subjects who elect not to continue on study medication and those currently in long-term follow-up will be discontinued from the study. Since Amendment INT-6, only serious adverse event information and drug accountability data will be collected and reported as outlined in [Attachment 10](#). Under Amendment INT-7, individual subjects who may continue to derive benefit from the treatment they are currently receiving, will be offered the opportunity to continue on their existing study medication and followed-up for safety for an additional duration of up to 3 years (ie, up to 20 September 2018) from the date previously stated (20 September 2015) in the Amendment INT-6. The situation may be reassessed periodically for subjects still receiving study medication.

## **3.2. Study Design Rationale**

### **Study Drug Dose**

The abiraterone acetate dose in this study is 1,000 mg/day, consistent with the dose recommended for Phase 2 by an ongoing Phase 1 study of abiraterone acetate in metastatic breast cancer (CR9304-21). Abiraterone acetate was well tolerated at doses ranging from 250-mg to

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2,000 mg/day. Considering PK, adrenal CYP17 inhibition, and efficacy signal from treatment of men with prostate cancer and women with metastatic breast cancer (CR9304-21), abiraterone acetate 1,000 mg offers consistent pharmacological effects without additional side effects and is the dose chosen for further efficacy and safety evaluation. This study uses the recommended dose of exemestane in metastatic breast cancer, 25 mg/day.

### **Randomization, Comparator, Special Design Considerations**

To improve the likelihood that subject attributes are balanced across groups and to enhance validity of statistical comparisons across groups, randomization is used in this study. Since patients with fewer prior lines of anticancer therapy are likely to be more sensitive to additional treatment, subjects are stratified by 2 factors: number of prior therapies in the metastatic setting (0 or 1 versus 2) and whether letrozole or anastrozole was administered in the adjuvant or metastatic setting (Puente 2010); simultaneous combination treatment is considered 1 line of therapy. To help assess abiraterone acetate efficacy, the active comparator (exemestane) in this study is the standard of care for postmenopausal women whose disease remains sensitive to endocrine therapy following disease progression after treatment with anastrozole or letrozole. To manage mineralocorticoid excess, abiraterone acetate is always taken with low-dose prednisone (prednisolone when prednisone is not available). To mitigate difficulties managing hypokalemia despite optimal potassium supplementation and adequate oral intake, the prednisone dose may be increased to 10 mg/day. To understand if continued aromatase inhibition maximally suppresses estrogen biosynthesis in the presence of abiraterone acetate plus prednisone, 1 treatment group receives combination therapy (abiraterone acetate plus prednisone combined with exemestane). To capture time to disease progression, imaging will be done on Day 1 of Cycles 3, 5 and 7, and then on Day 1 of every third cycle, thereafter; to facilitate accurate comparisons over time, the same modality (CT or MRI) should be used throughout the study; to comply with RECIST, positron emission tomography (PET) scans are not allowed. To rule out drug-drug interaction due to common abiraterone acetate and exemestane metabolic pathways, potential effects on exposure after coadministration of abiraterone acetate and exemestane are assessed in a PK study with a subset of subjects. Because almost all plasma concentrations of abiraterone acetate were below the limit of quantification in previous clinical studies, only plasma concentrations of abiraterone will be measured in this study.

### **Patient-Reported Outcomes**

As metastatic breast cancer progresses, patients often endure painful and debilitating metastases that may reduce quality of life. Because health-related quality of life is an important factor when evaluating treatment options (Bottomley 2007; Lemieux 2011), standardized PROs are used in this study to assess quality of life before, during, and after treatment. Instruments include 3 questionnaires extensively validated and widely used in breast cancer clinical trials: European Organization for Research and Treatment of Cancer Core 30 quality-of-life questionnaire

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(EORTC-C30) ([Attachment 2](#)), Euro-QOL quality-of-life questionnaire (EQ-5D-5L) ([Attachment 3](#)), and the pain intensity scale ([Attachment 4](#)) from the Brief Pain Inventory-Short Form (BPI-SF).

### **DNA and Biomarker Collection**

Circulating levels of adrenal steroids, including DHEA and its sulphate, DHEA-S, positively correlate with ER+/PR+ breast cancers (Eliassen 2006; Key 2002) and in vitro data indicate these ligands stimulate proliferation of breast cancer cell lines in a low-estrogen environment (Maggiolini 1999). These ligands function as weak ER agonists, indicating that steroidogenic enzymes upstream of aromatase may also contribute to disease progression (Chan 2002) by activating ER and possibly other steroid hormone receptors. Abiraterone is expected to attenuate this activity by suppression of androgenic steroids that may contribute to mitogenesis through stimulation of both AR and ER. To demonstrate attenuation on steroidogenic enzyme production following abiraterone acetate treatment, CYP17, CYP19, or 3 $\beta$ -hydroxysteroid dehydrogenase (HSD) expression levels will be evaluated and compared with baseline expression levels. To evaluate the impact of abiraterone on breast cancer subtypes, formalin-fixed paraffin-embedded (FFPE) tumor tissue will be evaluated for AR, ER, PR, human epidermal growth factor receptor 2 (Her2), and other biomarkers. The AR will be fully characterized to identify any anomalies in individual subjects and to determine the extent of nuclear localization of the ligand-bound complex before and after study drug initiation. Breast cancer subtypes may be further defined by characterizing the molecular profile (eg, microRNA [miRNA], mRNA, somatic anomalies) in FFPE tumor samples. Fresh tumor biopsies will be taken in a subset of subjects to characterize AR, ER, PR, CYP17, CYP19, or other candidate markers related to abiraterone or to breast cancer. Circulating tumor cell samples will be taken from all subjects to characterize AR, ER, PR, CYP17, CYP19, or other candidate markers related to abiraterone or to breast cancer. ER mutation analysis and RNA analyses may also be performed, as possible, on CTC and fresh biopsy samples. The overall intent is to demonstrate that CTCs can act as surrogates for tumor biopsies in future studies and that selected biomarkers will be predictive of response to abiraterone in breast cancer subtypes. Future studies will confirm these initial findings.

Genetic variation may be important in understanding individual differences in drug distribution and response as well as differential disease susceptibility and prognosis. Therefore, DNA will be collected, when separate informed consent is given by the study subject, to identify genetic factors that may influence abiraterone efficacy or be associated with metastatic breast cancer.

## **4. SUBJECT POPULATION**

Entry criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about any inclusion or exclusion criterion, the investigator should consult the appropriate sponsor representative before enrolling a subject in the study. Investigators should ensure that all study enrollment criteria have been met during Screening. If a subject's status

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changes (including laboratory results) after Screening but before first dose of study drug is taken such that she now meets an exclusion criterion, she should be excluded from participation in the study.

#### 4.1. Inclusion Criteria

Each potential subject must satisfy all following criteria to be enrolled in this study. If repeated clinical laboratory assessments are performed during Screening as part of the patient's routine management, results closest to the date of randomization are used to document study eligibility.

1. Woman  $\geq 18$  years of age and postmenopausal determined by one of the following:
  - bilateral, surgical oophorectomy
  - age  $\geq 60$  years
  - age  $< 60$  years, with amenorrhea  $\geq 24$  months and follicle-stimulating hormone and luteinizing hormone concentrations within postmenopausal range
2. Criterion modified per amendment
  - 2.1 Subjects with ER+, Her2- metastatic breast cancer, confirmed within 7 days before randomization with FFPE tissue from either primary or metastatic breast cancer site. In a subject with multiple biopsies of metastatic sites, the most recent biopsy prior to study entry should be submitted for evaluation of hormone receptor status.
3. Criterion modified per amendment
  - 3.1 Subjects with disease confined only to bone may be included but subjects with purely sclerotic lesions may not participate in the study (see Section 9.2.1)
4. Disease must have been sensitive to anastrozole or letrozole therapy prior to disease progression. Sensitivity to anastrozole or letrozole is defined as either stable disease or better for  $\geq 6$  months in the metastatic setting or relapse free for  $\geq 2$  years in the adjuvant setting.
5. No more than 2 prior lines of therapy in the metastatic setting, of which no more than 1 was chemotherapy [Note: Simultaneous combination treatment is considered one line of therapy.]
6. Eastern Cooperative Oncology Group (ECOG) performance status score of  $\leq 1$
7. Criterion modified per amendment
  - 7.1 Criterion modified per amendment
  - 7.2 Clinical laboratory values during Screening:
    - hemoglobin  $\geq 10.0$  g/dL
    - neutrophils  $\geq 1.5 \times 10^9/L$
    - platelets  $\geq 100 \times 10^9/L$

(NOTE: Subjects need to meet the above 3 criteria independent of growth factors and transfusions)

    - total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN)
    - alanine (ALT) and aspartate (AST) aminotransferase  $\leq 2.5 \times$ ULN

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- alkaline phosphatase  $\leq 6 \times \text{ULN}$  unless bone metastases with no liver disorder
  - serum creatinine  $< 1.5 \times \text{ULN}$  or creatinine clearance  $\geq 50$  mL/min
  - serum potassium  $\geq 3.5$  mM
  - serum albumin  $\geq 3.0$  g/dL
  - clinically normal prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT) per investigator assessment
8. Systolic blood pressure  $< 160$  mm Hg and diastolic blood pressure  $< 95$  mm Hg [Note: Hypertension controlled by antihypertensive therapy is permitted].
  9. Cardiac ejection fraction  $\geq 50\%$  measured by MUGA or ECHO done within 4 weeks before randomization.
  10. Criterion modified per amendment
    - 10.1 A bisphosphonate or denosumab may be initiated on the same day as the assigned study treatment
  11. Willing and able to adhere to prohibitions and restrictions specified in this protocol
  12. Signs an informed consent document within 4 weeks before randomization indicating she understands the purpose of and procedures required for the study and is willing to participate in the study
  13. Signs the informed consent document within 4 weeks before randomization for pharmacogenomics research indicating willingness to participate in the pharmacogenomic component of the study, where local regulations permit. [Note: Refusal to give consent for this component does not exclude a subject from participation in this clinical study.]

## 4.2 Exclusion Criteria

A potential subject who meets any of the following criteria is excluded from study participation.

1. Criterion modified per amendment
  - 1.1 Prior treatment with exemestane, ketoconazole, aminoglutethimide or a CYP17 inhibitor. [Note: Prior treatment with ketoconazole for  $\leq 7$  days is permitted and topical formulations of ketoconazole are permitted]
2. Criterion modified per amendment
  - 2.1 Anticancer immunotherapy or investigational agent within 4 weeks before randomization, or anticancer radiotherapy (except palliative) or anticancer endocrine therapy within 2 weeks before randomization [Note: Potential subjects must not have taken anastrozole, letrozole, fulvestrant, or any chemotherapy for at least 2 weeks (bevacizumab for at least 3 weeks) before randomization]
3. Serious or uncontrolled nonmalignant disease, including active or uncontrolled infection
4. Clinical or biochemical evidence of hyperaldosteronism or hypopituitarism
5. Any condition that, in the opinion of the investigator, would compromise the well-being of the patient or that could prevent, limit, or confound the protocol-specified assessments

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6. Major thoracic or abdominal surgery or significant traumatic injury with 4 weeks before randomization or plans surgery during study participation or within 4 weeks after the last dose of study drug [Note: Patients with planned surgical procedures to be conducted under local anesthesia are not excluded from the study.]
7. Persistent  $\geq$ Grade 2 toxicity from any cause [Note: Chemotherapy-induced alopecia and Grade 2 peripheral neuropathy are allowed.]
8. Symptomatic central nervous system disease or leptomenigeal disease
9. Gastrointestinal disorder interfering with study drug absorption
10. Criterion modified per amendment
  - 10.1 Active or uncontrolled disease that may require oral corticosteroid therapy
11. Positive serology for hepatitis B surface antigen or hepatitis C antibody
12. Active or symptomatic viral hepatitis or chronic liver disease
13. History of clinically significant heart disease, ie, myocardial infarction or arterial thrombotic event within 6 months, severe or unstable angina, or New York Heart Association Class III or IV heart disease
14. Known allergies, hypersensitivity, or intolerance to abiraterone acetate, exemestane, prednisone, or their excipients
15. Contraindications to the use of exemestane or prednisone per local prescribing information
16. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before the planned first dose of study drug or is currently enrolled in an investigational study

### 4.3 Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for study participation. The sponsor must be notified in advance (or as soon as possible) of any instance in which a prohibited therapy is administered. Prestudy and concomitant therapies are detailed in Section 8. Although exemestane is metabolized by CYP3A4, ketoconazole showed no significant influence on exemestane PK in a clinical study (Aromasin 2008). In a PK study in postmenopausal healthy volunteers pretreated with rifampicin, a strong CYP3A4 inducer, for 14 days followed by a single dose of exemestane, mean exemestane plasma  $C_{max}$  and  $AUC_{0-\infty}$  were decreased.

- CYP3A4 inducers listed in [Table 1](#) should be avoided or used with caution.
- No concurrent investigational agent other than abiraterone acetate is permitted.
- No concurrent anticancer agent other than exemestane, including megestrol acetate, is permitted.
- No radiotherapy other than small-field radiotherapy with palliative intent not involving response-assessable disease is permitted (unless initiated before study entry).
- For subjects participating in the PK study, no food or beverage containing grapefruit juice, Seville oranges, or quinine (eg, tonic water) should be consumed from 24 hours (72 hours in

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the case of grapefruit juice and Seville oranges) before each PK sampling day. On serial PK sampling days, these should not be consumed until after the last PK sample is collected.

Subjects who require any prohibited drug or therapy must be discontinued from study treatment and should enter the Follow-Up phase.

**Table 1: CYP3A4 Inducers**

Inducers		
barbiturates	carbamazepine	phenytoin
rifabutin	rifampicin	St. John's wort

## 5. TREATMENT ALLOCATION AND RANDOMIZATION

This is an open-label study using central randomization. Subjects are stratified by 2 factors: number of prior therapies in the metastatic setting (0 or 1 versus 2) and whether letrozole or anastrozole was administered in the adjuvant or metastatic setting (Puente 2010). On Day 1 Cycle 1 subjects are randomly assigned by an Interactive Voice Response System to 1 of 3 treatment groups in a 1:1:1 ratio and must commence study drug treatment within 2 days. Subjects withdrawn or discontinued from the study will not be replaced.

After approval of Amendment INT-6 by the Health Authority (HA) and Independent Ethics Committee/Institutional Review Board (IEC/IRB), subjects will be offered the choice of continuing on their randomized treatment or discontinuing from the study. Subjects who elect not to continue on study medication and those currently in long-term follow-up will be discontinued from the study. The procedures for Amendment INT-6 are outlined in [Attachment 10](#). Under Amendment INT-7, individual subjects who may continue to derive benefit from the treatment they are currently receiving, will be offered the opportunity to continue on their existing study medication and followed-up for safety for an additional duration of up to 3 years (ie, up to 20 September 2018) from the date previously stated (20 September 2015) in the Amendment INT-6. The situation may be reassessed periodically for subjects still receiving study medication.

## 6. DOSAGE AND ADMINISTRATION

All study drugs are oral and should be taken once daily. Abiraterone acetate 1,000 mg/day must be taken as four 250-mg tablets on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. Prednisone (prednisolone when prednisone is not available) 5 mg/day should be taken daily with abiraterone acetate; if gastric intestinal upset occurs, prednisone may be taken with food and separately from abiraterone acetate. Exemestane 25 mg/day should be taken as a single tablet, preferably after a meal.

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Study drugs are dispensed for each 28-day cycle and taken outside the clinic; sufficient study drug for 3 cycles will be dispensed when study treatment continues beyond 12 treatment cycles. Subjects participating in the PK assessment (selected study sites only) must be administered study drug at the study site on PK sampling days.

No dose or dosage adjustment is foreseen but an investigator may make an adjustment for a medical emergency, in which case the sponsor must be notified immediately. A missed dose of study drug, including prednisone, should be omitted and not made up.

### **6.1. Dose Reduction and Toxicity Management**

In clinical studies, both abiraterone acetate and exemestane were 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 adrenocorticotrophic hormone drive); in this study prednisone is expected to mitigate these effects (cortisol supplementation and abrogation of the adrenocorticotrophic hormone drive). The exemestane-related adverse event experienced by at least 10% of subjects was hot flashes (Aromasin 2008).

Since many adverse events may be related to progressing breast cancer, investigators should consider approaches other than dose reduction to address adverse events. Up to 2 dose reductions of abiraterone acetate are allowed for adverse events that the investigator attributes to abiraterone acetate. 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 events resolution and a discussion with the Sponsor's medical monitor. An abiraterone acetate dose of lower than 500 mg/day is not allowed. Study drug should not be resumed until resolution of the adverse events is documented.

Based on experience with exemestane at repeated doses up to 200 mg/day, exemestane lower than 25 mg/day is not recommended (Aromasin 2008, 2009) and exemestane dose cannot be reduced in this study; if interruption is required, exemestane should not be resumed until resolution of the adverse event is documented and the medical monitor approves.

During this study, prednisone is taken with abiraterone acetate. Following prolonged glucocorticoid therapy, patients 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 frank adrenal insufficiency. Discontinuation of prednisone will be individualized depending on investigator judgment. Abrupt discontinuation of prednisone after chronic therapy may trigger symptoms and signs consistent with adrenal insufficiency.

### 6.1.1. Management of Hypokalemia

At the initial observation of Grade 1 or 2 hypokalemia (serum potassium <lower limit of normal (LLN)-3.0 mM; using NCI-CTCAE, Version 4.0), oral potassium supplement should be initiated (Table 2). The dose of potassium supplement must be carefully titrated to maintain serum potassium between 3.5 and 5.0 mM, inclusive. Any subject with low potassium during the study or a history of hypokalemia from a preexisting or concurrent medical condition should undergo at least weekly laboratory electrolyte evaluation. The investigator should consider maintaining potassium  $\geq 4.0$  mM in these subjects.

If any subject experiences Grade 3 hypokalemia (serum potassium levels <3.0 to 2.5 mM, NCI-CTCAE Version 4.0) or life-threatening hypokalemia with potassium levels <2.5 mM (NCI-CTCAE hypokalemia Grade 4), abiraterone acetate plus prednisone treatment should be withheld and hospitalization considered for IV potassium replacement and cardiac monitoring. Resumption of abiraterone acetate plus prednisone treatment after normalization of potassium levels must be approved by the medical monitor.

**Table 2: Hypokalemia Management**

Serum Potassium	Grade of Hypokalemia	Action	Further Action and/or Maintenance
Low K+ and/or history of hypokalemia		At least weekly laboratory electrolyte evaluations	Titrate dose to serum K+ $\geq 3.5$ to $\leq 5.0$ mM; maintenance at $\geq 4.0$ mM is recommended.
<LLN-3.0mM	Grade 1 or 2	Initiate oral K+ supplementation	Titrate dose to serum K+ $\geq 3.5$ to $\leq 5.0$ mM; maintenance at $\geq 4.0$ mM is recommended.
<3.0 to 2.5mM	Grade 3	Withhold AA treatment and initiate i.v. K+ and cardiac monitoring	Call medical monitor before re-initiating AA treatment
<2.5mM	Grade 4	Withhold AAP treatment and initiate i.v. K+ and cardiac monitoring	Call medical monitor before resuming AAP treatment

AA=abiraterone acetate; AAP=AA + prednisone; i.v.=intravenous; K+=potassium; LLN=lower limit of normal

If hypokalemia persists despite optimal potassium supplementation and adequate oral intake, the dose of prednisone may be increased from 5 to 10 mg/day and documented in the study medication electronic case report form (eCRF).

### 6.1.2. Management of Hypertension

- Grade 1-2: Management per investigator; investigators should maintain blood pressure <160/95 mm Hg with antihypertensive agents; do not reduce abiraterone acetate dose.
- Grade 3-4: Withhold abiraterone acetate plus prednisone and adjust/add medications to mitigate the toxicity; when resolves to  $\leq$ Grade 1, resume abiraterone acetate 1,000 mg/day and prednisone.

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- If toxicity recurs, withhold study drug, and adjust or add medications to mitigate the toxicity. When toxicity resolves to  $\leq$ Grade 1, resume study drug with the first dose level reduction (3 tablets, 750 mg of study drug).
- If toxicity recurs, withhold study drug, and adjust or add medications to mitigate the toxicity. When toxicity resolves to  $\leq$ Grade 1, resume study drug with the second dose level reduction (2 tablets, 500 mg of study drug).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue abiraterone acetate.

### 6.1.3. Management of Edema and Fluid Retention

- Pedal edema: Supportive management per investigator; do not reduce abiraterone acetate dose.
- Anasarca or pulmonary edema requiring supplemental oxygen: Withhold abiraterone acetate plus prednisone and adjust/add medications to mitigate the toxicity; when resolves to  $\leq$ Grade 1, resume abiraterone acetate 1,000 mg/day and prednisone.
- If toxicity recurs, withhold study drug, and adjust or add medications to mitigate the toxicity. When toxicity resolves to  $\leq$ Grade 1, resume study drug with the first dose level reduction (3 tablets, 750 mg of study drug).
- If toxicity recurs, withhold study drug, and adjust or add medications to mitigate the toxicity. When toxicity resolves to  $\leq$ Grade 1, resume study drug with the second dose level reduction (2 tablets, 500 mg of study drug).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue study drug.

### 6.1.4. Management of Non-Mineralocorticoid Side Effects

- Grade 1-2: Management per investigator; do not reduce abiraterone acetate dose.
- Grade 3-4: Withhold abiraterone acetate plus prednisone and adjust/add medications to mitigate the toxicity; when toxicity resolves to  $\leq$ Grade 1, resume abiraterone acetate 1,000 mg/day and prednisone. [Note: Toxicities may include headache interfering with daily activities, nausea, vomiting (>6 episodes within 24 hours), diarrhea, or other toxicity judged related to abiraterone acetate and potentially jeopardizing subject safety.]
- If toxicity recurs, withhold study drug, and adjust or add medications to mitigate the toxicity. When toxicity resolves to  $\leq$ Grade 1, resume study drug with the first dose level reduction (3 tablets, 750 mg of study drug).
- If toxicity recurs, withhold study drug, and adjust or add medications to mitigate the toxicity. When toxicity resolves to  $\leq$ Grade 1, resume study drug with the second dose level reduction (2 tablets, 500 mg of study drug).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue study drug.

### 6.1.5. Management of Abnormal Liver Function Tests

- Grade 1 (AST or ALT >ULN- 3xULN; or total bilirubin >ULN-1.5xULN): Increase frequency of LFT monitoring if investigator judges the toxicity potentially related to abiraterone acetate or exemestane; no dose reductions are required.
- Grade 2 (if asymptomatic, AST or ALT >3 to 5xULN; if symptomatic, AST or ALT >3xULN; or total bilirubin >1.5 to 3xULN): Increase frequency of LFT monitoring if investigator judges the toxicity potentially related to abiraterone acetate or exemestane. Consider withholding study drugs and potentially hepatotoxic concomitant drugs. No dose reductions are required, but may be considered.
- Grade 3 (AST or ALT >5 to 20xULN or >5x for >2 weeks; or total bilirubin >3 to 10xULN): Withhold study drugs and potentially hepatotoxic concomitant drugs. Evaluate LFTs at least weekly until values return to baseline or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit is scheduled. If study drug resumption is considered (and the medical monitor agrees), resume abiraterone acetate at 750 mg when toxicity resolves to Grade 1 or baseline. Dose reduction of exemestane is not recommended per package insert. If Grade 3 LFT recurs at 750 mg, discontinue study drugs and do not rechallenge. Follow subjects until resolution of abnormal LFTs.
- Grade 4 (AST or ALT >20xULN; or total bilirubin >10xULN): Discontinue study drugs immediately and do not re-challenge. Follow subjects until resolution of abnormal LFTs.

## 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. Subjects should not miss doses, especially during PK sampling periods. Subjects should be instructed on compliance (and diary use, for those participating in the PK assessment). During the course of the study, the investigator and study personnel will be responsible for providing additional instruction to any noncompliant subject. Counts of study drug tablets will be conducted on Day 15 Cycle 1 as well as Day 1 of each subsequent treatment cycle. Drug non-compliance is defined as missing  $\geq 75\%$  of doses in 2 consecutive cycles or more than 14 days of therapy in 1 cycle.

## 8. PRESTUDY AND CONCOMITANT THERAPY

Potential subjects must not have taken anastrozole, letrozole, fulvestrant, or any chemotherapy for at least 2 weeks, and bevacizumab for at least 3 weeks, before randomization. Any prestudy therapy administered within 30 days before the first dose of study drug must be recorded during Screening. Subjects will be allowed to continue their prescribed medications (including vitamins) as medically necessary. Any new condition or worsening of an existing condition that requires concomitant therapy must be documented on the adverse events section of the eCRF.

**8.1. Required Study Medication NOT Reported as Concomitant**

Throughout the study, prednisone is administered daily with abiraterone acetate, is not considered concomitant therapy, and should be documented as a required study medication in the eCRF. The use of prednisone for any reason other than required study medication should be documented in the eCRF concomitant therapy section.

**8.2. Permitted Supportive Care and Interventions**

Subjects may receive supportive care, including transfusions, hematopoietic growth factors, antibiotics, analgesics, and antidiarrheal agents during the study per institutional guidelines. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy (except small-field radiotherapy with palliative intent, not involving response-assessable disease), or experimental medications are permitted during the study. Radiotherapy is permitted if initiated before study entry. Supportive therapy should be documented in the concomitant therapy section of the eCRF. Any disease progression requiring anticancer therapy other than study-permitted drugs will be cause for discontinuation from the study.

The following supportive-care medications are permitted during the study:

- Conventional multivitamins
- Additional systemic glucocorticoid administration such as “stress dose” glucocorticoid if clinically indicated for a life-threatening medical condition; in such cases, the use of steroids should be documented as concomitant drug
- Bisphosphonate or denosumab for bone disease [Note: Since all subjects are receiving additional anti-estrogen therapy the sponsor suggests investigators follow local protocols, practice guidelines, and standard of care for monitoring and treatment of bone health in postmenopausal women with breast cancer (Hillner 2003; Reid 2008)]
- Transfusions and hematopoietic growth factors per institutional practice guidelines

If the permissibility of a specific drug or treatment is in question, contact the study medical monitor.

If progression is not confirmed radiographically or clinically then the following are permitted:

- Palliative radiation: one course of involved-field radiation (single- or multi-fraction) to a single site; radiation to more than 1 site of disease is NOT permitted
- Bisphosphonates: addition of a bisphosphonate or denosumab or changing the type of bisphosphonate if a new skeletal related event or bone progression is suspected
- Glucocorticoids: an increase in prednisone dose or addition of a more potent glucocorticoid, such as dexamethasone, to treat breast-cancer-related signs and symptoms, such as fatigue and pain [Note: Prednisone may be increased to 10 mg/day for hypokalemia unmitigated by potassium supplementation, Section 6.1.1]

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Only systemic medications (prescription or over-the-counter, including vaccines, vitamins, and herbal supplements) taken at least 30 days before randomization and continued or begun during the study until 30 days after the final dose of study drug must be documented in the eCRF.

Occasional steroid use no more than 3 days/month for antiemetic prophylaxis is permitted. Treatment consistent with American Society of Clinical Oncology guidelines is recommended. Optional treatment with additional antiemetic drugs, such as 5-hydroxytryptamine antagonists or additional corticosteroids, is permitted and should be documented on the concomitant therapy section of the eCRF.

### **8.3 Special Concomitant Therapy**

The following concomitant therapies warrant special attention:

CYP2D6 substrates: Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

CYP3A4 inducers: 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  $AUC_{\infty}$  of abiraterone was decreased by 55%. Strong inducers of CYP3A4 (eg, phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with abiraterone acetate are to be avoided, or used with careful evaluation of clinical efficacy.

Anticoagulant therapy: Subjects taking warfarin may participate in this study but it is recommended that PT be monitored at least weekly for the first month and, if the INR is stable, monthly thereafter. Subcutaneous heparin is permitted.

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.

## **9. STUDY EVALUATIONS**

### **9.1. Study Procedures**

#### **9.1.1. Overview**

Study procedures to be performed under Amendment INT-6 are outlined in [Attachment 10](#). The Schedule of Events in this Attachment supersedes the Time and Events Schedule in the previous version of the protocol (Amendment INT-5).

The Time and Events Schedule summarizes the frequency and timing of all study evaluations. When study procedures occur on the same visit day, PROs should be completed before any other procedures or consultations for that visit.

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Blood samples (5 mL) are collected to measure coagulation, lipid profile, fasting glucose, hematology, chemistry with electrolytes, and LFTs; total blood volume drawn for a subject through 4 treatment cycles is estimated to be 120 mL (Table 3). Blood samples (2 mL, abiraterone acetate; 4 mL, exemestane) for PK assessment are collected at selected study sites for 20 subjects/treatment group; the approximate total blood volume ranges from 50 to 150 mL, depending on treatment group and treatment site. Sites that do not have a capability of overnight stays will not collect PK samples at 12, 16, and 22 hours after study drug dosing on Days 1 and 15 of Cycle 1. Blood samples (40 mL where local regulations permit) for CTC evaluation are collected at all sites. Tumor samples are collected for ER subtyping and other molecular analyses. DNA sampling will be completed only where regulations permit for subjects who consent separately to participate in the pharmacogenomic component of the study. Repeated or unscheduled blood samples may be taken if required for safety reasons.

Instructions for collection and shipment of pharmacogenomics samples are provided in the Study Laboratory Manual. In the event of DNA extraction failure, a replacement blood sample may be requested. Subjects participating in PK assessment will be provided a diary to record meal and dosing times for the 2 days before each PK sampling day.

**Table 3:** Approximate Blood Volume Through Four Treatment Cycles

Type of Sample	Volume per Sample (mL)	Samples per Subject	Volume per Subject (mL)
- Coagulation	5	2	10
- Lipid profile	5	2	10
- Hematology	5	5	25
- Chemistry	5	6	30
- Endocrine markers	15	3	45
- CTCs	40 <sup>a</sup>	3 <sup>b</sup>	120 <sup>b</sup>
<b>Without PK, CTC, DNA:</b>			<b>240</b>
- Pharmacokinetics (PK)			
- abiraterone group	2	19 or 25	38 or 50
- exemestane group	4	19 or 25	76 or 100
- abiraterone + exemestane group	6	19 or 25	114 or 150
- Pharmacogenomics (DNA)	10	1	10
<b>With PK, CTC, DNA:</b>			<b>48 – 160</b>
<b>With safety labs above</b>			<b>288 – 400</b>

PK=pharmacokinetics; CTC=circulating tumor cells

<sup>a</sup> Where local regulations permit

<sup>b</sup> If low CTCs are found in the baseline sample, no further CTC sampling should be done for the subject.

**Note:** Approximate total volume for PK analysis ranges from 38 mL (abiraterone acetate + prednisone group, sites that do not support overnight stays) to 150 mL (abiraterone acetate + prednisone combined with exemestane group, sites that do support overnight stays).

### 9.1.2. Screening Phase

Each subject must satisfy all entry criteria (Sections 4.1 and 4.2) and sign the consent form before any study procedure is performed. Potential subjects must not have taken anastrozole,

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letrozole, fulvestrant, or any chemotherapy for at least 2 weeks, and bevacizumab for at least 3 weeks, before randomization. Procedures and evaluations should be performed according to the Time and Events Schedule.

### **9.1.3. Treatment Phase**

Subjects should receive study drug until disease progression (Section 9.2.1), when subjects randomized to exemestane alone may be switched to abiraterone acetate plus prednisone at the discretion of the investigator; if not switched, these subjects must be discontinued from study drug. At disease progression, subjects randomized to either abiraterone acetate plus prednisone or abiraterone acetate plus prednisone combined with exemestane must be discontinued from study drug. Subjects with no disease progression for 12 treatment cycles may continue study treatment at the discretion of the investigator, in which case study visits will continue every 3 cycles for assessment of efficacy (CT or MRI, ECOG) and safety (physical examinations, vital signs, fasting glucose, hematology, chemistry with electrolytes, LFTs); PROs and lipid profiles will be continued every cycle and every 6 cycles, respectively. Concomitant therapy prohibited and allowed is detailed in Sections 4.3 and 8.2, respectively. Procedures and evaluations should be performed according to the Time and Events Schedule.

### **9.1.4. End-of-Treatment Procedures**

The End-of-Treatment visit occurs when the subject has met the criteria for discontinuation of study drug(s). This should be scheduled within 30 days after the final dose of study drug to collect posttreatment safety and efficacy data as well as a biomarker sample, as specified in the Time and Events Schedule.

### **9.1.5. Follow-Up Phase**

Subjects should enter the Follow-Up phase regardless of reason for study drug discontinuation and should be monitored every 3 months ( $\pm 7$  days) until death, loss to follow-up, consent withdrawal, or abiraterone acetate development in this indication is discontinued. Nonstudy anti-breast-cancer therapies (with start and stop dates) and survival status may be collected by telephone or chart review. PROs also should be completed. The total study duration will be extended up to September 2018.

Under Amendment INT-6, the follow-up phase will be stopped, and subjects currently in long-term follow up will be discontinued from the study.

## **9.2. Efficacy Evaluation**

### **9.2.1. Progression-Free Survival**

Determination of PFS will use radiographic progression defined by RECIST ([Attachment 1](#)) on measurable lesions captured by CT or MRI at baseline and, using the same modality, repeated every 2 cycles initially (Day 1 Cycle 3, Day 1 Cycle 5, and Day 1 Cycle 7) and every 3 cycles thereafter (eg, Day 1 Cycle 10, Day 1 Cycle 13) until, and including, the End-of-Treatment visit.

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The baseline image should be taken within 4 weeks before randomization as close as possible to Day 1 Cycle 1. Every effort must be made to ensure the same radiographic method (CT or MRI) is used before and throughout the study.

Since disease progression should be documented by CT or MRI, imaging with whichever modality was used at baseline should be completed as soon as possible if a new breast-cancer-related symptom appears that requires medical intervention, such as initiation of chemotherapy, palliative radiotherapy, or opiate therapy (or dose increase). When clinical progression cannot be confirmed by CT or MRI, such as when the disease site is skin, bone marrow, or central nervous system, the corresponding clinical examination finding will be recorded in the source documents and in the eCRF. See the Time and Events Schedule for frequency of physical examinations.

Disease progression should not be based on assessments of new sclerotic bone lesions. When bone disease is the only basis for determination of progression or response, only lytic bone lesions should be used.

All disease progressions should be confirmed by the sponsor company via a faxed confirmation form ([Attachment 5](#)).

### **9.2.2. Long-Term Benefit**

Survival status will be determined throughout the study and during Follow-Up. Survival status, including nonstudy anticancer therapy, may be monitored by telephone or chart review during Follow-Up.

The following PROs are self-administered, health-related quality-of-life questionnaires that assess subject-perceived disease burden, including pain, and should be conducted according to the Time and Events Schedule.

#### **EORTC-C30**

The EORTC-C30 ([Attachment 2](#)) is a 30-item questionnaire validated for clinical research in oncology (Aaronson 1993; Bottomley 2007; Fayers 2002) and is specifically validated and responsive in breast cancer patients (McLachlan 1998; Osoba 1994). The EORTC-30 comprises scales in function, symptoms, a global health subscale, as well as single items to assess specific symptoms.

#### **EQ-5D-5L**

The EQ-5D-5L ([Attachment 3](#)) is a 5-item instrument measuring mobility, self-care, usual activities, pain, discomfort, and anxiety/depression (EuroQol Group 1990) that generates a single utility score commonly used to calculate quality-adjusted life years, an outcome measure of cost effectiveness (Drummond 2005; Weinstein 1996).

**Pain Intensity Scale of BPI-SF**

Of the BPI-SF instrument, only the 4-item pain intensity scale ([Attachment 4](#)) is used in this study (Cleeland 1994).

**9.3. Safety Evaluation**

All study subjects who received any dose of study drug will be evaluable for safety. Adverse events, including laboratory adverse events, will be graded and summarized according to the NCI-CTCAE ([Attachment 6](#)). 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 following evaluations of safety will be performed at time points specified in the Time and Events Schedule.

**Cardiac Function**

The cardiac left ventricular ejection fraction should be evaluated by MUGA (ECHO if MUGA unavailable) before and after study treatment using the same assessment modality; subjects with prior anthracycline  $\geq 350$  mg/m<sup>2</sup> will have evaluations at baseline and every 3 cycles thereafter (eg, Day 1 Cycle 4, Day 1 Cycle 7). ECGs should be done within 4 weeks before randomization and Day 1 Cycle 4 and every 3 cycles thereafter (eg, Day 1 Cycle 4, Day 1 Cycle 7), and End-of-Treatment (see Section 11.9 for details); serum potassium <3.5 mM should be corrected before any ECG is recorded. At selected study sites, when PK sampling is Day 1 Cycle 1, an ECG should be recorded 2 hours after study drug dose. ECGs (12-lead) should be recorded at a paper speed of 25 mm/sec until 4 regular consecutive complexes are available. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the investigator.

**Physical Examination**

Physical examinations, including weight, should be conducted at every visit; height will be recorded at baseline only. Subject weight will be measured with the subject lightly clothed and without shoes. Any clinically significant change in physical findings noted during the study should be reported as an adverse event. Any clinically significant abnormalities persisting at the end of the study should be followed by the investigator until resolution or until reaching a clinically stable endpoint.

**Vital Signs**

Upright sitting blood pressure, heart rate, respiratory rate, and oral or aural body temperature, should be recorded.

**Clinical Laboratory Tests**

Blood samples for hematology and chemistry will be taken for evaluation of laboratory safety parameters ([Attachment 7](#)). The investigator must review the laboratory report, document this

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review, and record any clinically relevant changes during the study in the adverse event section of the eCRF. Baseline values, including Screening coagulation and dipstick urinalysis, should be measured within 7 days before randomization.

All laboratory test results should be classified according to NCI-CTCAE criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values will be the results from the last blood samples drawn on or before the first day of study treatment. On-study laboratory test values will be those results from blood samples drawn 1 day after the first study treatment until 30 days after the last dose of study treatment.

#### **9.4. Biomarker Evaluation**

Circulating levels of adrenal steroids, including DHEA and its sulphate, DHEA-S, positively correlate with ER+/PR+ breast cancers (Eliassen 2006; Key 2002) and in vitro data indicate these ligands stimulate proliferation of breast cancer cell lines in a low-estrogen environment (Maggiolini 1999). These ligands function as weak ER agonists, indicating that steroidogenic enzymes upstream of aromatase may also contribute to disease progression (Chan 2002) by activating ER and possibly other steroid hormone receptors. Abiraterone is expected to attenuate this activity by suppression of androgenic steroids that may contribute to mitogenesis through stimulation of both AR and ER.

##### **9.4.1. Formalin-Fixed Paraffin-Embedded Tumor Tissue**

To determine study eligibility, prior to randomization an FFPE tumor sample will be assessed for ER, PR, and Her2. In addition to these markers, samples may also be analyzed for expression levels of intratumoral nuclear AR, CYP17, CYP19, Ki-67, and 3 $\beta$ -HSD by immunohistochemistry or fluorescence in situ hybridization (FISH). Samples may also be analyzed for miRNA expression levels to define molecular subtypes of breast cancer or for mutations or amplification of the ER $\alpha$  gene, K303R or for other biomarkers (e.g. mRNA, somatic anomalies).

##### **9.4.2. Endocrine Markers**

For every subject, blood samples (15 mL) for assessment of endocrine biomarkers will be taken Day 1 of Cycles 1 through 3, and every 3 cycles thereafter (eg, Day 1 Cycle 6, Day 1 Cycle 9) up to, and including Day 1 Cycle 12, and at the End-of-Treatment visit. Estradiol, testosterone, and estrone levels will be evaluated for all subjects. Additional androgens or estrogens may also be evaluated.

##### **9.4.3. Circulating Tumor Cells**

Blood samples (40 mL where local regulations permit) will be taken Day 1 of Cycles 1 and 2 and during the End-of-Treatment visit for enumeration and characterization of CTCs and biomarkers such as AR, ER, PR, Her2, CYP17, CYP19, or other candidate markers. Other molecular analyses (eg, RNA or DNA based) may also be conducted. Sites will be notified when a subject's

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Day 1 Cycle 1 baseline sample does not meet a minimum threshold and no further CTC sampling should be done for the subject.

#### **9.4.4. Fresh Tumor Biopsies (Selected Study Sites)**

Consent to biopsy metastasized or primary tumor will be sought from subjects with superficial disease easily and safely amenable to successive tumor biopsies at selected study sites. Consent will be obtained for a biopsy at baseline and at least 1 treatment phase time point. If consent is granted for 3 time points, biopsies will be taken at screening, Day 1 Cycle 3, and Day 1 Cycle 5; missing time points will not be considered protocol violations. Biomarker studies may include global miRNA and gene-expression profiling, somatic mutational profiling, immunohistochemistry or FISH analyses of AR, ER, PR, Her2, CYP17, CYP19, Ki-67, and 3 $\beta$ -HSD. Additional androgens and estrogens also may be evaluated.

#### **9.5. Pharmacogenomics Evaluation**

There are 2 parts to the optional pharmacogenomics component of this study. The first part enables analysis of genes that may be relevant to abiraterone acetate or breast cancer. Candidate genes will be genotyped only if it may help resolve issues with clinical data. Genotyping of candidate genes related to abiraterone or breast cancer would be performed on identifiable samples. Additional genes may be added as more knowledge related to abiraterone or breast cancer becomes available.

The second part of the pharmacogenomics research allows for storage of DNA samples for future genetic research related to abiraterone acetate or breast cancer. Stored DNA samples will be double-coded and stored for a period of 5 years after the Clinical Study Report is issued.

Subjects may participate in either part, neither part, or both parts, where local regulations permit.

#### **9.6. Pharmacokinetics Evaluation (Selected Study Sites)**

##### **Evaluations**

The twenty (20) subjects/treatment group will participate in PK assessments on Days 1 and 15 of Cycle 1 for collection of serial venous blood samples (2 mL, abiraterone acetate; 4 mL, exemestane). On Days 1 and 15 of Cycle 1, PK samples will be collected before and 1, 1.5, 2, 3, 4, 8, 12, 16, 22, and 24 hours after study drug dosing. Sites that do not have the capability of overnight stays will not collect PK samples at 12, 16, and 22 hours after study drug dosing on Days 1 and 15 of Cycle 1. Predose samples only will also be collected Day 1 of Cycles 2 through 4. Study drug will be given at the study site on these days and subjects will be instructed to record study drug dosing times and meal times for 2 days before each PK sampling visit.

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### **Analytical Procedures**

Plasma abiraterone and exemestane concentrations will be determined using a validated liquid chromatography-mass spectrometry/mass spectrometry method under the supervision of the sponsor Bioanalytical Laboratory.

### **Pharmacokinetics Parameters**

PK analysis will be the responsibility of the sponsor in accordance with the current Clinical Pharmacokinetics Guideline. PK parameters to be estimated for abiraterone and exemestane from plasma data include the following:

$C_{\max}$	maximum plasma concentration
$t_{\max}$	time to reach the maximum plasma concentration
$AUC_{\text{last}}$	area under the plasma concentration-time curve from time 0 to time of last quantifiable plasma concentration
$t_{\text{last}}$	time to last quantifiable plasma concentration
$AUC_{24\text{h}}$	area under the plasma concentration-time curve from time 0 to 24 hours

Additional PK parameters will be calculated if deemed appropriate.

### **9.7. Sample Collection and Handling**

The actual dates and times of sample collection must be recorded on the laboratory requisition forms. If an indwelling catheter is used for sample collection, saline flushes (no heparin) should be used. PK sample collection, processing, storage, and shipping instructions are detailed in the Study Laboratory Manual.

## **10. SUBJECT COMPLETION/WITHDRAWAL**

### **10.1. Completion**

A subject will be considered as having completed the Treatment phase if she completes assessments until experiencing disease progression or unacceptable toxicity or medical condition that precludes further study treatment. A subject will be considered as having completed the study if she completes Treatment and Follow-Up phases (total study duration will be extended up to September 2018).

Under Amendment INT-6, the long-term follow-up phase will be stopped, and subjects in long-term follow up will be discontinued from the study (see [Attachment 10](#)).

### **10.2. Discontinuation of Study Drug**

Notification of study drug discontinuation for disease progression should be made to the sponsor by fax before treatment discontinuation and clearly documented on the appropriate eCRF. Once the sponsor has been notified of an acceptable reason for study treatment discontinuation, the subject can be discontinued from study drug(s) and entered into the Follow-Up phase after the

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End-of-Treatment visit. An exception to the discontinuation rule can be made if the treatment discontinuation is being made for safety reasons. The End-of-Treatment visit should be scheduled within 30 days after the final dose of study drug. When a subject withdraws consent for study treatment but is willing to continue in the study, posttreatment follow-up should report overall survival, subsequent non-study anti-breast-cancer therapies (with start and stop dates), and PRO score.

At disease progression, subjects randomized to exemestane alone may be switched to abiraterone acetate plus prednisone at the discretion of the investigator after notifying the sponsor; if not switched, these subjects must be discontinued from study drug after notifying the sponsor. Those subjects who cross-over to abiraterone acetate from exemestane will complete study visits starting again with Day 1 Cycle 1. However, the subjects that cross-over will not be required to provide additional samples for the sub-studies (i.e., PK, biopsy), or have further samples collected for biomarker, endocrine, CTCs and pharmacogenomic evaluations. At disease progression, subjects randomized to either abiraterone acetate plus prednisone or abiraterone acetate plus prednisone combined with exemestane must be discontinued from study drug.

In addition, an investigator may discontinue study drug for any of the following reasons:

- Dosing noncompliance
- Unacceptable toxicity
- Medical condition not served by continuing study drug treatment
- Administration of prohibited therapies or medications

### **10.3. Withdrawal From the Study**

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

- Loss to follow-up
- Withdrawal of consent
- Death

If a subject is lost to follow-up, every reasonable effort must be made by study site personnel to contact the subject to determine the reason for withdrawal and the measures taken to follow up must be documented. If a subject withdraws consent, the End-of-Treatment study visit should be completed within 30 days of the last dose of study drug.

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

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A subject who withdraws from the study will have the following options regarding pharmacogenomic research:

- The DNA extracted from the subject's blood will be retained and used in accordance with the subject's original pharmacogenomic informed consent.
- The subject may withdraw consent for pharmacogenomic research, in which case the DNA sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor site contact to request sample destruction. The sponsor site contact will, in turn, contact the biomarker/pharmacogenomics representatives to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

#### **Withdrawal From Pharmacogenomics Research Only**

A subject may withdraw consent for pharmacogenomic research while remaining in the clinical study. In such a case, any DNA extracted from the subject's blood will be destroyed. The sample destruction process will proceed as described above.

### **11. STATISTICAL METHODS**

Statistical analysis will be done by the sponsor or under the supervision of the sponsor. A general description of the statistical methods to be used to analyze efficacy and safety data is outlined below. Specific details are provided in the Statistical Analysis Plan.

Unless otherwise specified, continuous endpoints will be summarized using descriptive statistics, which will include subject number, mean, standard deviation, median, minimum, and maximum. Categorical endpoints will be summarized using frequencies and percentages. The baseline measurement will be the last value on or before the first dose of study medication.

#### **11.1. Sample Size Determination**

The primary analysis consists of 2 pair-wise comparisons of the experimental treatment groups (abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane) with the reference treatment group (exemestane alone). For each of the pair-wise comparisons, the statistical tests of treatment effects on primary endpoint of PFS will be conducted independently at the 2-sided 0.10 level of significance. No multiplicity adjustment to the Type I error will be made. A log-rank test will be used in the testing of the primary endpoint PFS. This study is event driven and will complete for primary analysis after a total of 220 PFS events in the 3 treatment groups have occurred over a total study duration of 19 months. It is assumed that PFS follows an exponential distribution with a constant hazard ratio. Assuming an underlying hazard ratio of any pair-wise comparison (abiraterone acetate plus prednisone and abiraterone acetate plus prednisone combined with exemestane, each compared with exemestane alone) is 0.65 (median PFS 6.2 and 4.0 months, respectively), the study has 80% power at a significance level of 0.10 (2-sided) to demonstrate a treatment difference with approximately 150 PFS events in each pair-wise comparison. Assuming an enrollment rate of 20 subjects per month

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for 15 months, a total sample size of approximately 300 subjects (100 subjects per group) is planned. In the case that randomization to 1 treatment group is discontinued based on the DRC recommendation after the interim analysis, the study may stop randomization when approximately 200 subjects are enrolled to the remaining 2 treatment groups. The final analysis would then be performed after the occurrence of 150 death or progression events within the remaining 2 treatment groups.

## **11.2. Analysis Populations**

Subject disposition and efficacy analyses will be performed on data from the intent-to-treat (ITT) population. All randomized subjects included in the ITT analysis will be classified according to assigned treatment group, regardless of actual treatment received. The primary efficacy analyses will be on the ITT population.

All subjects who receive at least 1 dose of study drug will be included in the analysis of safety (Safety Population).

## **11.3. Demographics and Baseline Characteristics**

Demographic variables will include age, race, ethnicity, height, and weight. Baseline disease characteristics (documented in the source documents and eCRF) will include time since diagnosis, disease sites, prior therapies (how many and whether nonsteroidal aromatase inhibitor was given in adjuvant or metastatic setting), duration of stable disease during prior aromatase inhibitor therapy, and hormone receptor status.

## **11.4. Efficacy Analyses**

### **11.4.1. Primary Efficacy Endpoint**

The primary efficacy endpoint, PFS, is measured from time of randomization to first occurrence of one of the following:

- Disease progression as defined in Section 9.2.1
- Death from any cause

### **11.4.2. Secondary Efficacy Endpoints**

- Overall survival will be measured from date of randomization to date of death from any cause. Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up.
- Overall response rate is defined as the proportion of subjects fulfilling respective criteria for response over the total number of subjects in the ITT population. Overall response for measurable disease is defined as a subject having a best overall response of either complete response or partial response based on RECIST ([Attachment 1](#)).
- PROs: EORTC-C30, EQ-5D-5L, and BPI-SF pain intensity scale scores ([Attachment 2](#), [Attachment 3](#), [Attachment 4](#))

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- Change in endocrine marker concentrations (estradiol, testosterone, estrone, and other biomarkers)
- PK characterization of abiraterone and exemestane

Other efficacy endpoints include ECOG ([Attachment 8](#)), pharmacogenomics evaluations, CTC characterization, and biomarker evaluations in fresh tumor biopsies.

#### **11.4.3. Analyses Methods**

Distributions of time-to-event variables will be estimated using the Kaplan-Meier product-limit method. Median times to event with 2-sided 95% confidence intervals will be estimated. The stratified log-rank test will be used as the primary analysis for treatment comparison. A Cox proportional-hazards model will be used to provide estimates of hazard ratios with 95% confidence intervals.

The relative risk (treatment:control) will be reported along with the associated 95% confidence interval. Statistical inference will be evaluated using Chi-square statistic; the Fisher's exact test may be used if the expected counts in some cells are small.

Scores from EORTC-C30, EQ-5D-5L, and BPI-SF pain intensity scale will be descriptively summarized by treatment group. Longitudinal analysis with repeated measures may be used as appropriate.

#### **11.5. Biomarker Analyses**

Biomarker studies are designed to identify markers predictive of response (or resistance) to abiraterone. The following biomarkers may be analyzed:

- protein levels quantified by immunohistochemistry and FISH (AR, ER, PR, Her2, CYP17, CYP19, Ki-67, and 3 $\beta$ -HSD)
- serum endocrine biomarkers (estradiol, testosterone, and estrone)
- CTCs
- gene expression, miRNA or somatic mutation profiling

The associations of the above biomarkers with clinical response or time-to-event endpoints will be assessed using the appropriate statistical methods (analysis of variance [ANOVA], categorical, or survival model), depending on the endpoint.

Analyses will be performed within each treatment group and difference by race will be explored. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints will identify responsive (or resistant) subgroups. For expression-related analyses, evaluations will determine whether patterns of expression change with acquired resistance to treatment.

**11.6. Pharmacokinetics Analyses**

The PK population will include all subjects with sufficient and interpretable PK assessments to estimate the noncompartmental PK parameters. PK parameter estimations of abiraterone and exemestane will be summarized by descriptive statistics by treatment group. The plasma abiraterone and exemestane concentrations of at each time point will be summarized by descriptive statistics by treatment group. Individual and mean plasma concentration-time profiles of abiraterone and exemestane will be plotted by treatment group. All subjects and samples excluded from analysis will be clearly documented in the study report. Further exploratory PK analyses may be performed, as deemed appropriate.

**11.7. Safety Analyses**

All subjects who receive at least 1 dose of study drug will be analyzed for safety. Treatment-emergent adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system and graded according to the NCI-CTCAE. Adverse events will be summarized by system organ class and preferred term, and will be presented overall and by treatment group. Deaths and other serious adverse events will be provided in a listing. Treatment-emergent adverse events resulting in study drug discontinuation, dose modification, and dose interruption or delay will also be listed and tabulated by preferred term. Other safety endpoints, including vital signs, clinical laboratory parameters, and ECG, will be summarized descriptively. Shift tables for select laboratory parameters will be presented. No formal statistical analyses are planned.

**11.8. Interim Analysis**

One interim analysis is scheduled when a total of approximately 110 (50%) of the PFS events have occurred. The interim analysis is expected to occur after approximately 75 PFS events in each of the 2 pair-wise comparisons: 1) abiraterone acetate plus prednisone versus exemestane alone, 2) abiraterone acetate plus prednisone combined with exemestane versus exemestane alone. The stopping boundaries for PFS-based futility and efficacy were calculated using East<sup>®</sup> software. Gamma-family spending functions determined the Type I error rate of 10% (2-sided) and Type II error rate of 20% for each comparison. After the review of interim data, the Data Review Committee (DRC) will make recommendations regarding the continuation of the study.

**11.9. Data Review Committee**

A DRC will be formed to monitor data on a regular basis to ensure the safety of the subjects enrolled in this study and to meet efficacy objectives. The DRC will consist of at least 1 medical expert in breast cancer and at least 1 statistician. Details regarding DRC responsibilities and interim analysis procedures will be provided in a separate DRC charter.

In addition to the planned interim analysis (Section 11.8), the DRC will meet periodically to review the cumulative safety data collected. One safety review by DRC will occur after the tenth

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subject in each treatment group (~30 subjects) has received study drug for 28 days (Cycle 1); subject accrual will continue only if no safety concerns arise. When the baseline and at least 1 posttreatment ECG are available for the first 25 subjects in each treatment group (75 subjects total), the DRC will determine if additional ECGs are needed for these and subsequent subjects.

## **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 noninvestigational) 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. Note: Definition is according to the 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

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- 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 1 of the 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.

### **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 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 will be used to grade the severity of adverse events. Adverse events not listed in the NCI-CTCAE Version 4.0 will 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
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor medicinal product, eg, name confusion)

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

**12.3. Procedures****12.3.1. All Adverse Events**

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until 30 days after the last dose of study drug. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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Disease progression will not be reported as an adverse event, as this information will be used for assessment of efficacy endpoints. However, the signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the serious adverse event definition (see Section 12.1.1, Adverse Event Definitions and Classification). 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 eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator 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 name of the investigational study drug, the study number, the investigator’s name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

### **12.3.2. Serious Adverse Events**

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

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

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

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- 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 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:

- Reasons described in the protocol, eg, drug administration, protocol-required testing
- Prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event
- Preplanned reasons (ie, planned prior to the start of treatment on study – must be documented in the eCRF). Prolonged hospitalization for a complication considered to be at least possibly related to the study medication remains a reportable serious adverse event
- As part of a standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event
- For the administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event As part of a procedure for protocol- or disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling), or hospitalization or prolonged hospitalization for a complication of such a procedure

#### **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.

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### **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, 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 within 24 hours 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 (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 Drugs**

Abiraterone acetate 250-mg tablets 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. Additional information is in the Investigator Brochure.

Exemestane is provided as 25-mg tablets.

Prednisone is provided as 5-mg tablets.

#### **14.2. Packaging**

Study medication is provided to each site in bulk form. The study site pharmacist dispenses study medication to each subject in accordance with this protocol under the guidelines of the site's dispensation standard operating procedure.

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### **14.3. Labeling**

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

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

Study drugs must be stored in a secure area and administered only to study subjects in accordance with conditions specified in this protocol. Abiraterone acetate and exemestane should be stored at room temperature (15 to 30°C; 59 to 86°F) in the original container. Prednisone should be stored at 20 to 25°C (68 to 77°F) and prednisolone should be stored below 25°C. Subjects should be instructed to keep medications out of reach and sight of children.

Abiraterone is contraindicated in women who are pregnant or may be pregnant. There are no human data on the use of abiraterone acetate in pregnancy. To avoid inadvertent exposure, women who are pregnant or may be pregnant should not handle abiraterone acetate without protection, eg, gloves. It is not known if either abiraterone acetate or its metabolites are excreted in human breast milk.

Additional information is provided in the abiraterone acetate Investigator's Brochure.

### **14.5. Drug Accountability**

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

Study drug must be handled in strict accordance with the protocol and the container label and should be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug and study drug returned by subjects must be available for verification by the sponsor site monitor during on-site monitoring visits. 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, 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 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 follow supplies:

- Investigator Brochure for abiraterone acetate
- eCRFs
- Study Pharmacy Manual
- Study Laboratory Manual
- Study PRO Booklets
- Subject diaries for subjects participating in PK assessment
- Collection tubes, labels, and other supplies required for collection and shipment of blood samples for PK and pharmacogenomic assessments
- Collection and shipping supplies for biomarker samples

## 16. ETHICAL ASPECTS

### 16.1. Study-Specific Design Considerations

Ongoing medical review by sponsor and DRC occurs as soon as a subject is enrolled in the study. Study recruitment will be on hold until the DRC reviews safety data from the first 30 subjects. The safety profile and dosing compliance of abiraterone acetate plus prednisone or abiraterone acetate plus prednisone combined with exemestane, compared with exemestane alone, must be comparable for recruitment to continue. An interim analysis reviewed by the DRC for safety and efficacy will occur when 110 events have occurred.

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 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
- 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), informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

- Protocol amendment(s) (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 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 subject safety or study conduct

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- Deviations from or changes to the protocol to eliminate immediate hazards to 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. Results from laboratory tests, medical procedures and imaging or scans done as part of standard of care that have been performed before the consent form signature date may be used for the study. The consent form used must be approved by both sponsor and reviewing IEC/IRB and be in a language the subject can read and understand. 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 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 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 applicable laws or regulations. By signing the informed consent form the subject is authorizing such access and allows the study physician to re-contact the subject for the

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purpose of obtaining consent for additional safety evaluations, subsequent disease-related treatments, or survival status and any new antitumor therapies.

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.

In accordance with local regulations, subjects will be required to sign an updated informed consent form to continue in the study under Amendment INT-6. Subjects who elect not to continue in the study and those in long-term follow up will be discontinued from the study.

Under Amendment INT-7, individual subjects who may continue to derive benefit from the treatment they are currently receiving, will be offered the opportunity to continue on their existing study medication and followed-up for safety for an additional duration of up to 3 years (ie, up to 20 September 2018) from the date previously stated (20 September 2015) in the Amendment INT-6. The situation may be reassessed periodically for subjects still receiving study medication.

#### **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.

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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.

Pharmacodynamics, biomarker, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

## **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 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 IEC/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 eCRF 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 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 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 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
- 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 assigned number.

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 eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, 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**

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

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the eCRF. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete eCRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

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

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

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

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

#### **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 study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

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

#### **17.7. Record Retention**

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 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

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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 eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

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

## **17.9. Study Completion/Termination**

### **17.9.1. Study Completion**

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject 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 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 and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor 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.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. 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.

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, 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:**  
Response Evaluation Criteria in Solid Tumors (RECIST)

**Eligibility**

- RECIST criteria will be used on measurable soft tissue and visceral lesions.
  - Measurable disease is the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
  - Measurable lesions: Visceral or extranodal lesions need to be  $\geq 10$  mm in one dimension using spiral CT; however, lymph nodes need to be  $\geq 20$  mm in at least one dimension to be considered as target or evaluable lesions to assess changes in size.
  - Non-measurable lesions are all other lesions, including small lesions (longest diameter  $< 20$  mm), leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment; nodal and visceral/extranodal disease will be recorded separately.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

**Methods of Measurement**

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a  $\leq 5$  mm contiguous reconstruction algorithm.
- Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound, endoscopy and laparoscopy should not be used to measure tumor lesions.
- Cytology and histology can be used to differentiate between Partial Response and Complete Response in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions).

**Attachment 1: (Continued)**  
Response Evaluation Criteria in Solid Tumors (RECIST)

**Baseline Documentation of TARGET and NON-TARGET Lesions**

- All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

**Evaluation of Target Lesions**

Complete Response:	Disappearance of all target lesions
Partial Response:	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease:	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease:	Neither sufficient shrinkage to qualify for Partial Response nor sufficient increase to qualify for Progressive Disease, taking as reference the smallest sum LD since the treatment started

**Evaluation of Non-Target Lesions**

Complete Response:	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease:	Appearance of new lesions and/or unequivocal progression of existing non-target lesions <sup>a</sup>

<sup>a</sup> Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

**Confirmations of PR and CR will be documented by a second CT or MRI at least 4 weeks after the initial response.**

**Attachment 1: (Continued)**  
Response Evaluation Criteria in Solid Tumors (RECIST)

**Evaluation of Best Overall Response**

The Best Overall Response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for Progressive Disease the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

**RESPONSE CRITERIA**

<b>Target Lesions</b>	<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>
Complete Response	Complete Response	No	Complete Response
Complete Response	Incomplete response/ Stable Disease	No	Partial Response
Partial Response	Non- Progressive Disease	No	Partial Response
Stable Disease	Non- Progressive Disease	No	Stable Disease
Progressive Disease	Any	Yes or No	Progressive Disease
Any	Progressive Disease	Yes or No	Progressive Disease
Any	Any	Yes	Progressive Disease

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

**Attachment 2:**  
European Organization for Research and Treatment of Cancer Core 30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birth date (Day, Month, Year):

Today's date (Day, Month, Year):

	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
<b>During the past week:</b>				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

**For the following questions please circle the number between 1 and 7 that best applies to you.**

29. How would you rate your overall <u>health</u> during the past week?	1	2	3	4	5	6	7
	Very poor						Excellent
30. How would you rate your overall <u>quality of life</u> during the past week?	1	2	3	4	5	6	7
	Very poor						Excellent

**Attachment 3:**  
Euro-QoL (EQ-5D-5L)

Under each heading, please check the ONE box that best describes your health TODAY.

**MOBILITY**

- I have no problems walking
- I have slight problems walking
- I have moderate problems walking
- I have severe problems walking
- I am unable to walk

**SELF-CARE**

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN / DISCOMFORT**

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

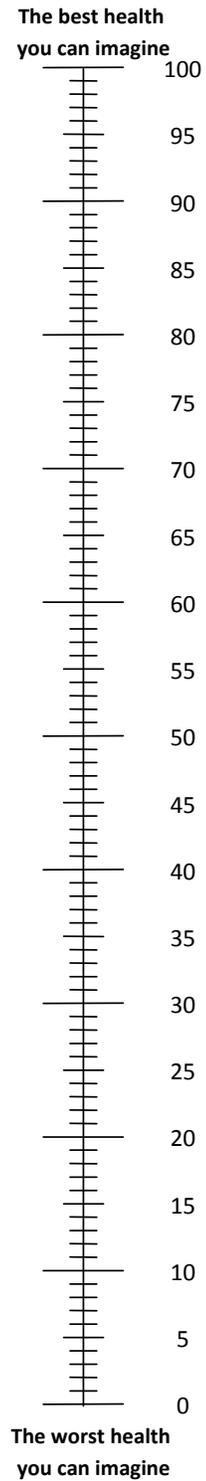
**ANXIETY / DEPRESSION**

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

**Attachment 3: (Continued)**  
Euro-QoL (EQ-5D-5L)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.  
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



**Attachment 4:**  
Pain Intensity Scale (of Brief Pain Index–Short Form)

Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please rate your pain by circling the one number that best describes your pain on the **average**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please rate your pain by circling the one number that tells how much pain you have **right now**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

**Attachment 5:**  
Progressive Disease Notification Fax

**FAX**

Protocol no.: 212082BCA2001

**Progressive Disease Notification Fax**

**Fax details**

<b>To:</b>	Dr. [REDACTED]*	<b>From:</b>	Include investigator name
<b>Fax no. :</b>	[REDACTED]	<b>Site no.:</b>	Include investigator site no.
<b>Cc:</b>	Janssen LTM (include name)	<b>Fax no.:</b>	Include investigator fax no.
<b>Fax:</b>	Include fax no.	<b>Tel no:</b>	Include investigator tel no.

\*in case of emergencies please contact  
[REDACTED] (fax no.: Janssen LTM include  
number) or [REDACTED] (fax no.: Janssen  
LTM include number) if [REDACTED] cannot  
be contacted

**Instructions**

Please complete this form as soon as the patient is documented to have progressive disease and FAX this form to the Sponsor Medical Representative and Local Trial Manager mentioned above.

**Patient details** *[please complete]*

<b>SUBJECT ID:</b> _____	<b>Date of PD:</b> ____ / ____ / ____ dd      mmm      yyyy
--------------------------	--

**Disease Progression should be confirmed by CT or MRI ideally (option 1 below). If clinical progression is confirmed please tick option 2 below:**

**1. Please, indicate the Radiological basis for diagnosis of progressive disease (per RECIST)**

**Target lesions**

<input type="checkbox"/>	At least a 20% increase in the sum of longest diameter of target lesions, taking as reference the smallest sum long diameter recorded since the treatment started
<input type="checkbox"/>	Appearance of any new lesion

**Non-target lesions**

<input type="checkbox"/>	Unequivocal progression of existing lesion
<input type="checkbox"/>	Appearance of any new lesion

**Please note - in bone only disease PD cannot be based on assessment of new sclerotic lesions (only lytic lesions can be used)**

The sponsor representative will complete and sign the lower part of this form and return it by fax.  
**Retain this fax as part of the subject's study records**  
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**Attachment 5: (Continued)**  
Progressive Disease Notification Fax

**FAX**

Protocol no.: 212082BCA2001

**Progressive Disease Notification Fax**

**2. Clinical progression**

<input type="checkbox"/>	When CT or MRI could not be used and symptoms indicate signs of disease progression
--------------------------	---

**Please indicate all sites of involvement:**

<input type="checkbox"/>	CNS
<input type="checkbox"/>	Bone marrow
<input type="checkbox"/>	Skin
<input type="checkbox"/>	Pulmonary
<input type="checkbox"/>	GI
<input type="checkbox"/>	Cardiac
<input type="checkbox"/>	Head and neck
<input type="checkbox"/>	Symptomatic deterioration caused by cancer
<input type="checkbox"/>	Other

**Investigator Name:** \_\_\_\_\_

**Investigator Signature:** \_\_\_\_\_

**Date:**

\_\_\_\_/\_\_\_\_/\_\_\_\_  
dd mmm yyyy

**For Sponsor medical representative use only:**

Agree, basis for diagnosis of PD is consistent with protocol criteria

Disagree: Specify: \_\_\_\_\_

\_\_\_\_\_

**Sponsor Medical Representative Signature:** \_\_\_\_\_

**Date:**

\_\_\_\_/\_\_\_\_/\_\_\_\_  
dd mmm yy

The sponsor representative will complete and sign the lower part of this form and return it by fax.

**Retain this fax as part of the subject's study records**

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**Attachment 6:**  
National Cancer Institute Common Terminology Criteria for Adverse Events

The descriptions and grading scales found in the revised NCI-CTCAE, Version 4.0 (published 28 May 2009) will be utilized for adverse event reporting. A copy of the NCI-CTCAE Version 4.0 can be downloaded from the Cancer Therapy Evaluation Program web site (<http://ctep.cancer.gov>).

**Attachment 7:  
Laboratory Tests**

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**Local Laboratory Tests**

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## Hematology:

- Hemoglobin
- Platelet count
- White blood cell count:
  - absolute neutrophil count
  - absolute lymphocyte count
  - absolute eosinophil count

## Coagulation Factors:

- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- International normalized ratio (INR)

## Urinalysis dipstick for:

- Blood
  - Protein
  - Glucose
- (Microscopic examination if abnormal)

## Clinical Laboratory:

- Luteinizing hormone (LH)
- Follicle stimulating hormone (FSH)

## Serum Chemistry and Electrolytes:

- Albumin
- Amylase
- Blood urea nitrogen
- Calcium
- Creatinine
- Glucose (fasting)
- Lactate dehydrogenase
- Liver Function Tests:
  - alkaline phosphatase
  - alanine aminotransferase (ALT; SGPT)
  - aspartate aminotransferase (AST; SGOT)
  - total bilirubin
  - direct bilirubin
- Lipids (fasting):
  - cholesterol
  - low-density lipoprotein
  - high-density lipoprotein
  - triglycerides
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Total protein

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**Central Laboratory Tests**

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- Immunohistochemistry (FFPE for AR, ER, PR, Her2, CYP17, CYP19, Ki-67, 3β-HSD)
  - Endocrine markers (estradiol, testosterone, estrone)
  - Pharmacokinetics (PK)
  - Circulating tumor cells (CTC)
  - miRNA, gene expression arrays
  - Pharmacogenomics
-

**Attachment 8:**  
Eastern Cooperative Oncology Group

- |   |  |
|---|--|
| 0 | Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)  |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work on a light or sedentary nature, eg, light housework, office work (Karnofsky 70-80) |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours (Karnofsky 50-60)                        |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)  |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair (Karnofsky 10-20)   |
| 5 | Dead   |

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**Attachment 9:**  
Amendment INT-5 Changes to Randomization and Crossover

Based on the DRC recommendations as described in Section 3.1 of the protocol, the following changes are being implemented with Amendment INT-5:

- The randomization ratio will now be 1:1 with randomization to the abiraterone acetate plus prednisone plus exemestane group or the exemestane only group. There will no longer be randomization to the abiraterone acetate plus prednisone group.
- No crossover is permitted. Subjects with disease progression must discontinue study drug.
- Subjects who were randomized to the abiraterone acetate plus prednisone group before implementation of Amendment INT-5 can decide whether or not to continue study drug.

**Attachment 10:****Modified Schedule of Events for Subjects Continuing to Receive Study Medication Under Amendment INT-6 (after the Clinical Cut Off Date for Final Analysis)**

The final analysis of Study 212082BCA2001 occurred as planned. The results did not show a significant benefit in PFS (the primary endpoint of the study) of adding abiraterone acetate to exemestane. Furthermore, there was a slight increase in reported adverse events for the abiraterone acetate group and the abiraterone acetate plus exemestane group compared with exemestane alone. This was most notable for hypokalemia, hypertension, and infections and infestations. No drug-related deaths were observed.

However, individual subjects might derive benefit from their current treatment with continued control of disease in the absence of significant toxicity. Therefore, the study has been amended to allow subjects to continue to receive their current study medication. As well, the number of required study-related procedures and amount of data to be collected have been reduced.

For subjects continuing on study medication, a final study follow-up visit will occur within 30 days after the last dose of study medication is administered. Subjects who elect not to continue on study medication and those currently in long-term follow-up will be discontinued from the study. At that time final patient disposition for these subjects will be recorded in the eCRF.

The study will be considered completed when the last subject completes the last study visit.

The following outlines instructions for the follow-up of subjects who continue to receive study medication under Amendment INT-6.

**Study Evaluations to be Performed Under Amendment INT-6**

Only serious adverse event information will be collected and drug accountability performed according to the Schedule of Events below. However, no further data will be collected in the eCRF. Assessments not specified in the Schedule of Events are at the discretion of the investigator. Investigators should monitor and assess the subjects according to routine practice. No further efficacy data are being collected by the sponsor.

Information regarding serious adverse events (as defined in Section 12.3.2) 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). No other safety data will be collected by the sponsor. An End-of-Treatment Visit or phone call for a safety assessment should take place within 30 days after the last dose of study medication is administered.

**Attachment 10: (Continued)**

Modified Schedule of Events for Subjects Continuing to Receive Study Medication Under Amendment INT-6 (after the Clinical Cut Off Date for Final Analysis)

**Treatment Phase Under Amendment INT-6**

Subjects must sign an updated informed consent form to continue in the study under Amendment INT-6. Subjects who elect to remain in the study will continue to receive study medication. Treatment may continue for up to 2 years from the date of the CCO-FA (ie, up to 20 September 2015) as long as the subject, in the opinion of the investigator, is receiving benefit and not experiencing unacceptable toxicity; or until such time that the subject needs to start other anti-cancer treatment, withdraws consent, or at the investigator's/subject's decision. At the end of the 2-year period, the situation will be reassessed for subjects still receiving study medication.

During the treatment phase, subjects will continue to receive daily treatment with abiraterone acetate plus prednisone/prednisolone and/or exemestane as they were up to the time of this amendment and according to the dosing regimens outlined in Section 6 Dosage and Administration. Subject's visits will be registered in the interactive voice response system, and the dispensing of study medication and drug accountability will occur every 3 months. Subjects will be supplied with 3 months of study drug at each visit. For consistency, the subjects will not restart their cycle number. Cycle "X" will be the first cycle under Amendment INT-6.

**Efficacy Evaluations to be Performed Under Amendment INT-6**

Investigators should monitor and assess the subjects for response to treatment or disease progression according to routine practice. No efficacy data will be collected by the sponsor under Amendment INT-6.

**Safety Evaluations to be Performed Under Amendment INT-6**

Safety assessments as outlined in the Schedule of Events provided in this Attachment will be performed while continuing treatment and for up to 30 days after the last dose of study medication. Only serious adverse events will be collected and reported. 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 above in this attachment. No other safety data will be collected by the sponsor.

**Study Drug Preparation and Dispensing Instructions**

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 drug accountability records including 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.

**Attachment 10: (Continued)**

Modified Schedule of Events for Subjects Continuing to Receive Study Medication Under Amendment INT-6 (after the Clinical Cut Off Date for Final Analysis)

**End-of-Treatment Visit Under Amendment INT-6**

This visit can take place as a scheduled visit or a phone call at the discretion of the investigator.

**Subject Completion**

A subject is considered to have completed the study after discontinuing treatment for any reason and having had a follow-up safety assessment within 30 days after the last dose of study medication is administered or the subject is lost to follow-up.

**Subject Withdrawal From the Study**

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

- Lost to follow-up
- Withdrawal of consent
- Discontinuation of study treatment
- Investigator's decision

A subject's study treatment will be discontinued if:

- The investigator or sponsor believes (eg, 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 and/or exemestane treatment
- The sponsor terminates the study

**Source Documentation**

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. This should also include: subject identification and study identification; study discussion and date of updated informed consent; dates of visits; serious adverse event information; drug receipt/ dispensing/ return records and study drug administration information. (See Section 17.4)

**Study Completion**

The study is considered completed with the last End-of-Treatment safety assessment for the last subject receiving study medication under Amendment INT-6 or upon a decision by the sponsor to terminate the study.

**Study Termination**

The sponsor reserves the right to close the investigational site or terminate the study at any time or 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.

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**Attachment 10: (Continued)**

Modified Schedule of Events for Subjects Continuing to Receive Study Medication Under Amendment INT-6 (after the Clinical Cut Off Date for Final Analysis)

**Schedule of Events for Subjects Continuing to Receive Study Medication Under Amendment INT-6**

Phase 2	Treatment Phase		End of Treatment
	Amendment INT-6 Cycle X <sup>1</sup>	Every Third Cycle Until Treatment Discontinuation	End-of-Treatment Visit
<b>Study Procedures<sup>2</sup></b>			
Informed consent <sup>3</sup>	X		
Dispense/ administer study drug <sup>4</sup>	X	X	
Drug accountability	X	X	X
Serious Adverse Events <sup>5</sup>	X	X	X <sup>6</sup>

<sup>1</sup> Cycle X will be the first cycle under Amendment INT-6.<sup>2</sup> Response and safety evaluations (other than serious adverse event reporting) are to be performed at the discretion of the investigator according to routine practice.<sup>3</sup> At the time of signing the informed consent for Amendment INT-6, only patient disposition information will be recorded for subjects in the eCRF.<sup>4</sup> Subject's visits will be registered in an interactive voice response system. Subjects will be supplied with 3 months of study drug at each visit.<sup>5</sup> 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). No other safety data will be collected by the sponsor.<sup>6</sup> An End-of-Treatment Visit (or phone call) for a safety assessment should take place within 30 days after the last dose of study medication is administered.

**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): Craig L. Tendler, MD

Institution: Janssen [redacted] Development

Signature: [redacted] Date: 29 APR 2015

(Day Month Year)

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